Integrated Trial Design Model Datasets?

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ABSTRACT

Creating integrated datasets for an Integrated Study of Safety or Efficacy can be a complicated process. Aside from the complexities of integrating dissimilar studies and the sheer size of some of the datasets, it can be confusing how much of the defined study level SDTM and ADaM requirements are applicable. ADaM guidance for integration has not yet been finalized, and the source for those integrated ADaMs is not fixed. Because of this, many of the decisions on the path to integrated analysis datasets need to be made by those working on the individual submission. Among the many considerations in creating integrated datasets, one area that has not had much attention is integrated Trial Design Model Datasets. The first decision to be made is whether or not they are necessary. From there, if it is decided that they will be created, there are different methods that could be used to create them, as well as unique considerations for each domain. Once they are created, they will need special care with interpreting and supplementing any traditional compliance check output, since checks are focused on single studies. The overall approach taken with Trial Design Model Datasets differs between sponsors. This paper will discuss cases in which they might be created, methods to create them, special considerations for each domain, and an example of generating integrated Trial Design Model Datasets, including the assumptions and decisions made in the creation, special issues that arose, and the process of checking and submitting them.

INTRODUCTION

Planning an integrated database is a challenge. There is still room for interpretation and user decision about the best way to get to integrated analysis for submission with several options and pathways to choose. While the requirements for integration are still not cemented, variability remains in the process. ADaM guidance around integration is not yet finalized with draft information not requiring a specific source for ADaM. The SDTM standards are defined at a study level as well. So, what do we do about the Trial Design Model (TDM) datasets? The TDM datasets describe the study structure and design. Unlike other SDTM domains that contain patient level data, TDM datasets contain only study level data. Trial Arms (TA) describes all planned arms in a study. Trial Elements (TE) defines each element within an arm and the start and end of each. Trial Visits (TV) describes all planned visits. Trial Disease Assessments (TD) describes the trial disease assessment schedule. Trial Disease Milestones (TM) describes the disease milestones that are expected during the study. Trial Inclusion/Exclusion (TI) lists all Inclusion and Exclusion criteria for the study. Trial Summary (TS) contains many parameters that are used to describe various parts of the study design including study name, treatments, number of patients, endpoints, and many other planned points about the study. Do datasets that describe a study's design apply to an integration of multiple studies and if so, how?

When the question of integrated Trial Design Model datasets (iTDM) arose, after looking for documentation around it, the question that came up was: How is everyone creating integrated data structures for SDTM, TDM, ADaM now? The answer to that was a variety of methods. Of the responses received when asking about this process, all of the following processes were described for integrations:

- iSDTM datasets were not created or submitted and no iTDM/iTS was created.

- iSDTM datasets were created, but no iTDM/iTS was created.

- iSDTM and iTS were created.

The intent of this paper is not to make that handling decision for you, but to raise questions for consideration, point to some resources to start your journey, and to provide some examples of lessons learned from an exercise in TS integration.

DO WE NEED INTEGRATED TDM?

Before jumping into the process of creating iTDM for a submission, it is helpful to first determine if this is something that should be done. The first and most important question along this path is: Is it required to create iTDM? Secondly, if not required, is it helpful to have iTDM?

TDM EXPECTATIONS

In an analysis of multiple studies, there is an expectation of integrated ADaM (iADaM). The Study Data Technical Conformance Guide (TCG) v5.0 (October 2022) states: "ADaM datasets should be used to create and to support the results in clinical study reports (CSRs), Integrated Summaries of Safety (ISS), and Integrated Summaries of Efficacy (ISE), as well as other analyses required for a thorough regulatory review." However, there is not a definitive requirement that the source of this iADaM must be integrated SDTM (iSDTM). At a study level, the absence of SDTM does not mean that TS is not required. The reason for highlighting TS is that there is guidance set for the requirement of TS or simplified TS in the TCG. FDA's automated eCTD validation process needs the value in parameter Study Start Date (SSTDTC) for the study start date from the TS domain. Simplified TS may be indicated for example in cases where SDTM and ADaM are not required so that there is a way to show via SSTDTC that the study start pre-dates the requirement. The TCG also states: "Unless a simplified ts.xpt is indicated (see below), all TDM datasets should be included with each SDTM study submission to describe the planned conduct of a clinical study." And more, one of the eCTD validation criteria, number 1734, checks for the presence of ts.xpt with study start date.

