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Trial Summary: The Golden Gate towards a Successful Submission

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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 TSPARAMCDs 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

Number:	1734
Group:	General
Description:	A Trial Summary (TS) dataset must be present for each study in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4 and in module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2
Severity Description:	High
US DTD Version	2.01 and 3.3
Effective Date:	TBD
Problem:	You have not submitted a Trial Summary (TS) dataset for each study in Module 4, section 4.2 or in Module 5, section 5.3
Corrective Action:	Resubmit, including a Trial Summary for each study in Module 4, section 4.2 and Module 5, section 5.3
Guidance Source:	Providing Regulatory Submissions in Electronic Format – Standardized Study; Study Data Technical Conformance Guide.

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 information[2]
- 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.

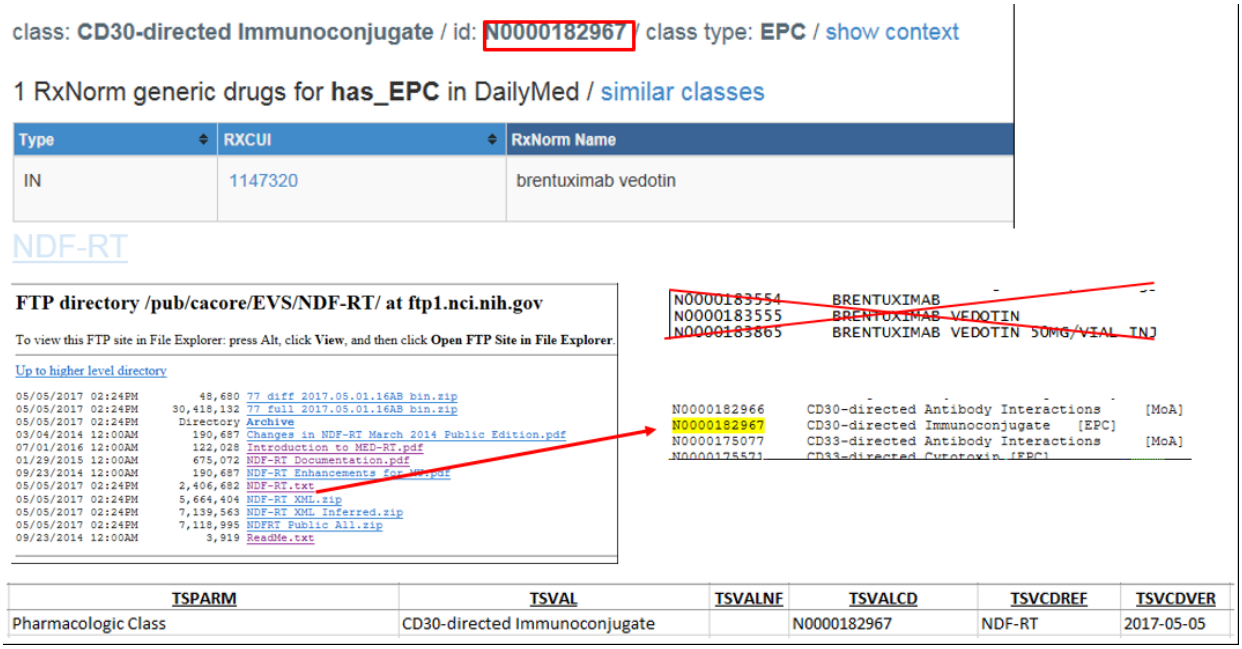

Figure 3. Deriving the correct values for the Pharmacological Class.

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.

