Paper DS04

TS does not mean T(o) S(uffer) – A hands-on guideline for a better understanding of the TS domain

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ABSTRACT

Creating the Study Data Tabulation Model domain TS leads repeatedly to a lot of headaches for statistical programmers. A lack of sufficient hands-on guidelines, information source knowledge, or plain confusion regarding various TS parameters can turn the creation of the TS domain into an arduous endeavor.

This paper aims to provide a step by step guideline for the creation of the TS domain with additional information about various parameters and lessons learned through experience.

INTRODUCTION

The Trial Summary (TS) domain is a crucial instrument to familiarize oneself with the key parameters of a clinical study at first glance. The intent of this paper is to provide a guideline for the creation of the TS domain. For this, the content and structure of the domain will be explained, followed by providing helpful resources and their application, finished by providing a step-by-step guideline on creating the TS domain combined with suggestions for the more or less grey-area parts of the TS domain.

FAMILIARIZATION WITH THE TRIAL SUMMARY DOMAIN

When facing the challenge of creating the Trial Summary (TS) domain it can be difficult to find a starting point, especially if SDTM structure and requirements are still unfamiliar and knowledge about finding the necessary information is still lacking. This first part of the paper functions as an introduction of the TS domain, detailing the purpose and structure of the domain as well as providing information about helpful CDISC based sources for a deeper comprehension of the TS domain as well as guidance for the creation of the domain.

PURPOSE AND STRUCTURE OF THE TRIAL SUMMARY DOMAIN

The Trial Summary domain is used to store information about the study at hand, such as the trial name, the indication or the study start and stop dates. The TS domains provides access to the core explanatory information about the study and its design in a condensed structure.

The domain has a fixed structure and is composed of a list of defined variables which cannot be extended. The list of TS variables can be found in chapter 7.4.2: Trial Summary in the Study Data Tabulation Model Implementation Guide for Human Clinical Trials (SDTMIG) version 3.3[1] and will be presented below.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	TS	Identifier	Two-character abbreviation for the domain.	Req
TSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset. Allows inclusion of multiple records for the same TSPARMCD.	Req
TSGRPID	Group ID	Char		Identifier	Used to tie together a group of related records.	Perm
TSPARMCD	Trial Summary Parameter Short Name	Char	(TSPARMCD)	Topic	TSPARMCD (the companion to TSPARM) is limited to 8 characters and does not have special character restrictions. These values should be short for ease of use in programming, but it is not expected that TSPARMCD will need to serve as variable names. Examples: "AGEMIN", "AGEMAX".	Req
TSPARM	Trial Summary Parameter	Char	(TSPARM)	Synonym Qualifier	Term for the Trial Summary Parameter. The value in TSPARM cannot be longer than 40 characters. Examples: "Planned Minimum Age of Subjects", "Planned Maximum Age of Subjects".	Req

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
TSVAL	Parameter Value	Char		Result Qualifier	Value of TSPARM. Example: "ASTHMA" when TSPARM value is "Trial Indication". TSVAL can only be null when TSVALNF is populated. Text over 200 characters can be added to additional columns TSVAL1-TSVALn. See Assumption 8.	Exp
TSVALNF	Parameter Null Flavor	Char	ISO 21090 NullFlavor enumeration	Result Qualifier	Null flavor for the value of TSPARM, to be populated if and only if TSVAL is null.	Perm
TSVALCD	Parameter Value Code	Char		Result Qualifier	This is the code of the term in TSVAL. For example, "6CW7F3G59X" is the code for Gabapentin; "C49488" is the code for Y. The length of this variable can be longer than 8 to accommodate the length of the external terminology.	Exp
TSVCDREF	Name of the Reference Terminology	Char		Result Qualifier	The name of the Reference Terminology from which TSVALCD is taken. For example; CDISC, SNOMED, ISO 8601.	Exp
TSVCDVER	Version of the Reference Terminology	Char		Result Qualifier	The version number of the Reference Terminology, if applicable.	Exp

The first two variables, STUDYID and DOMAIN, are also used in subject-based general-observation-class-domains. As TS is a trial-based domain, the sequence number TSSEQ fulfills a slightly different role than the --SEQ variables in subject-based domains. While in subject-based domains the sequence number is used to form a sequential order of all existing records for a subject in the respective domain, TSSEQ is used to differentiate between several possible values for one trial summary parameter.

The name, code name, value and value code (if applicable) of the trial summary parameters are stored in Variables TSPARM, TSPARMCD, TSVAL, TSVALNF (if applicable) and TSVALCD (if applicable). TSPARM and TSPARMCD store the name and code name of the study data that is usually mapped to the TS domain. As an example, the value “SSTDTC” for TSPARMCD represents the start date of the study.

