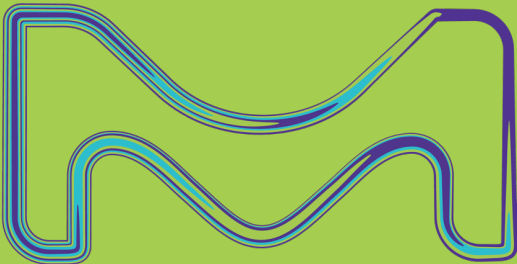


Handling Multiple Screenings Using the New Domain DC (Demographics for Multiple Participations) at Merck – Implementation of a New Mapping Process

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MERCK

Table of Content

1. Background

- FDA requirements
- Proposal of Demographics as collected (DC) domain from CDISC SDS Multiple Subject Instances (MSI) team
- Currently different usage of the DC domain between the CDISC proposal and Merck

2. Implementation at Merck

- General rules for subject identifiers USUBJID and SUBJID
- Representation of subjects in the Demographics (DM) domain
- Representation of subjects in the Demographics as collected (DC) domain
- Possible validation issues due to the new mapping process
- Conclusion

3. Q & A

Background – FDA requirements

FDA Study Data Technical conformance guide (must current version 5.4 from June 2023):

Chapter 4.1.1.2 – SDTM General Considerations

“Subject Identifier (SUBJID)

The variable SUBJID uniquely identifies each subject that participates in a study. If a single subject is screened and/or enrolled more than once in a study, then the subject’s SUBJID should be different for each unique screening or enrollment. For a study with multiple screenings and/or multiple enrollments per subject, SUBJID should be included in other related domains besides DM even though it may cause validation errors. It is recommended to include a table linking each SUBJID for a single subject to that subject’s USUBJID with any additional necessary explanation included in the relevant RG.”

Background – FDA requirements

FDA Study Data Technical conformance guide (must current version 5.4 from June 2023):

Chapter 4.1.1.2 – SDTM General Considerations

“Unique Subject Identifier (USUBJID)

The variable USUBJID is an identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product. 25 Each individual subject should be assigned a single unique identifier across the entire application. This is in addition to the subject ID (SUBJID) used to identify subjects in each study and its corresponding study report. An individual subject should have the exact same unique identifier across all datasets, including between SDTM and ADaM datasets. Subjects that participate in more than one study should maintain the same USUBJID across all studies. It is important to follow this convention to enable pooling of a single subject’s data across studies (e.g., a randomized control trial and an extension study).”

Background – FDA requirements

FDA Study Data Technical conformance guide (must current version 5.4 from June 2023):

Chapter 4.1.1.3 – SDTM Domain Specifications

“For subjects with multiple enrollments within a single study, the primary enrollment should be submitted in DM. Additional enrollments should be included in a custom domain with a similar structure to DM. Clarifying statements in the RG would be helpful.

For subjects with multiple screenings and no subsequent enrollment, include the primary screening in DM with additional screenings in a custom domain with a structure similar to DM.

For subjects with multiple screenings and subsequent enrollment, include the enrollment in DM with screenings in a custom domain with a structure similar to DM.”

Background – Proposal of Demographics as collected (DC) domain from CDISC SDS Multiple Subject Instances (MSI) team

- The CDISC SDS MSI proposed to create a new, custom domain to accommodate the FDA's requests – Demographics as collected (DC), with a similar structure as the Demographics (DM) domain
- The domain is still “under construction” and will be possibly published in SDTMIG v.4.0

Background – Currently different usage of the DC domain between the CDISC proposal and Merck

CDISC DC assumption	Merck DC assumption
DC domain is used for multiple participations of a subject within a study	DC domain is used for multiple participations of a subject within in a study as well as for roll-over studies
DC domain is used to display all participations of a subject within a study, including the primary participation, which will be derived into the DM domain	The primary participation is displayed only in the DM domain, while further participations are displayed in the DC domain

Implementation at Merck – General rules for subject identifiers USUBJID and SUBJID

- Each physical subject has a single unique subject identifier (USUBJID) throughout one trial, respectively through multiple trials in case of roll-over trials or participation of one subject in multiple trials within one program.
- Within Merck, the USUBJID consists of the Study ID and the SUBJID, which consists of the Site ID and the subject ID.