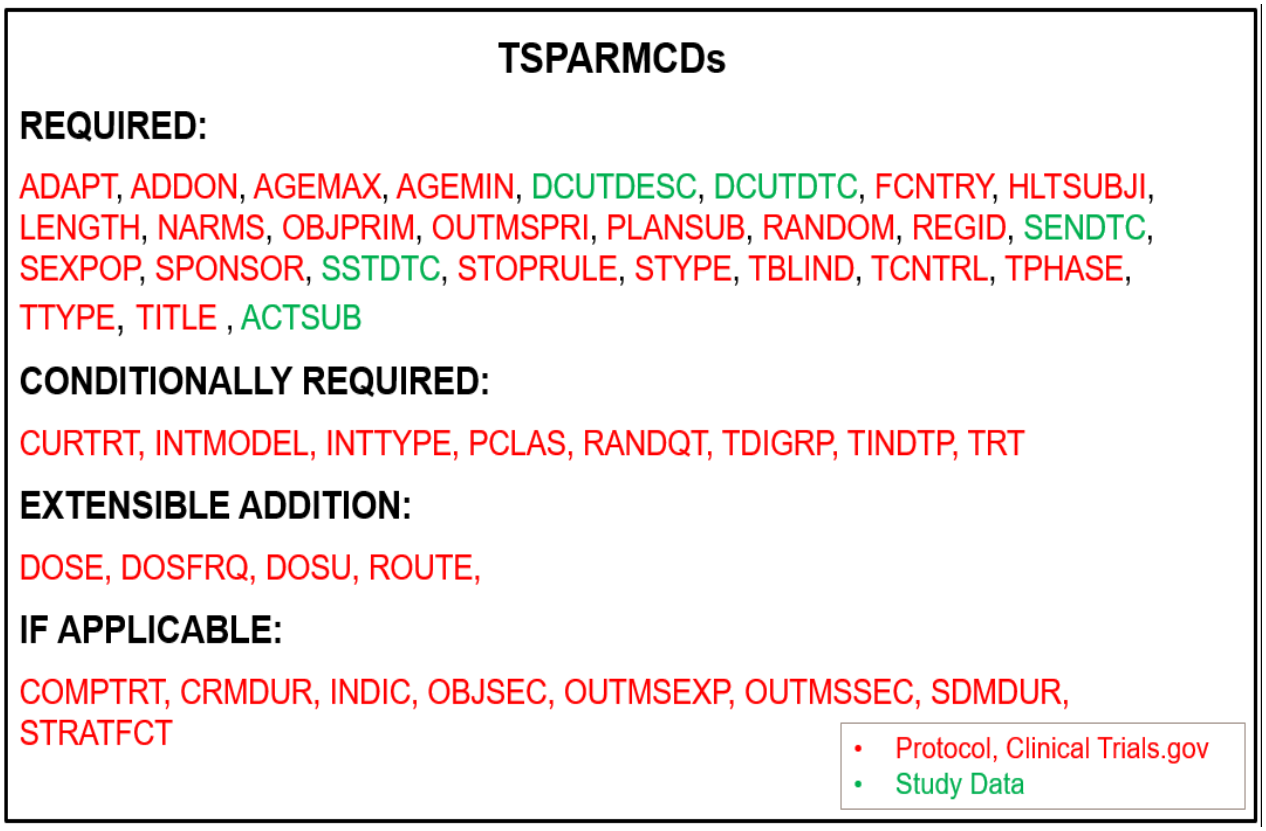

Figure 3. The Key Parameters from the SDTM IG.

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.

Code	Codelist Code	Codelist Extensible (Yes/No)	CDISC Submission Value	CDISC Synonym(s) (same as test name submission value)	ClinicalTrial.gov Preferred Term
C66738		Yes	TSPARMCD	Trial Summary Parameter Test Code	
C126062	C66738		KEYWORD	Protocol Keyword	Keywords
C126064	C66738		OBSMODEL	Observational Model	Observational Study Model
C126065	C66738		OBSTIMP	Observational Time Perspective	Time Perspective
C126058	C66738		BIOSPRET	Biospecimen Retention Contains DNA	Biospecimen Retention
C126072	C66738		RTSPCDES	Retained Biospecimen Description	Biospecimen Description
C126077	C66738		TRGFUDUR	Target Follow-Up Duration	Target Follow-Up Duration
C126063	C66738		NCOHORT	Number of Groups/Cohorts	Number of Groups/Cohorts
C126066	C66738		OBSTPOPD	Obs Study Population Description	Study Population Description
C126067	C66738		OBSTSMM	Observational Study Sampling Method	Sampling Method
C126068	C66738		OBSTSMMD	Obs Study Sampling Method Description	Sampling Method Detailed Description
C49660	C66738		TTYPE	Trial Type	Study Classification