Variables TSVAL and TSVALNF on the other hand store the actual study information that is represented by TSPARM and TSPARMCD. TSVALNF stores a so called “null flavor”, which is a coded value that offers additional information if TSVAL cannot be filled. TSVAL and TSVALNF are never filled at the same time. More information about TSVALNF and a list of coded “null flavor” values can be found in chapter 7.4.2.1: Use of Null Flavor in SDTMIG v3.3.
If controlled terminology exists for a parameter value, the respective code is stored in the variable TSVALCD, while variable TSVCDREF stores the name of the reference terminology from which the code in TSVALCD is taken and variable TSVCDVER holds information about the version of the reference terminology.

In some cases, TSVAL will have to store a value that is over 200 characters long. As it is required that the SDTM domains are submitted in a SAS v5 transport format, large values cannot be stored in one variable and need to be split - this means a necessity for additional “storage” variables. Unlike with variables of the general observation classes, additional “storage” variables that are derived from TSVAL are kept in the TS domain instead of being transposed into entries in SUPP-domains.

Long values should be split between words around the 200 characters mark. A value can never be longer than 200 characters. The first part of the split value is to be stored in TSVAL. For every following approximately 200 characters additional TSVAL variables are created and given sequential names by appending a one-digit integer, starting with 1 (TSVAL1, TSVAL2, etc.).

FINDING AND USING CDISC BASED TS INFORMATION

The most important sources of information about the TS domain consist of the SDTMIG as well as the routinely updated Controlled Terminology for SDTM, which is released by the National Cancer Institute[2] in collaboration with CDISC.
Chapter 7.4.2 of SDTMIG v3.3 contains the overview information about the TS domain. It provides the needed variables that have been listed in this paper, a list of assumptions which provides more detailed information about the

design of the TS domain and characteristics of different parameters as well as information about "null flavor" values as mentioned before. Appendix C1: Trial Summary Codes, also available in the SDTMIG, provides a list of parameters that should be included in the TS domain to make it truly informative. The list also includes the requirement level of the parameters and useful information in the "Notes" column. The list, including additional notes from myself for a compact summary of the most crucial information about the parameters, is available in Appendix I of this paper.

The SDTM Controlled Terminology contains the code lists for the parameter codes and names. The number of possible parameters for the TS domain is not fixed. This means, one can add parameters - following the CDISC naming conventions - if the respective information one wants to list in the TS domain is not already covered by the existing parameters. For every parameter a CDISC definition is available which can help getting a better understanding of what information should be presented by the respective parameter.

Some parameters will have their own value code lists, which can also be found in the SDTM Controlled Terminology. On the CDISC wiki page the CT Relationships Sub Team provides a detailed list[3] of TS parameters, names and codes of potential value code lists, as well as potential external dictionaries or formats associated with the respective parameters.

CDISC also provides SDTMIG Conformance Rules with requirements for the different available SDTM domains. Regarding TS, the conformance rules provide information about several rules and requirements regarding different TS variables and TS parameters. The SDTMIG v3.2 Conformance Rules v1.0[4] have already been published, while as of right now, no conformance rules have been published for SDTMIG v3.3.

FINDING AND USING FDA BASED TS INFORMATION

When creating the TS domain, CDISC based documents are not the only ones that can and should be consulted. The U.S. Food and Drug Administration (FDA) released several documents that can help gaining a better understanding of the TS domain in general as well as making sure that the submitted TS domain conforms to FDA requirements.

FDA's Study Data Technical Conformance Guide[5] "provides specifications, recommendations, and general considerations on how to submit standardized study data […]" (Study Data Technical Conformance Guide, page 10) and elaborates on TS specific requirements in various parts of the document. Appendices B and C of the Study Data Technical Conformance Guide provide lists of FDA desired TS parameters for clinical and nonclinical studies.
In addition, the FDA publishes Business rules[6] and Validator rules[7]. The business rules provide general guidance for the submission of clinical and non-clinical data in a standard format. The validator rules then explain how the individual business rules as well as the CDISC conformance rules are to be implemented in the individual SDTM domains.

FINDING AND USING PMDA BASED TS INFORMATION

The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) has initiated the submission of electronical clinical data in October 2016. From April 1st, 2020 submission of standardized electronical data will be mandatory. The PMDA has published its own versions of a Technical Conformance Guide on Electronic Study Data Submission[8] (newest revision from 2019-01-24), a Data Standards Catalog[9] (2017-03-03) and Study Data Validation Rules[10] (2015-11-18). As with the FDA, these guidelines are not restricted to the TS domain but provide information for it as well.
The Study Data Validation Rules are of particular interest. Although there is quite a lot of overlap regarding the submission requirements between the two agencies, differences can be found nonetheless and need to be taken into consideration when submitting electronic data in Japan.

CREATING THE TRIAL SUMMARY DOMAIN

This chapter will provide information on how to create the TS domain in regard to the content of the domain. The technical part of creating a ts.xls file will be disregarded at this point as this is handled differently from company to company.

