

SDTM/ADaM IG Nuances



Question	Teams Collective Response
Is there a recommended standard for how sponsor organisations should be handling the mapping of inclusion/exclusion criteria into the SDTM IE domain? Should 'like' or 'similar' inclusion/exclusion criteria be mapped into a similar IETESTCD?	<p>PHUSE Team Response : 25 April 2023</p> <p>The SDTM TI and IE domains together reflect the inclusion and exclusion criteria data for any given study. The TI SDTM domain should reflect what is/was in the protocol at the time (assuming different versions are present due to amendments). The SDTM IG v3.4 mentions the following assumptions for the TI domain in section 7.4.1 with respect to protocol amendments:</p> <ol style="list-style-type: none">1. If inclusion/exclusion criteria were amended during the trial, then each complete set of criteria must be included in the TI domain. TIVERS is used to distinguish between the versions.2. Protocol version numbers should be used to identify criteria versions, though there may be more versions of the protocol than versions of the inclusion/exclusion criteria. For example, a protocol might have versions 1, 2, 3 and 4, but if the inclusion/exclusion criteria in version 1 were unchanged through versions 2 and 3, and only changed in version 4, then there would be two sets of inclusion/exclusion criteria in TI – one for version 1 and one for version 4.3. Individual criteria do not have versions. If a criterion changes, it should be treated as a new criterion, with a new value for IETESTCD. If criteria have been numbered and values of IETESTCD are generally of the form INCL00n or EXCL00n, and new versions of a criterion have not been given new numbers, separate values of IETESTCD might be created by appending letters, e.g. INCL003A, INCL003B. <p>There are no additional expectations from the regulatory agencies. The FDA expects sponsors to manage the inclusion/exclusion criteria updates.</p>

<p>Historical Data Consideration in the SV Domain (under SDTMIG v3.4) Assumption 13 under SDTM IG v3.4 for the SV domain states: "Therefore dates prior to informed consent are not part of the determination of SVSTDTC." But some protocols allow historical results within a period (e.g. test results within 4 weeks prior to informed consent date) as valid screening results. Protocols also allow these pre-screening tests to be collected, primarily for verifying inclusion/exclusion criteria (e.g. a specific gene mutation test that was done two or three years before informed consent for a study). If we don't consider these dates as the determination of SVSTDTC, VISIT in that particular domain will have to set to null. Is this reasonable?</p>	<p>PHUSE Team Response: 09 December 2022</p> <p>Pre-study findings, such as tests performed at the time the disease was diagnosed, can be assigned to the initial screening visit. In this case, the content of the visit variable represents the visit when the test result was recorded in the CRF. The date of the test (or sample collection date) will be stored in the –DTC variable of the applicable domain (e.g. MIDTC).</p> <p>In cases where historical data is stored as a finding, these historical test/sampling dates should not be taken into account when populating SVSTDTC for the particular visit. In your case, you can set MI.VISIT to 'Screening', MIDTC=date of test, and SV.SVSTDTC will be the date of the first day of the screening visit and will not take MIDTC into account.</p> <p>References: CDISC guidelines: https://www.cdisc.org/kb/articles/sdtm-timing-variables-pre-study-findings</p> <p>Assumptions 13 for the SV domain in SDTMIG v3.4: "13. Algorithms for populating SVSTDTC and SVENDTC from the dates of assessments performed at a visit may be particularly challenging for screening visits, since baseline values collected at a screening visit are sometimes historical data from tests performed before the subject started screening for the trial. Therefore dates prior to informed consent are not part of the determination of SVSTDTC."</p>
<p>How should the sex of transgender patients be collected and analysed in clinical trials? Should the sex at birth be collected only or should the gender preference also be collected? Which laboratory normal ranges should be assigned to transgender patients' laboratory test results? How does hormone therapy affect data collection and/or analysis for transgender patients?</p>	<p>PHUSE Team Response: 30 June 2022</p> <p>The CDISC CDASH team is currently working to publish either an updated guidance or white paper planned for 2025 on recommendations on capturing the sex for transgender patients. In the draft version, the recommendation would be to collect a two-stage question (note that the controlled terminology and collection text are a draft stage and not finalised): 1. "Sex at Birth" (Male Female Don't know Prefer not to answer) and 2. "Sexual Identity" (Male Female Intersex Transgender ... Don't know Prefer not to answer Self-describe). In the interim, each sponsor should determine how the data should be collected. It is recommended to provide clarity on the definition of each question, perhaps within the CRF Completion Guidelines. For example, does Sex at Birth pertain to sex stated on the birth certificate, and how to complete the data entry if a patient does not have a birth certificate.</p> <p>The following articles may be reviewed to determine how hormone therapy affects laboratory results and, in general, analysis for transgender subjects:</p> <ol style="list-style-type: none"> 1. "Common Hormone Therapies Used to Care for Transgender Patients Influence Laboratory Results", Humble, R. et al, 2018, <i>American Association for Clinical Chemistry</i>. 2. "Interpreting Laboratory Results in Transgender Patients on Hormone Therapy", Roberts, T. et al, 2014, <i>The American Journal of Medicine</i>. 3. "Impact of Hormone Therapy on Laboratory Values in Transgender Patients", SoRelle, J. et al, 2019, <i>Clinical Chemistry</i>. 4. "Approach to Interpreting Common Laboratory Pathology Tests in Transgender Individuals", Cheung, A. et al, 2021, <i>The Journal of Clinical Endocrinology & Metabolism</i>. 5. "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline", Hembree, W. et al, 2017, <i>The Journal of Clinical Endocrinology & Metabolism</i>.