Figure 1 shows FDA eCTD validation criteria number 1734 for ts.xpt.

Number:	1734
Group:	General
Description:	A dataset named ts.xpt with information on study start date 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	3.3
Effective Date:	9/15/2021 (CBER module 4 sections, 03/16/2023)
Problem:	You have not submitted a dataset named ts.xpt with information on study start date for each study in Module 4, section 4.2, or in Module 5, section 5.3
Corrective Action:	Resubmit, including a dataset named ts.xpt with information on study start date 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 Data; Study Data Technical Conformance Guide.

Figure 1. FDA eCTD validation criteria number 1734

So how could this apply to the case of an integration? The TCG also has detail around both CDER and CBER expectation of the presence of TS or simplified TS for both clinical and nonclinical studies and in which modules and submodules. In this list, module 5.3.5.3, titled "Reports of analyses of data from more than one study", is not present and is present in the list of sections to which eCTD validation for study data (Technical Rejection Criteria) will not apply. But this is not the end of our investigation.

Figure 2 displays the applicability to eCTD sections from the TCG's Appendix F: Technical Rejection Criteria for Study Data Validation Important Information.

eCTD validation for study data (Technical Rejection Criteria) **WILL APPLY** to the following eCTD sections:[87]
- 4.2   Study Reports
- 5.3   Clinical Study Reports and Related Information

eCTD validation for study data (Technical Rejection Criteria) **WILL NOT APPLY** to the following eCTD sections:[88]
- 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[89]
- 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. TCG Appendix F List of eCTD sections

ITDM USEFULNESS

Setting necessity aside, would iTDM datasets be helpful to have?

Positives

Similar to the way TDM datasets are used at the study level for cross checking to SDTM, they can provide this service for integrated data as well. This can help in checking ARM/ARMCD values in DM from TA, IETEST/IETESTCD in IE from TI, Elements from TE, and VISIT/VISITNUM from TV to any visit level domains. The caution with this is to make sure that any checking is done with STUDYID in any sorting, merging or checking keys. There may be values between studies that appear inconsistent if STUDYID is not considered. For example, if study level SDTM are set together maintaining original values at the iSDTM level, where VISITNUM=1, VISIT=BASELINE in one study, another may be VISITNUM=1, VISIT=PRE-DOSE in another study. When cross checking, if STUDYID is included as a key, it would ensure that the check is done at the study level.

If iTDM are considered early in the integration planning, they could add even more benefit. For example, before studies are pooled, an integrated TA (iTA) could give an efficient list of all of the possible arm values that have been defined across the studies. From this list you could see what possible arms need to be considered for analysis, grouped, or if there are equivalent treatment groups with inconsistent text across studies that may need consistent terminology applied in the iSDTM creation process itself. Similarly, integrated TV (iTV) could quickly show you all of the planned VISIT and VISITNUM values for each study even if a study is in its early stages and not all visits have been reached. In this case study level SV and other patient level domains would not have all visits present yet, but iTV would be complete and available to work out visit alignment decisions.

Negatives

Creation of iTDM would incur additional time and planning, but if it is able to be created by existing clean study level TDM, that effort might be small. Also, with the additional integrated domains, there will likely be more compliance messages generated that will need to be triaged and addressed in some way. Both of these issues will add time and effort and will be expanded on below.

HOW COULD WE CREATE INTEGRATED TDM?

If the decision is made to integrate TDM, how could that be done? Each method has its appropriate use. The method used to integrate TDM needs to take into consideration the method of integrating the rest of the SDTM. This process should mirror the methodology used to generate the iSDTM. If iSDTM are created by simply setting together each study SDTM then this method would be possible for iTDM. Otherwise, another option is needed.

SET STUDY TDM

Simply setting study TDM is the quickest and easiest method. But for this process to work, each study would need to have good, clean TDM already. Also, the iSDTM would have needed to be created by method of setting study SDTM. If iSDTM was created from study SDTM and then VISIT/VISITNUM were made consistent for example, iTDM created by solely setting study TDM would not align and may result in inconsistent VISIT/VISITNUM between iTDM and iSDTM. The creation process and level of uniformity needs to be consistent between the integrated datasets.