PARAMETER VALUE FORMATS

When filling TSVAL for every TSPARM(CD) that is included in the TS domain, one would consult study specific documents like the clinical study protocol (CSP) and the statistical analysis plan (SAP) as well as the study data itself. Some TS parameters can be filled without terminological restrictions, such as the title of the study or the trial

objectives. For other parameters, values must be expressed bound to controlled (CDISC) terminology or specific formats. Additionally, some parameter values may not be found within the study documentation but require external research, such as the study registry number on clinicaltrials.gov. Possible terminology/formats used in the TS domain are:

- CDISC SDTM Controlled Terminology
- ISO 8601
- ISO 3166-1 alpha-3
- external sources
    - SNOMED CT
    - Unique Ingredient Identifier (UNII)
    - Data Universal Numbering System (DUNS)
    - clinicaltrials.gov/EudraCT/JAPIC
    - Medication Reference Terminology (MED-RT)

Appendix I shows which parameters are linked to which terminology/format, if applicable.

ASSIGNING PARAMETER VALUES USING CDISC SDTM CONTROLLED TERMINOLOGY

Before assigning a value to a TS parameter, one should check if the respective parameter is bound to CDISC controlled terminology and if so, determine the name of the respective code list. Oftentimes the code list shares the same name as the corresponding parameter, but this is not always the case. Therefore, I would suggest consulting the abovementioned TS parameter list on the CDISC wiki page to determine possible code list names. The code list names for the most common parameters are also listed in the SDTMIG.

As an example, let's take a look at the trial phase parameter TPHASE. One would probably consult the study protocol to determine the phase of the respective study. Let's assume the study at hand is a phase 1 study. Without controlled terminology this information could be documented in more than one way in the TS domain, e.g. as "Phase 1", "phase I" or simply "1". Now, parameter TPHASE is bound to a CDISC controlled terminology code list, which is also named "TPHASE". The possible values of this code list can be looked up in the SDTM controlled terminology that has already been mentioned in this paper. The screenshot below shows some of the available values from the TPHASE code list:

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
C66737		Yes	Trial Phase Response	TPHASE	Trial Phase Response
C48660	C66737		Trial Phase Response	NOT APPLICABLE	NA; Not Applicable
C54721	C66737		Trial Phase Response	PHASE 0 TRIAL	0; Pre-clinical Trial; Trial Phase 0
C15600	C66737		Trial Phase Response	PHASE I TRIAL	1; Trial Phase 1
C15693	C66737		Trial Phase Response	PHASE I/II TRIAL	1-2; Trial Phase 1-2

The SDTM controlled terminology also includes definitions of the values as well as NCI preferred term values. Column "CDISC Submission Value" provides the values that are to be used to present study data in a CDISC compliant format. In our example, the correct value to use for the variable TSVAL for the TPHASE parameter would be "PHASE I TRIAL". From the screenshot it is obtainable that the code for the value in question is "C15600". This code is used in the TSVALCD variable (Parameter value code).

One would also fill the TSVCDREF variable (Name of the reference terminology) with the value "CDISC" and the TSVCDVER variable (Version of the reference terminology) with the date of the respective SDTM terminology used for the study in ISO 8601 format, e.g. "2019-06-28". If more than one study phase would be applicable for the study at hand, one would create another observation and sequence these two observations with the TSSEQ variable (Sequence number):

STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
ABC	TS	1		TPHASE	Trial Phase Classification	PHASE I TRIAL		C15600	CDISC	2019-06-28
ABC	TS	2		TPHASE	Trial Phase Classification	PHASE I/II TRIAL		C15693	CDISC	2019-06-28

ASSIGNING PARAMETER VALUES USING EXTERNAL SOURCES

Some TS parameter values that are obtained from study documentation need to be presented in a format from an applying external source or must be even obtained from an external source in the first place. In my experience, these parameters seem to provide the most struggle when it comes to creating the TS domain, oftentimes stemming from a lacking understanding of the content, but also because of grey areas, where a clear, single solution is not available. In this part of the paper I would like to expand on these parameters and provide suggestions and explanations, based on my personal experience regarding the different TS parameters.

TSVALCD = SPONSOR

The parameter "SPONSOR" is a required parameter for which the name of the responsible clinical trial sponsor and their DUNS number need to be provided. The sponsor's name is to be displayed in TSVAL, while the corresponding DUNS number is to be displayed in TSVALCD. DUNS numbers can be searched on the UPIK® portal [11] or directly on the dun & bradstreet website dandb.com[12]. In my opinion, using the dun & bradstreet number look-up option leads to more successful searches in regards to receiving any information if a company is even registered with d&b. However, unfortunately the associated DUNS number is not directly listed with the search result. Although there is a possibility to receive the needed DUNS number via e-mail, it seems one needs to hold an associated account to be able to receive the requested information.

On the other hand, a search using the UPIK® portal leads - if successful - directly to the desired DUNS number. In my experience though, the search for a DUNS number using the UPIK® portal can be quite error prone and can require several attempts. Also, not always the same logic seems to be applied to all stored company names. For example, searching for a sponsor, including the abbreviated form of organization "AG" (Aktiengesellschaft -joint stock corporation) did not lead to any results, the full name of the form of organization had to be entered. On the other hand, a search for a sponsor including the abbreviated form of organization "KGaA" (Kommanditgesellschaft auf Aktien - partnership limited by shares) lead to the correct result with the full name of the form of organization.