<p>How do you proceed in providing the reason for the missing code? Do you collect the reason for the missing LOINC code or do you just provide a predetermined reason?</p> <p>The LOINC working group recommend providing a reason for missing code in the cSDRG. (See the extracted text from the Reference: https://www.fda.gov/media/109376/download)</p> <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> <p>For any lab test where a LONIC code is not submitted, the reason for its omission should be noted in the clinical Study Data Reviewers Guide.</p> <ul style="list-style-type: none"> • The Working Groups proposes that a starter set of reasons be predetermined (perhaps as CDISC terms) for consistency of reporting, including: <ul style="list-style-type: none"> ◦ Performing laboratory unable to determine if appropriate LONIC code exists ◦ Performing laboratory indicates that no appropriate LONIC code currently exists </div> <p>The FDA TCG 4.6 recommends providing the LOINC code of the laboratory parameters for studies starting after March 2020, but nothing is mentioned in the case of missing code.</p>	<p>PHUSE Team Response: 07 February 2022</p> <p>If the laboratory hasn't sent the LOINC code, it is recommended to go back to the laboratory to obtain it. Per the team members' experience, the FDA accepts if the laboratory hasn't provided the LOINC code and it is missing. In the cSDRG, it notes the reason for it missing as "Lab did not provide the code", or as noted in the LOINC working group's screenshot. (Reference: https://www.fda.gov/media/109376/download)</p> <p>One solution would be to request the LOINC code from the lab at the study initiation phase, but it is expected that not all lab tests will have a corresponding LOINC code assigned.</p>
<p>There are a couple of papers which offer guidance for maintaining 1-1 maps between AVAL and AVALC. Things like:</p> <p>https://www.lexjansen.com/wuss/2017/79_Final_Paper_PDF.pdf</p> <p>https://www.pharmasug.org/proceedings/2012/DS/PharmaSUG-2012-DS16.pdf</p> <p>However, neither of these papers explain how to consistently create derived records, where AVALC is a rounded version of AVAL, which satisfies the 1-1 criteria. For example, suppose (within a single PARAMCD) I need to compute an average and then present that in a list to 1 dp. For example, let's say AVAL=45.333333 so for the listing I want to show 45.3. I've computed an average for another subject where AVAL=45.26 which I also want to show as 45.3 in a listing. If AVALC=45.3 for both records, then this is not a 1-1 mapping. I obviously can't round AVAL, because that would represent a loss of numerical precision in other calculations. One solution might be 'do not populate AVALC, do the rounding when producing the report'. However, this leaves a lot of work in the reporting program if many parameters are to be listed; the programmer would have to determine the rounding on a per-parameter basis. Ideally the 'heavy lifting' should already have been done at the dataset level.</p>	<p>PHUSE Team Response: 08 July 2020</p> <p>Rounding values of AVAL for listing purpose - where to do the rounding and how/where to store the rounded value.</p> <p>Storing a rounded value in AVAL is not good practice as it typically results in a loss of precision for calculations in the tables. Storing rounded values in AVALC goes against the ADaM rule that there has to be a 1-1 mapping of AVAL to AVALC. Also, it is not the intent to store the character version of a numeric analysis value in AVALC. AVALC should be populated only when the character value is used for analysis. See ADaM IG v1.1, section 3.3.4, 'PARAM, AVAL, AVALC' paragraph 3.</p> <p>There is no ADaM guidance as to variable naming for variables used for listing purpose only.</p> <p>Rounding the analysis result can be done in the listings program, or alternatively, if one wants to store rounded value in the ADaM dataset, a custom variable can be added with an intuitive meaning, eg LISTVAL, to store the rounded value.</p>
<p>Study treatment regimen will be A-B-C-D, therefore planned ARMCD can be ABCD. Most of the patients actual ARM ACTARMCD will also be ABCD. But a few patients may skip D or repeat ABC part which is ABC or ABCABCD. Shall we put UNPLANN in actors or put the real ABC or ABCABCD in the ACTARMCD?</p>	<p>PHUSE Team Response: 09 January 2020</p> <p>The planned treatment should be reflected in ARMCD/ARM, while the actual regimen received should be reflected in ACTARMCD /ACTARM. In general, TA should reflect the protocol-specified treatment regimens to be administered. If the protocol specified the skipping of a treatment regimen by design, then it is acceptable to find inconsistencies between ARMCD and ACTARMCD. However, these should be noted in the cSDRG and explained in further detail.</p>
<p>In SV domain, we search all the by-visit source data to get the min and max date of each CRF visit. If due to some reason, there are 1-2 days overlap among 2 consecutive CRF visits in SV domain, we can explain in SDRG or always make visits in SV without overlap which means we assign the overlapped days to 1 CRF visit in SV rather than keep the days in both visits as the source data shown?</p>	<p>PHUSE Team Response: 09 January 2020</p> <p>Acceptable to have the overlap on the visits in SV domain. There will be no P21 consequences due to this, and as such it is not required to explain further in the DRG. The explain in the DERG would be left to the Sponsor's determination.</p>