SET STUDY TDM AND FURTHER PROCESS

If the iSDTM was created by setting the study SDTM and making common consistent text for terminology such as VISIT/VISITNUM to make BASELINE and PRE-DOSE terminology consistent, study TDM could be set, but then a similar set of terminology updates applied to the iSDTM would need to be applied to the iTDM.

CREATE A MASTER TDM SPEC FROM STUDY LEVEL

Creating a master iTDM spec and then generating the iTDM datasets from a new spec might be necessary if any studies did not have TDM created prior or had incomplete TDM. This approach is a bit more cumbersome, but it could also help to alleviate some other issues that may be present when combining old and new study TDM such as special characters, typos, and inconsistent values.

With any method selected, the resulting arms defined in iTA, elements in iTE, visits in iTV and so forth will need to align between iTDM and iSDTM. If they are one-to-one in iSDTM they need to be one-to-one in iTDM. While the main concerns for iTDM is that they are complete and support the studies structure of iSDTM, integrated TS poses additional issues. TS references external dictionaries and controlled terminology libraries which can change over time between the first and last study's individual TS were created. Also, the list of SDTM required or agency required or desired parameters may change. This means that the first study may have had a complete TS, but that terminology may have changed or the agency list of desired parameters could have changed and there could be differences between the first study and last study. This results in more decisions to be made in the creation process of iTS.

Do you set the study SDTM datasets and leave it at that?
Do you set the study SDTM datasets, update for terminology differences, and create additional parameters?
Or start fresh from specification level and create an integrated specification and updated value list from which to create the iTS dataset?
Should TS describe the set of integrated data rather than the individual studies?

INTEGRATED TS EXERCISE

Working through the exercise of integrating TDM, specifically focusing on iTS with its additional complexities, several challenges arose. Some of these were expected issues similar to what we would normally encounter when creating iSDTM. Others were unique to iTS. This exercise began with the expectation of a quick setting together of study level TS to create iTS, but a series of findings resulted in looking back over this quick set with much more detail than expected.

From this learning experience, here are some of the things that could occur that you should be on the lookout for. Each needs to be assessed and decisions made in each case whether to action or explain in the reviewer guide.

Let us take a look at TS as defined by SDTM IG 3.3 as a reminder of its structure, content, and requirements to see those elements that are unique to TS. Seeing what makes TS different will help to understand why these pieces may need additional review when setting together data from multiple studies. TS contains the Study Identifier (STUDYID), Domain Abbreviation (DOMAIN), and Group ID (TSGRPID) with function and assignments consistent with other domains. Trial Summary Parameter Short Name (TSPARMCD), Trial Summary Parameter (TSPARM), and Parameter Value (TSVAL) function similar to xxTESTCD, xxTEST, xxORRES in findings domains or PARAM/PARAMCD/AVALC in ADaM to capture the description of the information that is captured on that record. This dataset's Sequence Number (TSSEQ) is a common variable fragment. However, it differs from other domains. In patient level domains, xxSEQ is assigned uniquely to records within Unique Subject Identifier (USUBJID). Since TS is not a patient level dataset, TSSEQ is a sequence number that differs across TSPARMCD when there is more than one present. Unique to TS are Parameter Null Flavor (TSVALNF), Parameter Value Code (TSVALCD), Name of the Reference Terminology (TSVCDREF), Version of the Reference Terminology (TSVCDVER) as well as a possible additional variable TSVAL1-TSVALn to continue the result value from TSVAL if it is over 200 characters.

Figure 3 is the TS structure as defined by SDTM IG 3.3.

TS – Specification

ts.xpt, Trial Summary Information — Trial Design, Version 3.2. One record per trial summary parameter value, Tabulation.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format[1]	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
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

[1] In this column, * indicates the variable may be subject to controlled terminology, and CDISC/NCI codelist code values are enclosed in (parenthesis).

Figure 3. TS structure as defined by SDTM IG 3.3.