Figure 4. TS Parameters correlating with the ClinicalTrial.Gov Preferred Terms

Code	Codelist Code	Codelist Extensible (Yes/No)	CDISC Submission Value	CDISC Synonym(s) (same as test name submission value)	EudraCT Preferred Term
C66738		Yes	TSPARMCD	Trial Summary Parameter Test Code	
C101302	C66738		THERAREA	Therapeutic Area	Therapeutic Area
C126060	C66738		EURSBIND	EudraCT Resubmission Indicator	Is Resubmission
C126071	C66738		RESUBLTR	Resubmission Letter	Resubmission Letter
C126069	C66738		PIPIND	Pediatric Investigation Plan Indicator	Trial Part of a PIP
C126059	C66738		EMPIPDCN	EMA Decision Number for PIP	PIP Decision Number
C126074	C66738		SRNCAIND	SUSAR Reporting to NCA Indicator	SUSAR Reporting to NCAs
C126073	C66738		SREVIND	SUSAR Reporting to EVCTM Indicator	SUSAR Reporting to EVCTM
C126061	C66738		EVSNDID	EudraVigilance Sender ID	EV Sender ID
C126090	C66738		EVSNDORG	EudraVigilance Sender Organization	EV Sender Organization
C126070	C66738		RDIND	Rare Disease Indicator	Condition a Rare Disease
C126076	C66738		SSTDYIND	Substudy Planned Indicator	Has a Sub-study
C126075	C66738		SSTDYDTL	Substudy Details	Sub-study Details
C49660	C66738		TTYPE	Trial Type	Trial Scope

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 ClnicalTrials.Gov

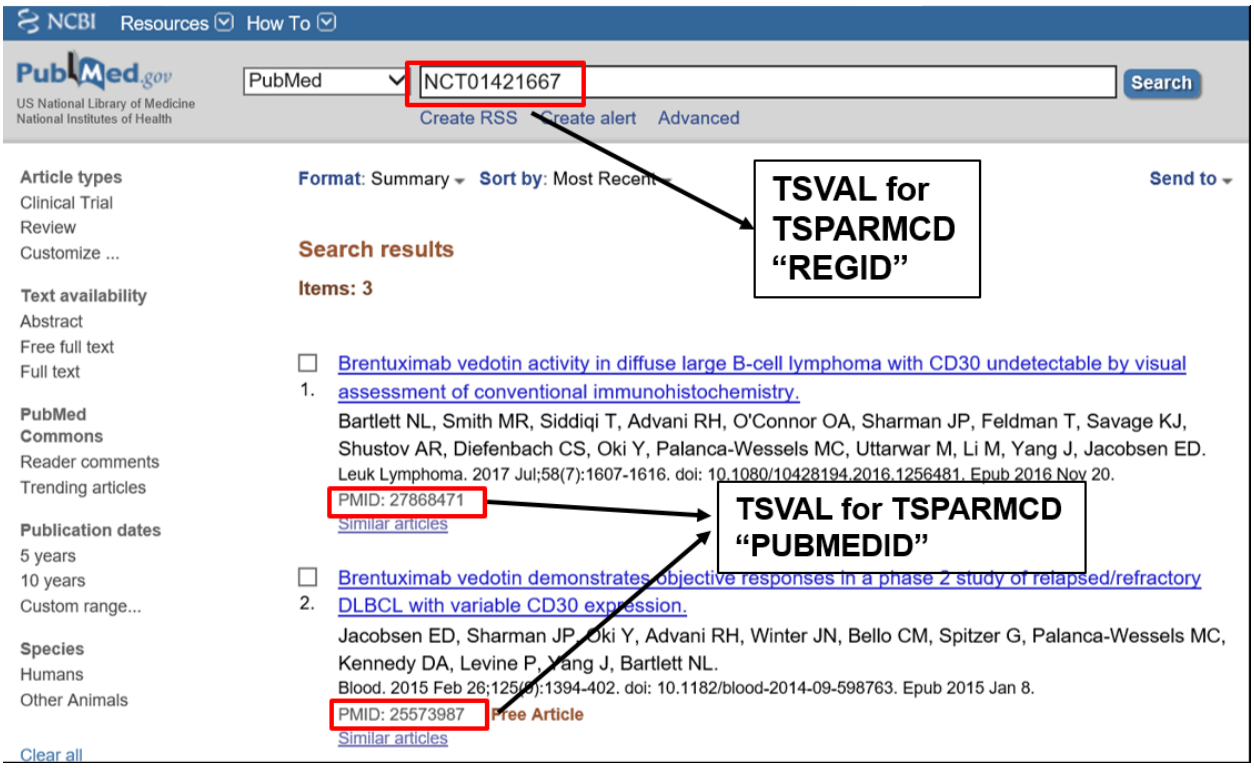

Figure 7. Using REGID to retrieve the PUBMEDID of the associated publications.

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.

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RECOMMENDED READING

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