<p>For the Table like 'Summary of Common (\geqX%) Adverse Events by Overall Frequency', should the flags for common AEs be created in the ADAE dataset?</p>	<p>PHUSE Team Response: 31 July 2019</p> <p>5pct, 2pct custom flag variables can be added to ADAE Derivation of the flag variable depends on the definition in SAP/table Janssen - If derivation rule is complicated enough, include it in ADAE.</p> <ul style="list-style-type: none"> • have an internal macro to derive the variable with parameter being the x of x% • internal macro is a reporting macro, not tied to the ADAE <p>Other companies do not include in the ADAE and handle it in the table generating programs.</p> <ul style="list-style-type: none"> • can also explain in the ADRG • if this table calls into the category of the primary/secondary key safety and efficacy, you will need to submit the program • can also be included in the ARM
<p>FDA impressed the wish to keep ETCD/ELEment to facilitate reviewer to review the data in 2011 CDER Common Data Standards Issues Document. However, in all later FDA published Study Data Technical Conformance Guide up to V4.1 published in 2018, only EPOCH is required.</p> <p>EPOCH by it's own should have been informative enough. FDA validator rules V1.2 published in DEC2017 still mentions that variables requested by FDA in Policy documents should be included in the dataset, e.g. EPOCH and ELEMENT. Do you know if FDA still require ELEMENT/ETCD in all domains? If yes, I would suggest to CDISC SDTM team to include those 2 variables in the parent domain and not the SUPP domain.</p>	<p>PHUSE Team Response: 04 July 2018</p> <p>ETCD/ELEMENT Variables: The reference to the 2011 CDER Common Data Standards Issues document is no longer relevant and superseded by the FDA Study Data Technical Conformance Guide**. Therefore, any such references must be in alignment with current FDA guidelines. The inclusion of ETCD/ELEMENT within other domains other than those identified within the SDTM/SDTMIG** is not recommended.</p> <p>EPOCH Variables: Section 2.2.5 of the SDTM* allows for the timing variable EPOCH within any of the three general observation class domains, except where explicitly stated otherwise in the SDTMIG. Therefore, EPOCH inclusion to facilitate the recommendations identified in section 4.1.4.1 of the FDA Study Data Technical Conformance Guide** is in alignment with CDISC SDTM/SDTMIG*.</p> <p>Additional References:</p> <ul style="list-style-type: none"> • CDISC SDTM V1.4/SDTMIG V3.2 • FDA Study Data Technical Conformance Guide V4.1
<p>How should OTHER be represented for variables bound by non-extensible codelists?</p>	<p>PHUSE Team Response: 07 June 2017</p> <p>Existing SDTMIGs (e.g., v3.1.2, v3.1.3, v3.2) do not explicitly define how "OTHER" should be implemented universally for all non-extensible codelists.</p> <p>Additional References:</p> <p>N/A</p>
<p>How should MULTIPLE be used for variables bound by non-extensible codelists?</p>	<p>PHUSE Team Response: 07 June 2017</p> <p>Existing SDTMIGs (e.g., v3.1.2, v3.1.3, v3.2) do not explicitly define how "MULTIPLE" should be implemented universally for all non-extensible codelists.</p> <p>Additional References:</p> <p>N/A</p>
<p>What are best practices for creating CT for/representing questionnaire responses?</p>	<p>PHUSE Team Response: 07 June 2017</p> <p>It is recommended to review SDTMIG (v3.1.2, v3.1.3, or v3.2) Section 4.1.3 Coding and Controlled Terminology Assumptions. Furthermore, please also review existing questionnaire CDISC Controlled Terminology (CT) and CDISC Questionnaires, Ratings & Scales (QRS) supplements and related details found on the QRS page – see reference below.</p> <p>Additional References:</p> <p>https://www.cdisc.org/qrs</p>