EXPECTATIONS OF TS THAT ARE PROBLEMATIC FOR INTEGRATION

Trial Summary Parameter Variables

In general, there can be multiple records for the same TSPARM within TS. In these cases, TSSEQ will help to identify the unique records. However, this is not the case for every parameter. It would be common for TSPARM (TSPARMCD) = Planned Country of Investigational Sites (FCNTRY) to have multiple records, one for each country planned for the study for example. But TSPARAM (TSPARAMCD) = Planned Maximum Age of Subjects (AGEMAX) would be expected to be a single value and have one

planned result record per study. If using a compliance checker like Pinnacle 21 (P21), this is a check unique to TS that will fire when running on iTS because each study would have its own record for AGEMAX. P21 is following study level compliance rules so it does not see that they are differentiated by STUDYID.

The parameters expected to be present in TS have also changed over time. In SDTM IG version 3.1.2, the minimum recommended parameters were: "TITLE, INDIC, TCNTRL, RANDOM, TRT, COMPTRT (when applicable), AGESPAN, AGEMIN, AGEMAX, AGEU, SEXPOP, PLANSUB, OBJPRIM, OBJSEC." In SDTM IG version 3.3 there are over 40 required or expected parameters. If simply setting study level TS there may be studies that do not have all parameters present in iTS. The differences should be reviewed to determine if the additional parameters would be applicable to be created and populated. This is one case where compliance checking may not help to identify this occurrence. Since compliance checkers are likely expecting study level data and not checking that each is present by STUDYID, the check may see an instance of a parameter from a newer study and the data will pass that check even though it is not present for all studies. For those parameters that are expected to have multiple responses, they may also have a different type of compliance issue to explain. Since TSSEQ is assigned uniquely within STUDYID, in the complete iTS made of setting study level TS the TSSEQ will look like it is not unique if STUDYID is not considered.

Value Result Related Fields

Parameter Value (TSVAL) has expected CDISC and non-CDISC controlled terminology for some parameters.

These terminology lists have been updated over time. Earlier studies may have needed to create a study defined value if an appropriate value was not present in an extensible code list, where later studies could select a value from an updated terminology list that may be similar in meaning, but differing in text. Trial Blinding Schema & Trial Type are examples of lists that have been updated.

TSVALCD, TSVCDREF, TSVCDVER, and TSVALNF variables all have direct relationship to TSVAL. TSVCDREF is the terminology type that applies to TSVAL on that record. This could be CDISC or a non-CDISC terminology. This variable itself does not have Controlled Terms, Codelist or Format though some examples of values are included in the SDTM Implementation Guide (IG): CDISC, SNOMED, ISO 8601. It is possible that these values might differ between study TS. For example, using "CDISC" vs "CDISC TERMINOLOGY" as the text to indicate CDISC based terminology lists might have occurred. CDISC terminology is updated regularly, so TSVCDVER is used to document the version of the terminology list that was used. It is possible and likely that setting together study TS datasets will result in iTS with TSVCDREF=CDISC and TSVCDVER differing. Within the TSVCDREF terminology list in the terminology version in TSVCDVER, the TSVALCD is the value level code for the value found in TSVAL. Though TSVCDVER may differ, across TSVCDREF, each TSVAL should still have a consistent value of TSVALCD.

The null flavor stored in TSVALNF explains why a TSVAL is null. TSVALNF is subject to ISO 21090 terminology. It can contain values such as 'UNK' for simply Unknown or something more specific like 'PINF' for Positive Infinity. 'PINF' could be used for TSPARMCD=AGEMAX in studies with no upper limit on planned age. Since TSVAL for TSPARMCD=AGEMAX is subject to ISO 8601 and there is not a standard way to identify the unlimited upper value, TSVALNF terminology is used for this case. This is another place where inconsistencies could arise since older studies may have filled in some non-standard text into TSVAL to indicate this. In that case, running a current validator, a message would be generated for these old-style values to indicate that the TSVAL for AGEMAX did not correctly use the ISO 8601 format. If by chance the TSVAL for an older study did use 'PINF' or some value from the ISO 21090 list that under the current structure should appear in TSVALNF, it would also result in a validation message. These would be updated or explained.

Since there are some versions of SDTM TS that did not contain these additional results variables in addition to TSVAL, it is possible that in the set of study TS, there are inconsistencies arising from having the same TSVAL with different or missing TSVALCD, TSVCDREF, or TSVCDVER.