Implementation at Merck – General rules for subject identifiers USUBJID and SUBJID

- The USUBJID is based on the subject identifier (SUBJID) that is allocated when the subject is finally enrolled in the trial.

STUDYID	SITEID	SUBJID
ABC	101	101001

→ Screen Failure

STUDYID	SITEID	SUBJID	USUBJID
ABC	101	101002	ABC101002

→ Re-screened successfully

Implementation at Merck – General rules for subject identifiers USUBJID and SUBJID

- If a subject is screened multiple times within a trial without a subsequent enrollment, the USUBJID is based on the SUBJID of the primary screening.

STUDYID	SITEID	SUBJID
ABC	101	101001

→ Screen Failure

STUDYID	SITEID	SUBJID
ABC	101	101002

→ Screen Failure

→

STUDYID	SITEID	SUBJID	USUBJID
ABC	101	101001	ABC101001

- If a subject is screened multiple times within a trial with a subsequent enrollment, the USUBJID is based on the SUBJID of the successful screening.

Implementation at Merck – General rules for subject identifiers USUBJID and SUBJID

- If a subject is rolled over from a parent trial into an extension trial and records from the SDTM domains of the parent trial need to be included in the SDTM domains of the extension trial, the USUBJID from the parent trial is kept throughout the extension trial.

STUDYID	SITEID	SUBJID
ABC	101	101001

→ Parent trial

STUDYID	SITEID	SUBJID
DEF	103	103002

→ Extension trial →

STUDYID	SITEID	SUBJID	USUBJID
DEF	103	103002	ABC101001

Implementation at Merck – General rules for subject identifiers USUBJID and SUBJID

- The SUBJID is based on the respective screening and is included in any domain that holds information about multiple screenings/enrollments for the same subject (e.g., DC, SV, or DS) in order to differentiate between the different enrollments and screenings of a subject.
- If a subject is rolled over from a parent trial into an extension trial and the SUBJID does not change between trials, the --LNKID variable is used for differentiation between records of the parent and of the extension trial.

Implementation at Merck – Representation of subjects in the Demographics (DM) domain

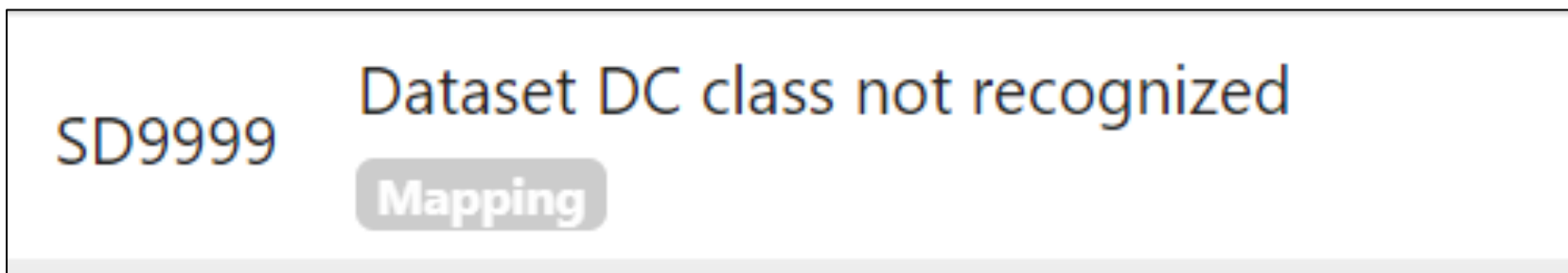
- The Demographics (DM) domain, together with the Demographics as collected (DC) domain is one of the most important domains for the display of multiple enrolled or multiple screened subjects.
- If a subject is enrolled multiple times within one trial, the primary enrollment is submitted in the DM domain.
- If a subject is screened multiple times within a trial without a subsequent enrollment, the primary screening is submitted in DM.
- If a subject is screened multiple times within a trial with a subsequent enrollment, the successful enrollment is submitted in DM.

