Trial Summary: The Golden Gate towards a Successful Submission
Bhargav Koduru, and Girish Kankipati, Seattle Genetics Inc.

ABSTRACT

Trial Summary (TS) has gained importance in the recent submissions due to specific guidelines introduced in the recent versions of FDA's Study Data Technical Conformance Guide (latest version was released in Oct 2017). As of December 2016, it is required to use UNII, NDF-RT and SNOMED CT in NDAs, ANDAs and certain BLAs (FDA Data Standards Catalog v4.10 updated in Oct 2017), while entering the input for certain TSPARMCDs like TRT, CURTRT, COMPTRT, and PCLAS etc. In addition, failure to include TS dataset in the submission package would result in a technical rejection with a high severity.

With the limited description provided for the TSPARMCDs in the CDISC Controlled Terminology (CT), it is often not clear how to derive certain CT. This can lead to improper derivation, which jeopardizes the entire submission. For example, NDF-RT houses the values for all the following TSPARMCDs PCLAS, TRT and CURTRT. This increases the possibility to assign an incorrect value to PCLAS if not clear on the assigned value, at pharmacological level.

In this paper, we would like to present the use of certain valid resources like RxClass by NIH to correctly recognize the TSPARMCD value for PCLAS and outline the preferred terms of ClinicalTrials.Gov and EUDRA, and their correlation in completing TS domain. We will also present how to use some new TSPARMCDs like PUBMEDID.

INTRODUCTION

Trial Summary (TS) provides a quick overview of the submitted clinical trial to the reviewer, without the need to comb through the entire protocol. TS has quickly evolved from a fancy optional dataset in the past to a required dataset, in the absence of which a submission package would receive a Technical Rejection as shown in Figure 1. FDA’s eCTD validation software will look in TS domain for the Study Start Date (SSTDTC) record indicating whether the study requires standardized data, as per FDA’s guidance released in December 2014. Hence, making TS mandatory for even legacy studies as outlined in Figure 2 (US Food and Drug Administration., 2017). Lee (2017) has discussed in great detail regarding the consequences of Trial summary's omission in the submission and responding to technical rejection in his paper “How will FDA Reject non-CDISC submission?”. Study Data Tabulation Model Implementation Guide (SDTM IG) is the source to understand the basic architecture of the TS domain but it lacks many intricate details on how to derive the values (TSVAL) for some key TS parameters (TSPARAM) such as TRT, CURTRT, COMPTRT, and PCLAS. The recent PharmaSUG papers bridge the gap where the SDTM IG falls short (Kelly, Salyers, & Wood, 2016) (Liu, Erskine, & Read, 2015). However, considering the complexity of these parameters and the need for some pharmacological and/or medical background, there is still a wide margin for errors due to incorrect interpretation of the guidelines.

In this paper, we will present some reliable lookup sources, in addition to the pharmacological details that would help the programmers to avoid some common pitfalls when deriving the TSVAL for PCLAS. The paper will also help with the further enhancement of the TS dataset by presenting the usage of some new TSPARMCDs that are available in the more recent SDTM Controlled Terminology versions (National Cancer Institute, 2017), to make TS a champion of the trial for a successful submission.
**eCTD Technical Rejection Criteria for Study Data**

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**Figure 1. Technical Rejection details pertaining to Trial Summary exclusion.**

**IMPORTANT**

A Trial Summary dataset (ts.xpt) must be presented for each study in sections identified below even if the study started prior to December 17, 2016. Nonclinical legacy data submitted in PDF format should be submitted with a TS dataset.

Study data validation **WILL APPLY** to the following eCTD sections:

- 4.2 Study Reports
- 5.3 Clinical Study Reports and Related Information

Study data validation **WILL NOT APPLY** to the following eCTD sections:

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3.3 Genotoxicity
- 4.2.3.5 Reproductive and Developmental Toxicity
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies
- 5.3.1.3 In Vitro – In Vivo correlation Study reports and related information
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies
- 5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
- 5.3.3.5 Population PK study reports and related information2
- 5.3.5.3 Reports of Analyses of Data from More than One Study
- 5.3.5.4 Other Study Reports and Related Information
- 5.3.6 Reports of Postmarketing Experience

**Figure 2. Trial Summary is mandatory for all Study Submissions**
PHARMACOLOGICAL CLASS OF ACTION

‘Pharmacologic Class’ (TSPARMCD=‘PCLAS’) is a ‘Conditionally Required’ parameter in the TS dataset. PCLAS becomes a ‘Required’ Parameter for the dataset when the value (TSVAL) is ‘INTERVENTIONAL’ for the parameter ‘Study Type’ (TSPARMCD=‘STYPE’) and TSVAL is ‘DRUG’ or ‘BIOLOGIC’ for another associated parameter ‘Intervention Type’ (TSPARMCD=‘INTTYPE’), i.e., any trial involving a Biological or drug intervention would require “PCLAS” to be included in their TS dataset.

The following is the FDA’s definition (U S Food and Drug Administration, 2015) for the Pharmacological Class

“Pharmacologic class is a group of active moieties that share scientifically documented properties and is defined on the basis of any combination of three attributes of the active moiety:

- Mechanism of action (MOA)
- Physiologic Effect (PE)
- Chemical Structure (CS)

An FDA “Established Pharmacologic Class” (EPC) text phrase is a pharmacologic class associated with an approved indication of an active moiety that the FDA has determined to be scientifically valid and clinically meaningful. It is generally the MOA, PE, or CS that is clinically meaningful.”