Other Differences That May Arise

At the integrated level, any team would be hoping to start with clean and compliant study level TS. But what is considered clean and compliant could change over time. As noted above, older studies created before updates to TS in the SDTM IGs may not have all of the parameters present that newer studies have in addition to the TSVAL or other terminology differing. Not every difference means that the original TS was incorrect, but it may have followed an earlier standard or an earlier understanding of requirement.

Also, working through this process did really reinforce the understanding that just because P21 did not result in a compliance message does not make it correct. Something might not have been obvious as a stand-alone, but when multiple studies set together and the inconsistency is pointed out in value/terminology, more attention is drawn to that point to escalate and find the consistent solution. There are also things that are not yet checked that could be added in the future. For example, there is not a check for the presence of TSVALCD if TSVCDREF=CDISC. This check would be challenging to program since some of the terminology lists are extensible, so there could be missing TSVALCD. But that is something that may have unintentionally occurred in older studies that could be flagged by validation checks if one was added. The increasing robustness of P21's checking has impact as well helping each study level TS to become more compliant to the evolving standard.

With this process, it becomes necessary to weigh the importance of consistency with source study TS vs consistency within new iTS. If there was a typo in TSVAL previously, should we have consistency with the study level or consistency within the new iTS? Since TS is not patient data, but assigned from protocol values, there is the capacity to assign and document the assigned values. The solution may be to update and document or to keep the difference and document. Either way, the CSDRG or creation algorithms are available to document.

Along with years of updates in versions of terminology, SDTM, and P21, the study team knowledge, growth, and understanding of the standards and expectations may have changed significantly from the creation of the first TS though the last TS and integration and there may be a difference in completeness due to this growth.

Newer studies may have had more attention paid to special non-ASCII characters and had some process to resolve them. Since TS is sometimes created by creating a spreadsheet of values and reading that in, it is at a higher risk for non-ASCII characters to be introduced. One benefit of the methodology of creating TS from a new spec of integrated TS would be to be able to create this iTS spec with care not to introduce the troublesome characters. When setting the study level TS, if there is a process put in place to replace or remove special characters, this is something that should be documented as well.

Validator Impacts

At a study level, typically, the P21 results relating to TS would be expected to be fairly clean. But since the iTS contains more than one study, the checks will provide some warnings or errors that would not be expected at a study level, but is understandable at the integrated level. P21 appears to check with the expectation of the presence of one study, so there were several messages to explain regarding having multiple instances of parameters that were expected to appear only once per study.

As P21 is evolving over time and updates occur, use caution if you are preparing to finish up documentation of messages around the time of a new version. If not completed before up-versioning, be prepared for unexpected changes in messages and the need to review them to make sure that any new messages are addressed. This unexpected event could occur as a matter of unfortunate/fortunate timing. Unfortunate in that there are new issues identified, however fortunate in that those issues are able to be addressed either by updating the TS or by acknowledging the messages in the Reviewer's Guide. For example, while P21 does check that there are not multiple of some parameters present, it does not check all. There is not a check for multiple SSTDTC. If that check is added in a future update, that may trigger another message that may need to be documented in a set together iTS.

Most of the validation messages that arose from set together iTS fell into three main categories. Reviewing all of the validation rules, here are some examples that could fall into each of those categories.

1) Those that are good study level TS checks, but would likely be triggered in iTS because the data met the rule, but within STUDYID.

2) Items that would be problematic in any case and would likely not be integration related.

3) Differences that could be related to having an older study with a TS created before some of the newer variables TSVALCD/TSVALNF/TSVCDREF/TSVCDVER were added.

Below are just some examples of the validation messages that fit into those groups.

Figure 4 shows some of the TS related validation messages categorized for integration review.