Furthermore, a search with the same parameters, conducted at different time points, can lead to different resulting outcomes. I've experienced this with different internet browsers and different devices. Therefore, I concluded that an unsuccessful search outcome does not necessarily mean that the company in question does not have a registered DUNS number. Especially if the regarding company is of a certain size, chances are that the search has simply gone wrong and not that the company does not have a registered DUNS number. In the absence of a better system I would therefore recommend using the UPIK® portal while making sure via the d&b number look-up option that the company in question is indeed registered with a DUNS number.

Based on my experience, my recommendation regarding the searching for a DUNS number would be as follows:

1) Make sure to search for the full, official company name and the country of the corresponding headquarter
2) If this result is not successful, search for parts of the full company name
3) Keep in mind the city of the corresponding headquarter and the official form of organization of the company to choose the correct one from the list of possible matches
4) The resulting list will show headquarters and single locations, choose the headquarter
5) The correct entry should include the full company name, the official form of organization, the country and city of the corresponding headquarter, and the mention of "headquarter" for the entry in the findings listing; choose the DUNS number for this entry as TSVALCD

Regarding the name of the sponsor, there are no specifications whether the company's name from the DUNS entry has to be chosen for TSVAL or not. It is incumbent upon the sponsor to choose the desired company's name for the TS domain.

TSVALCD = REGID

The parameter "REGID" holds information about the registry identifier(s) of a study, which were assigned to the study protocol by registries/databases of clinical trials, such as clinicaltrials.gov or EudraCT. If a clinical trial is conducted in the European Union, the EudraCT registration number can oftentimes be found in the clinical study protocol. Both clinicaltrials.gov and EudraCT provide search functions to look up a specific study. Please keep in mind the possibility that the clinical trial at hand might not be registered on one of the websites. If a clinical trial is registered with more than one registry, several entries can be created in the TS domain that are distinguished by the TSSEQ variable.

TSVALCD = TRT

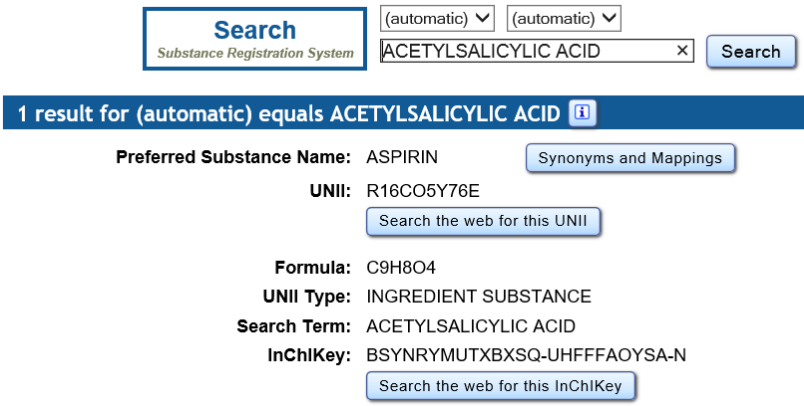
The parameter "TRT" represents the investigational therapy or treatment based on the naming convention of FDA's Global Substance Registration System[13] (GSRS): the Unique Ingredient Identifier (UNII). UNII codes are used "to identify active ingredients (specifically, active moieties) that are administered to investigational subjects in a study (either clinical or nonclinical)" (Study Data Technical Conformance Guide, page 39). They are also used for TS parameters CURTRT (Current Therapy or Treatment) and COMPTRT (Comparative Treatment Name). The parameter "TRT" needs to be included in the TS domain if the study type is an interventional one.

The GSRS "classifies substances as chemical, protein, nucleic acid, polymer, structurally diverse, or mixture as detailed in the ISO 11238 (International Organization for Standardization) and ISO DTS 19844"[14] and assigns a UNII code for each classified substance. The parameter "TRT" therefore does not hold merely the trade name of the trial medication but the actual ingredient(s) of said drug. Searching for these ingredients in the GSRS can easily become a complicated matter. Chances are, that the person who is responsible for the creation of the TS domain (usually a statistical programmer or data manager) is not someone with deep knowledge about the fundamental or main elements of the trial medication. Therefore, study drug information or knowledge about available UNII codes should be provided to the TS domain creator by the appropriate body within the sponsor's organization.