What is the general recommendation/approach for generating/submitting custom domains (e.g. non-standard CDISC SDTM domains) to regulatory agencies?

PHUSE Team Response: 12 September 2017

As per CDISC SDTM IG version 3.2: A sponsor should submit the domain datasets that were actually collected (or directly derived from the collected data) for a given study. Decisions on what data to collect should be based on the scientific objectives of the study, rather than what is present in SDTM. Note that any data that was collected and will be submitted in an analysis dataset must also appear in tabulation dataset.

Both PMDA and FDA allow the creation/submission of custom domains if the study data does not fit into a standard SDTM domain however, custom domain may only be created if the data are different in nature and do not fit into an existing published domain (e.g. standard SDTM, Therapeutic Area Standards)*.

- **NOTE:** When assessing the need for a custom domain, also storing of data in supplemental qualifier (SUPP--) or findings about (FA--) domains should be considered. Helpful references on when to use findings about or supplemental qualifiers are present in the CDISC SDTM IG ("When to Use Findings About", "How to Determine where data belong in SDTM Compliant Data Tabulations" and the Supplemental Qualifiers section). Another reference is the PHUSE Paper "Findings About".

The overall process for creating a custom domain are clearly explained in the SDTM IG and must always be based on one of the three SDTM general observation classes (interventions, events or findings).

Custom domains must be clearly described in the cSDRG/SDRG and specifically PMDA prefers to be consulted beforehand when considering storing data in a custom domain.

Source for FDA:
Study Data Technical Conformance Guide

Source for PMDA:
Revision of Technical Conformance Guide on Electronic Study Data Submissions

Source for CDISC:
CDISC SDTM IG

Source for PHUSE:
Findings about "Findings About"