Rule ID	Message	Description	Domains	Integration Considerations
SD1038	Non-unique value for TSSEQ variable within TSPARMCD	Sequence Number (TSSEQ) must have a unique value for a given value of Trial Summary Parameter Short Name (TSPARMCD) within the domain.	TS	Is it unique within STUDYID?
SD1216	Multiple AGEMAX records	Trial Summary (TS) domain must contain only one record for 'AGEMAX' Parameter.	TS	Is it unique within STUDYID?
SD1222	Multiple PLANSUB records	Trial Summary (TS) domain must contain only one record for 'PLANSUB' Parameter.	TS	Is it unique within STUDYID?
SD1221	Invalid TSVAL value for PLANSUB	TSVAL for PLANSUB record must be numeric.	TS	Not integration related
SD1223	Invalid TSVAL value for RANDOM	TSVAL for RANDOM record must be 'Y' or 'N'.	TS	Not integration related
SD1268	TSVCDREF is null when TSVCDVER is populated	The Name of the Reference Terminology (TSVCDREF) must be populated when the Version of the Reference Terminology (TSVCDVER) is populated.	TS	Not integration related
SD2213	Missing TITLE Trial Summary Parameter	'Trial Title' (TITLE) record must be populated in Trial Summary (TS) domain. It is expected for SDTM IG v3.1.2 data and required for data in all more recent SDTM versions.	TS	Not integration related
SD2214	Missing TPHASE Trial Summary Parameter	'Trial Phase Classification' (TPHASE) record must be populated in Trial Summary (TS) domain. It is expected for SDTM IG v3.1.2 data and required for data in all more recent SDTM versions.	TS	Not integration related
SD2247	Invalid TSVAL value for SSTDTC	TSVAL variable value must be in ISO 8601 format, when TSPARMCD='SSTDTC'.	TS	Not integration related
SD1278	Inconsistent value for TSVALCD within TSVAL	Parameter Value Code (TSVALCD) and Parameter Value (TSVAL) should have a one-to-one relationship.	TS	Study pre-TSVALCD?
SD1215	Invalid TSVAL value for AGEMAX	TSVAL value must be either ISO 8601 format for time period (e.g. P80Y) or null, when TSPARMCD='AGEMAX'.	TS	Study pre-TSVALNF?
SD1297	TSVAL is populated with a value from the ISO 21090 null flavor codelist	TSVAL should not be populated with a value from the ISO 21090 null flavor codelist, or synonyms of the values. The TSVALNF variable should be used to capture these values, not TSVAL.	TS	Study pre-TSVALNF?
SD2017	Missing values for both --VAL and --VALNF	Value for Parameter Value (--VAL) variable must be populated. --VAL can only be null when Parameter Null Flavor (--VALNF) variable value is populated.	TS	Study pre-TSVALNF?
SD2240	Invalid TSVCDREF value for INDIC	TSVCDREF variable value must be 'SNOMED', when TSPARAMCD='INDIC'.	TS	Study pre-TSVCDREF?
SD2244	Invalid TSVCDREF value for FCNTRY	TSVCDREF variable value must be 'ISO 3166', when TSPARMCD='FCNTRY'.	TS	Study pre-TSVCDREF?

Figure 4. displays a categorized subset of TS related validation checks.

After creation of iTS by means of setting study level TS, the data and compliance checks were reviewed to determine what would be updated and what would be explained. As with any study checking, just because P21 gives a compliance message, it does not always mean that there is a change required. Like with all other parts of SDTM and ADaM, P21 is a great help to raise questions, but it is a supplement to, not a replacement for, knowledge, investigation and thorough review. P21 has evolved to check and catch more with over 100 Rule IDs just related to TDM, but it also does not know the study and what should be there. It is up to us as the humans involved in the process to take the programmed compliance check result messages, requirements, and context and determine the next appropriate steps.

CONCLUSION

The determination of requirement of iTDM including iTS, lies in the review of the current guidance, documentation, and available agency requirements at the time of submission. There is a need to interpret the information available and the clarity and certainty around it. With that in mind, an assessment of the risks of not producing iTDM, but documenting, versus the time and efforts to generate basic iTS or all iTDM needs to be done. If not required, iTDM could still provide some benefit and early consistency checking. The interpretation of need, benefit to creating, and ultimate decision may differ across teams, but the starting place for the path forward is the investigation and interpretation of the requirements.

The conclusions of necessity and solutions are in the opinion of the author based on information available at the time of writing. Current guidance, documentation, and requirements should be referenced before making submission decisions.

REFERENCES

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https://www.pinnacle21.com/validation-rules/sdtm

Study Data Tabulation Model Implementation Guide: Human Clinical Trials Version 3.3

Study Data Technical Conformance Guide v5.0 (October 2022)

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