My personal approach towards researching UNII codes (based on the point of view of a statistical programmer in a contract research organization) is structured as follows:

1) Gather available information about the ingredients of the trial medication (e.g. from the clinical study protocol or published package leaflets)
2) Check the GSRS for (an) available UNII code(s) for the ingredient(s)
3) Correspond findings or lack thereof to the sponsor
4) If sponsor agrees with gathered UNII codes, include name(s) of ingredient(s) in TSVAL and UNII code in TSVALCD;
5) if sponsor does not agree with chosen UNII code(s) but GSRS entry is available for the ingredient(s) of the trial medication, sponsor should provide correct UNII code(s)
6) if sponsor confirms that no entry in GSRS is available for ingredient(s) of trial medication, sponsor needs to decide on further proceeding:
    - The FDA recommends sponsors to obtain UNII codes for yet unapproved substances "as early in drug development as possible" (Study Data Technical Conformance Guide, page 39)
    - other possibilities: do not fill TSVAL and TSVALCD for this entry but fill TSVALNF with a Null Flavor enumeration and TSVCDREF with "ISO 21090"; alternatively use substance name of trial medication for TSVAL, do not fill TSVALCD and TSVCDREF, therefore stating only the trial medication without any registered code

Let's assume that we want to search for the UNII code of a trial drug which main ingredient is acetylsalicylic acid. If we consult the GSRS we would receive the following result to fill the respective TS variables:



STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
ABC	TS	1		TRT	Investigational Therapy or Treatment	ASPIRIN		R16CO5Y 76E	UNII	

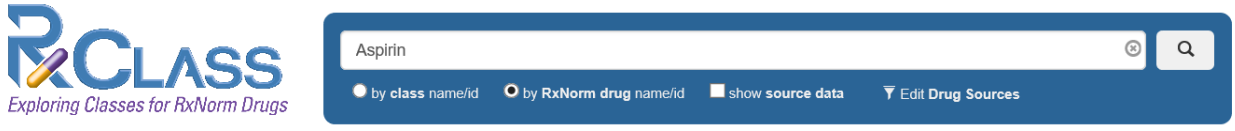
TSVALCD = PCLAS
The parameter "PCLAS" holds information about the established pharmacological class of the active substance(s) of the respective trial medication. The FDA defines an established pharmacological class (EPC) as "a pharmacologic class associated with an approved indication of an active moiety that the FDA has determined to be scientifically valid and clinically meaningful."[15] The FDA provides a guidance[16] and a manual of policies and procedures (MAPP)[17] with detailed information about pharmacological classes, both named "Determining the Established Pharmacologic Class for Use in the Highlights of Prescribing Information".

As with the TS parameter "TRT", filling parameter "PCLAS" can become a complicated matter for the responsible statistical programmer or data manager due to an understandable lack of deep pharmacological and toxicological substance knowledge. The person responsible for the creation of the TS domain has (limited) options to search for the applicable EPC, but as with the determination of the UNII code(s), results must always be discussed and confirmed with the responsible personnel within the sponsor's organization. In general, the responsibility for providing the correct established pharmacological class (if available) for the trial medication lies with the sponsor.

In the case of an unavailable pharmacological class, the FDA recommends: "If the established pharmacologic class is not available for an active moiety, then the sponsor should discuss the appropriate MOA, PE, and CS terms with the review division. For unapproved investigational active moieties where the pharmacologic class is unknown, the PCLAS record may not be available." (Study Data Technical Conformance Guide, page 41)

My EPC search suggestion would be to use the TSVAL value for parameter "TRT" (preferably a UNII term) to search for the established pharmacological class of a substance, using the RxClass browser[18] of the U.S. National Library of Medicine. The Medication Reference Terminology (MED-RT) is the successor to the Veterans Health Administration's National Drug File (NDF-RT) and provides the EPC terms.

To continue from our previous example, let's search for the UNII term "Aspirin", using the search function "by RxNorm drug name/id":



The search provides 58 classes, including two EPC classes:

Usually, a substance would only belong to one established pharmacological class, but in rare cases, more than one EPC can be identified (Guidance for Industry and Review Staff. Labeling for Human Prescription Drug and Biological Products. Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information, page 5). In this example, we would use both EPC terms and codes in the TS domain:

class: **Nonsteroidal Anti-inflammatory Drug** / id: **N0000175722** / class type: **EPC** / show context

class: **Platelet Aggregation Inhibitor** / id: **N0000175578** / class type: **EPC** / show context

STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
ABC	TS	1		PCLAS	Pharmacologic Class	Nonsteroidal Anti-inflammatory Drug		N0000175722	MED-RT	
ABC	TS	2		PCLAS	Pharmacologic Class	Platelet Aggregation Inhibitor		N0000175578	MED-RT	

If a MED-RT term cannot be determined for the trial substance, an alternative route to provide an EPC value could be using a suitable Anatomical Therapeutic Chemical (ATC) code, if available. However, this needs to be agreed upon with the responsible reviewers within the authorities.

TSVALCD = INDIC

The parameter "INDIC" informs about the trial indication - "The condition, disease or disorder that the clinical trial is intended to investigate or address." (SDTM Terminology 2019-06-28). This information is usually found in the clinical study protocol but needs to be coded according to SNOMED CT. These terms can be looked up in the SNOMED CT international browser[19]. As with the parameters "TRT" and "PCLAS" it is advisable to confirm one's findings with the appropriate experts.

STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
ABC	TS	1		INDIC	Trial Disease/Condition Indication	Cluster headache		193031009	SNOMED	

TSVALCD = TDIGRP

The parameter "TDIGRP" describes the diagnosis group(s), respective the study population(s) of a clinical trial. A diagnosis group is defined as "A grouping of individuals on the basis of a shared procedure or disease, or lack thereof." (SDTM Terminology 2019-06-28). If the study population is comprised of only healthy subjects (TSVAL = "Y" for TSPARMCD = "HLTSUBJI") this parameter is not expected, otherwise the parameter informs about the diagnosis/diagnoses of the study population(s), expressed in SNOMED CT codes.

Information about the study population can be obtained from the clinical study protocol, for example within the inclusion criteria. The diagnosis of the study population can be simply the indication of a trial. If a trial investigates cluster headaches and the study population is described as men and women between 18 and 65 years old with a diagnosis of cluster headaches, then the values of TSVAL and TSVALCD would be the same for the parameters "INDIC" and "TDIGRP".

The diagnosis group can also be a more specific manifestation of an umbrella term represented in the "INDIC" parameter. When investigating cluster headaches, several diagnosis groups could be included in the clinical trial, such as patients with chronic or episodic cluster headaches.

Furthermore, the trial indication could be investigated within patients with specific other conditions, e.g. an investigation of cluster headaches within patients with a diagnosis of an acute maxillary sinusitis.

STUDYID	DOMAIN	TSSEQ	TSGRPID	TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD	TSVCDREF	TSVCDVER
ABC	TS	1		TDIGRP	Diagnosis Group	Acute maxillary sinusitis		68272006	SNOMED	

CONCLUSION

The SDTM Trial Summary domain is an important part of a SDTM submission as it provides a precise overview of the key parameters of a clinical trial. Creating the TS domain can be a complicated and confusing matter due to scattered information and a requirement of specific knowledge beyond the borders of SDTM. This paper attempted to consolidate the most important information sources regarding the TS domain as well as provide suggestions for grey areas based on the author's experience. The correct creation of a meaningful TS domain requires the knowledge of several experts and sponsors are advised to determine the correct reference personnel within their organization for the retrieval of crucial TS information.

REFERENCES

1: Study Data Tabulation Model Implementation Guide for Human Clinical Trials (SDTMIG). Clinical Data Interchange Standards Consortium (CDISC) Submission Data Standards (SDS) Team. Version 3.3. November 2018
2: National Cancer Institute, CDISC Terminology, Study Data Tabulation Model (SDTM)
3: CDISC Wiki, CT Relationships Sub Team
4: Study Data Tabulation Model: Conformance Rules User Guide, Clinical Data Interchange Standards Consortium (CDISC) Submission Data Standards (SDS) Team. Version 1.0. December 2016
5: U.S. Department of Health and Human Services: Food and Drug Administration. Study Data Technical Conformance Guide version 4.3, March 2019
6: U.S. Department of Health and Human Services: Food and Drug Administration. FDA Business Rules. Version 1.5. May 2019
7: U.S. Department of Health and Human Services: Food and Drug Administration. FDA Study Data Validator Rules. Version 1.3. October 2018
8: Pharmaceuticals and Medical Devices Agency. Revision of Technical Conformance Guide on Electronic Study Data Submissions. January 2019
9: Pharmaceuticals and Medical Devices Agency. PMDA Data Standards Catalog. March 2017
10. Pharmaceuticals and Medical Devices Agency. PMDA Study Data Validation Rules. November 2015
11: UPIK® - Unique Partner Identification Key
12: Dun & Bradstreet (D&B)
13: U.S. Department of Health and Human Services: Food and Drug Administration. FDA's Global Substance Registration System Search Function
14: U.S. Department of Health and Human Services: Food and Drug Administration. FDA's Global Substance Registration System.
15: U.S. Department of Health and Human Services: Food and Drug Administration. Pharmacological Class
16: U.S. Department of Health and Human Services: Food and Drug Administration. Guidance for Industry and Review Staff. Labeling for Human Prescription Drug and Biological Products. Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information, October 2009
17: U.S. Department of Health and Human Services: Food and Drug Administration. Manual of Policies and Procedures. Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information, July 2018
18: U.S. National Library of Medicine. RxClass browser
19: SNOMED CT International Browser

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RECOMMENDED READING

- Koduru, Bhargav, “Trial Summary: The Golden Gate towards a Successful Submission”, 2018
- Kelly, Kristin, Salyers, Jerry, Wood, Fred, “SDTM Trial Summary Domain: Putting Together the TS Puzzle”, 2016
- Liu, Yi, Erskine, Jenny, Read Stephen, "Summing up - SDTM Trial Summary Domain", 2015
- Tambascia, Nicola, “A ‘How-to Guide’ for Trial Summary”, 2016

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Web: https://www.clinipace.com/