National Drug File - Reference Terminology (NDF-RT) contains the codes for both the drug of interest (TSPARMCD=‘TRT’) and its PCLAS, leaving a chance for confusion between the codes and the risk that the wrong TSVALCD is mapped in the Trial Summary for TSPARMCDs: PCLAS and TRT. Rxclass (U.S. National Library of Medicine., n.d.) is a great resource to find the EPC of the drug of interest. The top portion of Figure 3 below shows how the “class” of the drug “Brentuximab Vedotin” is revealed as “CD30-directed Immunoconjugate” when the class type is selected as “EPC” from the search results. The bottom portion of Figure 3 confirms the above retrieved result with its associated code from the NDF-RT repository.

Figure 3. Deriving the correct values for the Pharmacological Class.
Unlike PCLAS, there are other key parameters in TS for which reliable tools do not exist, and it becomes necessary for the programmer to have these values reviewed by the respective subject matter experts. For instance, Medical monitor is the best source to verify the SNOMED Controlled Terminology values for TSPARMCDs: INDIC (Trial Disease/Condition Indication), TDIGRP (Diagnosis Group); and the statistician can confirm the values for TSPARMCDs: TTYPE (Trial Type), INTMODEL (Intervention Model), if not mentioned in the statistical analysis plan or study protocol.

**ENHANCING THE TRIAL SUMMARY**

CDISC SDTM Controlled Terminology is updated every few months and the current version (National Cancer Institute, 2017) has 108 Trial Summary related parameters. SDTM IG and the open CDISC validator (Pinnacle 21) rules outline only a few key parameters displayed in Figure 3. There is no detailed information available for the rest of the parameters, except for the “CDISC Definition” column in the Controlled Terminology document. Thus, it becomes the responsibility of the programmer to correctly interpret and use the parameters in conjunction with the appropriate subject matter experts.

![Figure 3. The Key Parameters from the SDTM IG.](image)

**TSPARMCDs**

**REQUIRED:**

ADAPT, ADDON, AGEMAX, AGEMIN, DCUTDESC, DCUTDTC, FCNTRY, HLTSUBJI, LENGTH, NARMS, OBJPRIM, OUTMSPRI, PLANSUB, RANDOM, REGID, SENDTC, SEXPOP, SPONSOR, SSTDTC, STOPRULE, STYPE, TBLIND, TCNTRL, TPHASE, TTYPE, TITLE, ACTSUB

**CONDITIONALLY REQUIRED:**

CURTRT, INTMODEL, INTTYPE, PCLAS, RANDQT, TDIGRP, TINDTP, TRT

**EXTENSIBLE ADDITION:**

DOSE, DOSFRQ, DOSU, ROUTE,

**IF APPLICABLE:**

COMPTRT, CRMDUR, INDIC, OBJSEC, OUTMSEX, OUTMSSEC, SDMDUR, STRATFCT

- Protocol, Clinical Trials.gov
- Study Data

**CLINICALTRIAL.GOV AND EUDRA**

Majority of the clinical trial submissions are directed through FDA and EUDRA. CDISC has an Excel document with key TS parameters that are related to the preferred terms used in the protocol registration in ClinicalTrials.Gov (U.S. National Library of Medicine, 2017) and the EUDRA website. We have updated this Excel document from the CDISC website (Clinical Data Interchange Standards Consortium, 2016) with the latest parameter information and codes, as shown in Figures 4 and 5. If the listed preferred terms are being used in the ClinicalTrials.Gov or EUDRA, then it would be ideal to reflect those in the associated Trial Summary dataset in the submission.
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*Figure 4. TS Parameters correlating with the ClinicalTrials.Gov Preferred Terms*
### Trial Summary: The Golden Gate towards a Successful Submission, continued

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**Figure 5. TS Parameters correlating with the EUDRA Preferred Terms**
PUBMEDID

Many clinical trials are presented to the scientific community either in the form of a manuscript or as a conference presentation. A manuscript accepted for publication in a scientific journal would undergo multiple reviews by the experts in the field. Listing these publications in the trial submission would make it easier for the reviewer to access the studies similar to the submitted trial and highlight the importance of the trial of interest, displaying the importance it has garnered in the scientific community through citations or reviews. “PUBMEDID” is the TSPARMCD that facilitates the linking for the scientific publications associated with the trial. In Figures 6 and 7 we show how the REGID is used to search the associated publications from pubmed.gov, and retrieve the PUBMEDID using a completed study from Seattle Genetics as an example. It is not surprising that REGID is interchangeable with PUBMEDID as the U.S. National Library of Medicine manages both ClinicalTrials.Gov and PUBMED.

Figure 6. Identifying the REGID in ClinicalTrials.Gov
CONCLUSION

Considering the impact Trial Summary has on the submission and the depth of details it encompasses, it is no longer the sole responsibility of the programmer but a collective effort involving input from all parts of the study team including the Medical Monitors, Statisticians, Data Managers, Medical Writers and the Regulatory Affairs personnel. It is prudent to verify the values, and rely on the selective expertise of each study team member. With active engagement from all branches of the study team TS can become the Golden Gate for a successful submission.

REFERENCES


Trial Summary: The Golden Gate towards a Successful Submission, continued


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We would like to acknowledge Vinodita Bongarala, Balavenkata Pitchuka and Shefalica Chand for their valuable suggestions and comments to improve this paper.

RECOMMENDED READING


CONTACT INFORMATION
Your comments and questions are valued and encouraged. Contact the authors at:

Bhargav Koduru
Seattle Genetics, Inc.
(425) 527-4715
bkoduru@seagen.com

Girish Kankipati
Seattle Genetics, Inc.
(425) 527-2104
gkankipati@seagen.com

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