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Practical Application of Multiple Screenings/Enrollments

Proma Debnath and Martha O'Brien,

Reata Pharmaceuticals, Dallas, USA

Abstract:

Multiple screenings/enrollments of subjects have become more common, but there remains to be clear guidance on SDTM mapping strategies in compliance with both the FDA and CDISC Standards. The November 2020 FDA Technical Conformance Guide (TCG) suggests that the primary enrollment be included in SDTM Demographics (DM) and the additional enrollments/previous screen failures be included in a custom domain in similar structure to DM. The TCG also suggests that SUBJID be included in domains where previous screening data is included. Unfortunately following this guidance at the current time will result in CDISC conformance issues, but these are known issues under review. This paper will delve into multiple screenings and how to handle them in SDTM.

Introduction:

Multiple screenings and enrollments have become common for several reasons. This includes subject recruitment cost savings, discrete body part enrollment (ophthalmology studies), and for our purposes, rare diseases with smaller patient pools. Some of the major challenges of SDTM mapping for rescreening records include multiple consent dates, different screening numbers for the same subject, and the requirement of consistent USUBJID within and across studies for a submission involving the product. The FDA has acknowledged the unique cases in which multiple screenings are required and has included suggestions in their Technical Conformance Guide.

The FDA TCG, November 2020 states, "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 also states, "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." This recommendation is consistent with the FDA TCG, October 2022. The main takeaways from these guidelines are that SUBJID should be included in relevant domains, and additional failed screening attempts should be included in a custom domain similar to DM.

Our example allows patients to rescreen to qualify for the study. When a patient repeats screening, the patient is given a new subject number and re-screening procedures are completed under the new subject number. For patients who are rescreening, previous screening numbers are collected on the informed consent page.

For example, in our "Rainbow" study a patient can initially screen under subject number "Unicorn1". The patient can fail screening and re-screen under subject number "Unicorn2". In this case, when the patient is screening under "Unicorn2", their previously screened number "Unicorn1" is collected on the informed consent page.

Informed consent raw data:

Study Name	Subject Number	Informed Consent Date	Previous Subject Number
Rainbow	Unicorn1	Jan 1 2020	
Rainbow	Unicorn2	Jan 1 2021	Unicorn1

Often, subjects have lab/vital signs visits before they are determined to be screen failures. Using our example, Unicorn1 will have vital signs and labs collected before determined to be a screen failure. Once they successfully re-screen under Unicorn2, they will also have labs/vital signs collected.

Vital Signs raw data:

Study Name	Subject Number	height	weight	temp	Visit date
Rainbow	Unicorn1	170	56	97	Jan 2 2020
Rainbow	Unicorn2	170	57	97.5	Jan 2 2021

The USUBJID for both of these records will be a concatenation of the study name (Rainbow) and the successful screening attempt number (Unicorn2): “RainbowUnicorn2”. With our historical mapping conditions, we now run into the issue of how to determine that our first row of results is associated with subject number Unicorn1.

Converting raw data to SDTM (using SDTMIG 3.2):

STUDYID	USUBJID	height	weight	temp	Visit date
RAINBOW	RAINBOW-UNICORN2	170	56	97	Jan 2 2020
RAINBOW	RAINBOW-UNICORN2	170	57	97.5	Jan 2 2021

Our current solution to this problem is to follow the FDA TCG and include SUBJID in any domain that includes previously failed screening records. To aid in visibility, we also include xxGRPID. The xxGRPID variable will either be null or contain the value “PREVIOUS SCREENING ATTEMPT”, if from a previously failed screening attempt. The SUBJID variable will contain the subject number at the time of that visit. The practical advantage of having a xxGRPID populated this way allows for easy filtering for screen failure records downstream. For example: ISS and other pooling as well, where typically we would shed Screen Failure experience records for enrolled subjects.

SDTM.VS:

STUDYID	USUBJID	SUBJID	VSGRPID	VSTEST	VSTESTCD	VSORRES	VSDTC
RAINBOW	RAINBOW-UNICORN2	Unicorn1	PREVIOUS SCREENING ATTEMPT	Height	HEIGHT	170	2020-01-02
RAINBOW	RAINBOW-UNICORN2	Unicorn1	PREVIOUS SCREENING ATTEMPT	Weight	WEIGHT	56	2020-01-02
RAINBOW	RAINBOW-UNICORN2	Unicorn1	PREVIOUS SCREENING ATTEMPT	Temperature	TEMP	97	2020-01-02
RAINBOW	RAINBOW-UNICORN2	Unicorn2		Height	HEIGHT	170	2021-01-02
RAINBOW	RAINBOW-UNICORN2	Unicorn2		Weight	WEIGHT	57	2021-01-02
RAINBOW	RAINBOW-UNICORN2	Unicorn2		Temperature	TEMP	97.5	2021-01-02

Continuing to follow the TCG, we create a custom domain that is similar in structure to DM, to include all previously failed screening attempts (YD – Demographics of Previous Screenings). YD includes all variables from DM. It is only created if there is at least one subject that has screened more than once. It will only contain records from previously failed screenings. All records will have SUBJID populated and can be uniquely identified using SUBJID.