APPENDIX I: TRIAL SUMMARY CODES WITH ADDITIONAL NOTES

TSPARMCD	TSPARM	TSVAL (Codelist Name or Format)	Record with this Parameter	CDISC Notes	Additional Notes
ADDON	Added on to Existing Treatments	No Yes Response	Required		No Yes Response Codelist Code: C66742 (SDTM Terminology 2019-06-28)
AGEMAX	Planned Maximum Age of Subjects	ISO 8601	Required	If there is no maximum age, TSVALNF = "PINF".	Example: Max. age of 60 years: P60Y. Only one max. age value is permitted for the entire study. Suggestion: If max. age can differ in one study (e.g. depending on trial arm), choose greatest value. Please see chapter 4.4.3 Intervals of Time and Use of Duration for --DUR Variables in SDTMIG v3.3 for further information.
AGEMIN	Planned Minimum Age of Subjects	ISO 8601	Required	If there is no minimum age, populate TSVAL with "P0Y".	Example: Min. age of 18 months: P18M. Only one min. age value is permitted for the entire study. Suggestion: If min. age can differ in one study (e.g. depending on trial arm), choose lowest value. Please see chapter 4.4.3 Intervals of Time and Use of Duration for --DUR Variables in SDTMIG v3.3 for further information.
LENGTH	Trial Length	ISO 8601	Required		Trial Length is defined as “Planned length of observation for a single subject.” Only one trial length value is permitted for the entire study. Suggestion: If trial length can differ in one study, choose longest value. Please see chapter 4.4.3.1 Intervals of Time and Use of Duration of SDTMIG v3.3 for further information.
PLANSUB	Planned Number of Subjects	number	Required		To be found in the study protocol
RANDOM	Trial is Randomized	No Yes Response	Required		No Yes Response Codelist Code: C66742 (SDTM Terminology 2019-06-28)
SEXPOP	Sex of Participants	Sex of Participants	Required		Sex of Participants Codelist Code: C66732 ((SDTM Terminology 2019-06-28))
STOPRULE	Study Stop Rules	text	Required	Protocol-specified stopping rule. If there is no stopping rule, record "NONE" in this field.	To be found in the study protocol
TBLIND	Trial Blinding Schema	Trial Blinding Schema	Required		Trial Blinding Schema Codelist Code: C66735 (SDTM Terminology 2019-06-28)
TCNTRL	Control Type	Control Type	Required		Control Type Codelist Code: C66785 (SDTM Terminology 2019-06-28)
TDIGRP	Diagnosis Group	SNOMED CT	Conditionally Required	If the study population is healthy subjects (i.e., healthy subjects flag is "Y"), this parameter is not expected. If the healthy	Attention: With SDTM Terminology version of 2019-06-28 no Diagnosis Group Codelist available anymore. Websites to search for terms:

TSPARMCD	TSPARM	TSVAL (Codelist Name or Format)	Record with this Parameter	CDISC Notes	Additional Notes
				subject flag is "N", then this parameter would contain the diagnosis/medical problem of the study population. [Validation rule: IF healthy volunteers = "N" then TDIGRP must be present and not null.]	bioportal.bioontology.org ihtsdotools.org ncit.nci.nih.gov
INDIC	Trial Disease/Condition Indication	SNOMED CT	If Applicable	If applicable. Don't include if the sole purpose is to collect PK data. See TS Assumption 13. Use as many rows as needed.	Websites to search for terms: bioportal.bioontology.org (SNOMEDCT) ihtsdotools.org ncit.nci.nih.gov (SNOMED)
TINDTP	Trial Intent Type	Trial Indication Type	Conditionally Required	If study type is "INTERVENTIONAL", this parameter is required. A study in healthy volunteers may have TSVAL null and TSVALNF = "NA".	Trial Intent Type Codelist Code: C66736 (SDTM Terminology 2019-06-28)
TITLE	Trial Title	text	Required	Use as many rows as needed.	To be found in the study protocol
TPHASE	Trial Phase Classification	Trial Phase	Required		Trial Phase Codelist Code: C66737 (SDTM Terminology 2019-06-28)
TTYPE	Trial Type	Trial Type	Required	Use as many rows as needed.	Trial Type Codelist Code: C66739 (SDTM Terminology 2019-06-28)
CURTRT	Current Therapy or Treatment	SRS Preferred Substance Name (or Device Name)	Conditionally Required	Required when ADDON equals "Y". Use as many rows as needed for combination or multiple therapies.	Website to look up UNII codes: fdasis.nlm.nih.gov
OBJPRIM	Trial Primary Objective	text	Required		To be found in the study protocol
OBJSEC	Trial Secondary Objective	text	If Applicable	If applicable. Use as many rows as needed.	To be found in the study protocol
SPONSOR	Clinical Study Sponsor	DUNS	Required		Websites to look up DUNS numbers: upik.de dandb.com
COMPTRT	Comparative Treatment Name	SRS Preferred Substance Name	If Applicable	If applicable. Don't include if there are no active comparators. Use as many rows as needed.	Website to look up UNII codes: fdasis.nlm.nih.gov
TRT	Investigational Therapy or Treatment	UNII	Conditionally Required	If study type is "INTERVENTIONAL", this parameter is required.	Website to look up UNII codes: fdasis.nlm.nih.gov
RANDQT	Randomization Quotient	number	Conditionally Required	Required only when there is only one investigational treatment. The value is always a number between 0 and 1. There are cases where the ratio is 1 (e.g., crossover study or open label study where	