Implementation at Merck – Representation of subjects in the Demographics as collected (DC) domain

- The DC domain is used to fulfill the requirements of the FDA.
- Within Merck, the DC domain presents the same structure as the DM domain.
- If a subject is enrolled multiple times within one trial, any additional enrollments besides the primary enrollment are submitted in the DC domain.
- If a subject is screened multiple times within a trial without a subsequent enrollment, any additional screenings besides the primary screening are submitted in DC.
- If a subject is screened multiple times within a trial with a subsequent enrollment, the unsuccessful screenings are submitted in DC.

Implementation at Merck – Possible validation issues due to the new mapping process

- Inclusion of DC domain: The DC domain is supposed to have a similar structure as the DM domain, which is a special purpose domain; as there has not yet been an official publication of the domain, the class of the DC domain has not yet been recognized.



Implementation at Merck – Possible validation issues due to the new mapping process

- Inclusion of the SUBJID variable in other domains than DM:
 - Under the currently published SDTM model versions, it is not foreseen to include the SUBJID variable in any other domain than DM.
 - This can lead to records that appear as duplicates, triggering a validation error, if the SUBJID is not recognized as a key variable in the validation program



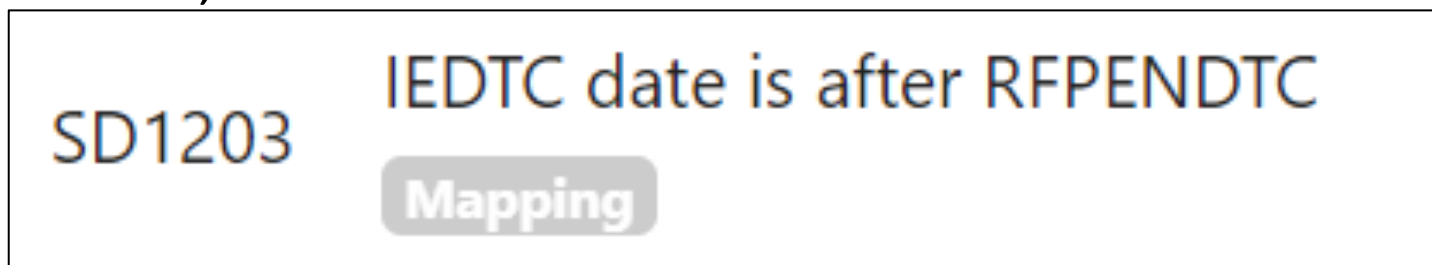
Implementation at Merck – Possible validation issues due to the new mapping process

- Study date issues:
 - If a subject was re-screened after a previous screen failure, the successful screening, and with it its date of informed consent (RFICDTC) will be displayed in the DM domain; any records of the previous screening would thus include dates before this date of informed consent



Implementation at Merck – Possible validation issues due to the new mapping process

- Study date issues:
 - If a subject was screened several times but remains a screen failure, the first screening attempt will be documented in the DM domain and with it the date of the end of the participation for the subject (RFPENDTC); any records of subsequent screenings, e.g. in the Inclusion/Exclusion criteria Not Met (IE) domain, would have a date after this RFPENDTC date



➔ **Conclusion: all possible validation issues need to be explained in the Study Data Reviewer's Guide**

Implementation at Merck – Conclusion

- So far Merck has had only limited experience with the implementation of the DC domain but will be going forward with its use in each newly conducted study.
- In order to satisfy internal study needs, the usage of the DC domain within Merck has differed from the currently proposed usage by the CDISC SDS MSI team; this will be updated with the official publication of the DC domain by CDISC.

Questions?



Thank you