SDTM.YD:

STUDYID	USUBJID	SUBJID	RFICDTC	AGE	SEX	RACE	ARMCD	ARM
RAINBOW	RAINBOW-UNICORN2	Unicorn1	2020-01-01	63	F	ASIAN	SCRNFAIL	Screen Failure
RAINBOW	RAINBOW-UNICORN43	Unicorn40	2022-03-25	35	F	WHITE	SCRNFAIL	Screen Failure
RAINBOW	RAINBOW-UNICORN55	Unicorn54	2022-04-07	41	M	BLACK OR AFRICAN AMERICAN	SCRNFAIL	Screen Failure
RAINBOW	RAINBOW-UNICORN67	Unicorn62	2022-05-18	54	F	WHITE	SCRNFAIL	Screen Failure
RAINBOW	RAINBOW-UNICORN70	Unicorn68	2022-07-23	61	M	ASIAN	SCRNFAIL	Screen Failure
RAINBOW	RAINBOW-UNICORN85	Unicorn84	2022-10-12	29	F	WHITE	SCRNFAIL	Screen Failure

P21:

Including the previously failed screening records in the SDTM produces a few expected P21 issues. These will remain until conformance standards are updated to handle the new rules for multiple screenings. The following issues appear in the P21 report and the associated reasonings are included in the SDTM Reviewer's Guide (CSDRG). We also recommend including a table linking each SUBJID to the subject's USUBJID with relevant explanations in the CSDRG, as suggested in the FDA TCG.

Source	Pinnacle 21 ID	Message	SDRG comment
DS			
	SD0058	Variable appears in dataset, but is not in SDTM model	SUBJID added to reflect the subject number associated with the screening attempt for each record
	SD1088	DSSTDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
	SD1319	DSSTDTC is before RFICDTC	Records are from previously failed screening attempts. Informed consent date for successful screening attempt is post event date
	SD1201	Duplicate records in DS domain	Not true duplicates. Records are from previous screening attempt. SUBJID/GRPID can be used to differentiate
LB			
	SD0058	Variable appears in dataset, but is not in SDTM model	SUBJID added to reflect the subject number associated with the screening attempt for each record
	SD1084	LBDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
	SD1117	Duplicate records	Not true duplicates. Records are from previous screening attempt. SUBJID/GRPID can be used to differentiate
SE			
	SD0058	Variable appears in dataset, but is not in SDTM model	SUBJID added to reflect the subject number associated with the screening attempt for each record
	SD1088	SESTDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
	SD1092	SEENDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
	SD1076	Model permissible variable added into standard domain	SUBJID added to reflect the subject number associated with the screening attempt for each record
SV			
	SD0058	Variable appears in dataset, but is not in SDTM model	SUBJID added to reflect the subject number associated with the screening attempt for each record
	SD1088	SVSTDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
	SD1092	SVENDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
	SD1076	Model permissible variable added into standard domain	SUBJID added to reflect the subject number associated with the screening attempt for each record
VS			
	SD0058	Variable appears in dataset, but is not in SDTM model	SUBJID added to reflect the subject number associated with the screening attempt for each record
	SD1084	VSDY variable value is not populated	Records are from previously failed screening attempts. DY variables for screen failure records will remain null
YD			
	SD9999	Dataset YD class not recognized	Subjects had multiple screenings. The successful/most recent screening is included in DM and previously failed screenings are in YD, a custom domain with a structure similar to DM

CDISC developed a draft on what demographics for multiple participations would look like. DC was decided as the abbreviation (DP was taken by SEND), but instead of Demographics as Collected it is 'Demographics for Multiple Participations'. This domain has all the variables in DM plus FOCID and DCSEQ. DC will only be needed if at least one subject has multiple participations, it should not be created otherwise. The major difference between DC and our custom domain (YD) is that DC contains all records in DM in addition to the previously failed screening records. Using the FDA guidance, our mapping strategy for YD was to only include previously failed screening records that weren't in DM. We expect CDISC to finalize the DC domain in the SDTM IG 4.0 in June, 2023. We also expect the addition of SUBJID to domains other than DM. These new standards will result in reduced P21 errors due to multiple screenings.

Conclusion:

Our database/CRF was structured to collect previous screening IDs when multiple screenings occurred. This made mapping YD and DM easier. In other domains, where records from previously failed screenings were collected, we included SUBJID and xxGRPID to aid in determining records that were linked to a previously failed screening. This mapping strategy creates additional output in P21 reports which the FDA is aware of. These are easily confirmed and should be explained in the SDRG.

Having multiple screenings/enrollments creates additional moving parts, but once a standard process is developed using the FDA guidelines, it becomes much easier to implement in future studies. This was the best mapping strategy for our purposes. The implementation for FOCID was not needed in our study, hence out of scope for this paper.

References:

CDISC references -

- SDTM Draft Domains Project: https://wiki.cdisc.org/display/SDD/SDTM+Draft+Domains+Home
- Multiple Subject Instances Project: https://wiki.cdisc.org/display/MSI/Multiple+Subject+Instances+Home
- Previous presentation on the subject: https://wiki.cdisc.org/download/attachments/113577697/Updates%20on%20Handling%20Multiple%20Enrollments%20and%20Screenings%20Subjects%20in%20SDTM%20-%20ClinBuild%20-%20Eanna%20Kiely%20-%20V1.0.pdf?version=1&modificationDate=1602659826225&api=v2

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- FDA TCG 2022 : Study Data Technical Conformance Guide_v4.9_March 2022 (fda.gov)

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Contact Information:

Your comments and questions are valued and encouraged. You may contact the authors at:

Martha O'Brien
Reata Pharmaceuticals
martha.obrien@reatapharma.com

Proma Debnath
Reata Pharmaceuticals
proma.debnath@reatapharma.com