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				all subjects are exposed to investigational therapy).	
STRATFCT	Stratification Factor	Any allowable variable name	If Applicable	If applicable. Use as many rows as needed, one for each factor.	Used if applicable in randomized studies. Example factors are age or sex.
REGID	Registry Identifier	CLINICALTRIALS.GOV/EUDRAC	Required	Use as many rows as needed, one for each registry ID	Websites to look up potential registry identifier: clinicaltrials.gov clinicaltrialsregister.eu (EudraCT) clinicaltrials.jp (JAPIC) (Japanese registry of clinical trials)
OUTMSPRI	Primary Outcome Measure	text	Required	Use as many rows as needed.	To be found in the study protocol
OUTMSSEC	Secondary Outcome Measure	text	If Applicable	If applicable (i.e., if the trial has a secondary outcome measure). Use as many rows as needed.	To be found in the study protocol
OUTMSEXP	Exploratory Outcome Measure	text	If Applicable	If applicable (i.e., if the trial has exploratory outcome measure). Use as many rows as needed.	To be found in the study protocol
PCLAS	Pharmacologic Class	MED-RT	Conditionally Required	If study type is "INTERVENTIONAL" and if Intervention Type is one for which pharmacological class is applicable, this parameter is required.	MED-RT is the evolutionary successor to the Veterans Health Administration National Drug File (NDF-RT). As of August 2019, MED-RT has not been added to a community version of Pinnacle 21, this is targeted for version 3.1.0. Websites to look up PCLAS terms: mor.nlm.nih.gov/RxClass (look for terms where class type: EPC) nciterms.nci.nih.gov (MED-RT) (look for terms where CONCEPT_TYPE = EPC) bioportal.bioontology.org (MEDRT)
FCNTRY	Planned Country of Investigational Sites	ISO 3166-1-alpha-3	Required	Use as many rows as needed, one for each country.	Example: Germany = DEU; United Kingdom of Great Britain and Northern Ireland = GBR; since SDTMIG v3.3 the coded value is to be stored in TSVALCD while the decoded country name is to be stored in TSVAL. According to SDTMIG v3.2 the coded value is to be stored in TSVAL as well as in TSVALCD.
ADAPT	Adaptive Design	No Yes Response	Required	Does the protocol include any adaptive design features?	No Yes Response Codelist Code: C66742 (SDTM Terminology 2019-06-28)

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DCUTDTC	Data Cutoff Date	ISO 8601	Required	Use GRPID to associate the Data Cutoff Date to Data Cutoff Description.	Examples would be the date of an interim analysis or the date of the database lock
DCUTDESC	Data Cutoff Description	text	Required	Use GRPID to associate the Data Cutoff Date to Data Cutoff Description.	Examples would be an interim analysis or the database lock
INTMODEL	Intervention Model	Intervention Model	Conditionally Required	If study type is "INTERVENTIONAL", this parameter is required.	Intervention Model Codelist Code: C99076 (SDTM Terminology 2019-06-28)
NARMS	Planned Number of Arms	number	Required		
STYPE	Study Type	Study Type	Required		Study Type Codelist Code: C99077 (SDTM Terminology 2019-06-28)
INTTYPE	Intervention Type	Intervention Type	Conditionally Required	If study type is "INTERVENTIONAL", this parameter is required.	Intervention Type Codelist Code: C99078 (SDTM Terminology 2019-06-28)
SSTDTC	Study Start Date	ISO 8601	Required		Defined as “the earliest date of informed consent among any subject that enrolled in the study.”
SENDTC	Study End Date	ISO 8601	Required		Defined as “the date on which the final data item for a clinical study was collected from the last study participant.”
ACTSUB	Actual Number of Subjects	number	Required		Defined as the number of enrolled subjects and can also include subjects that were not randomized.
HLTSUBJI	Healthy Subject Indicator	No Yes Response	Required	If the healthy subject indicator is "N", then TDIGRP value should be provided.	No Yes Response Codelist Code: C66742 (SDTM Terminology 2019-06-28)
SDMDUR	Stable Disease Minimum Duration	ISO 8601	If Applicable	If applicable.	Example: two years = P2Y; please see chapter 4.4.3 Intervals of Time and Use of Duration for --DUR Variables in SDTMIG v3.3 for more information
CRMDUR	Confirmed Response Minimum Duration	ISO 8601	If Applicable	If applicable.	Example: two years = P2Y; please see chapter 4.4.3 Intervals of Time and Use of Duration for --DUR Variables in SDTMIG v3.3 for more information