

Challenges and Solutions for Handling Re-screened Subjects in SDTM

Charity Quick, Paul Nguyen, Rho, Inc.

ABSTRACT

A common issue with SDTM is tabulating data for subjects who enroll multiple times in a single trial. Currently, the FDA advises that as long as there is one USUBJID for each specific subject, a different subject identifier (SUBJID) value can be used for each screening attempt. However, it can be challenging to handle this data while conforming to both the SDTM Implementation Guide and FDA-published validation rules.

This paper will detail how to deal with subjects who have multiple screening visits while conforming to SDTM and FDA rules. The intention is to produce high quality data while maintaining traceability with the multiple screening visits. We will look at how to structure the Demographic Domain (DM) and the accompanying supplemental qualifiers data set accordingly. Furthermore, we explore how to identify additional domains that could be affected by re-screening.

INTRODUCTION

Allowing a subject to re-screen after a failed screening attempt can be advantageous for both the clinical trial and subject. By allowing a subject to re-screen, clinical trials can save the cost of subject recruitment. For the potential subject, re-screening can make sense depending on the circumstance of why the screening failed. Reasons that may qualify for a re-screening include 1) consent conflict due to personal issues or timing 2) medication stabilizing or ending 3) an acute event that has now resolved or any circumstance that is deemed appropriate by a medical monitor.

Re-screening a subject can create challenges for SDTM mapping. What if there is more than one informed consent date for a subject? If there is more than one screening visit, should you create extra visits that are only applicable for re-screened patients? How would this impact your Trial Design data? Would it impact your ARM values since this could be considered a different study path?

The FDA Study Data Technical Conformance Guide clearly suggests using a different SUBJID for a single person every time the person enters the trial. That's a great solution! Not only is it what the FDA suggests, but it is a very tidy solution to a messy problem. What's the catch? The catch is that the only SDTM domain where SUBJID is currently permitted according to the SDTM Model is the DM domain. Therefore, any SDTM domain that has SUBJID added will incur conformance Errors (P21/PMDA ID SD0058 and FDA ID FDAC027) that will drive down the Pinnacle 21 score of the submission package that is often very important to sponsors.

Here, we suggest creating one record in the DM domain for a re-screened trial subject, using the latest SUBJID value, and saving previous subject identifiers in SUPPDM. From there, the ability to link observations with the subject's previous SUBJID value(s) in supplemental qualifier data and the use of VISIT and EPOCH values will facilitate the mapping of most trials involving re-screened subjects. And the unique SUBJID values for each rescreening attempt are kept in the appropriate domain clearly linked to each associated data point.

In future versions of the SDTM Model, SUBJID will likely be permitted within other domains since the FDA clearly values the traceability it provides. But until that time, this method will likely satisfy the SDTM Model, Pinnacle 21 conformance checks, and sponsors that value a high conformance score.

KNOW YOUR STUDY

The first step in mapping any study to SDTM should be reading the study protocol. In a trial that involves the potential to re-screen subjects, the protocol may describe, in detail, what path a subject will take with regards to screening. You may see a description of additional timepoints for re-screening or a study path diagram that will map out what additional procedures or information, if any, were taken.

Often, though, this is not the case. Many times there is no mention of allowing subjects to re-screen. It is likely that re-screening is permitted only under certain circumstances and at the discretion of the medical monitor on a case-by-case basis. In these situations, the most helpful part of the protocol will be the Schedule of Events. This chart will help you determine what events happen at screening and what SDTM domains will likely be impacted by additional records for a re-screened subject. Medical History (MH) and Concomitant Medications (CM) are sometimes collected at study screening visits and will usually be collected again when a subject returns after a failed first screening attempt. Other domains that can be collected at screening include Laboratory (LB) and Vital Signs (VS). Checking the protocol Schedule of Events will provide insight as to what other domains might be impacted from re-screening a subject.

The next step in the mapping will be to look at the Case Report Form (CRF) to see if there are additional pages specifically added for re-enrolled subjects or re-screening attempts. An example of a CRF page specifically for Re-screen is given below.

Subject:
Page: **Rescreen: Inclusion / Exclusion Criteria Summary (RESC)** ?

Complete this form after all Screening Visit 1 and Visit 2 assessments have been completed and the subject's eligibility is determined.

If the subject is eligible to be Randomized, please mark 'Did the subject meet all eligibility criteria?' Yes and complete remaining forms.

If the subject is not eligible, please mark 'Did the subject meet all eligibility criteria?' No and complete only the following forms: Visit Record at Screening Visit 1, Informed Consent, Demographics, PERT, Inclusion/Exclusion Criteria Summary, Inclusion/Exclusion Criteria, Screen Failure, and Adverse Event (if applicable).

Did the subject meet all eligibility criteria? ? ☐ Yes ☐ No

If No, will the subject be re-screened?
(If re-screening for a second time, permission must be obtained from the study sponsor.) ☐ Yes ☐ No

Figure 1. Re-screen CRF page

If you do find additional CRF pages specific to re-screening, you should expect to find additional data sets in the raw data for these pages. At times, the CRF will not have an extra page for a re-entry attempt. Instead there will likely be a new SUBJID value field on the CRF page.

Subject:
Page: **Subject Eligibility (ELIG)** ?

1. Based on the eligibility criteria reviewed on the screening visit date, is the subject eligible to continue onto the baseline visit? ☐ Yes ☐ No

2. If No, will the subject return to reconfirm meeting Inclusion Criteria 9 and 10? ☐ Yes ☐ No
If No, please complete the Screen Failure form.

3. Is the subject rescreening after failing to meet inclusion criteria 05, 07, and/or 08? **-HIDDEN** ☐ Yes ☐ No

4. If Yes, please enter the previous subject ID: **-HIDDEN**

Figure 2. Re-screen CRF page

It is also a good idea to talk to your data management lead and take a look at any actual data collected. At times subjects may be assigned a new SUBJID value in the raw data, even if they should not have been, due to confusion on the part of the site data collection team. It's best to find out if your data contains any non-conforming values as early in the process as possible. It is important to determine if your data will contain more than one identifier for a subject and if your data will contain additional data points for re-screening, the solution put forth here will work for both of these scenarios.

DATA RECONCILIATION

After looking at the Schedule of Events in the study protocol, you should have an idea of what data will be collected at screening and, therefore, which domains are likely to be affected by potentially being collected in duplicate when a subject is re-screened. The CM and MH domains are going to be of particular interest when mapping re-screened subject's data. For example, if a subject reports taking cough syrup from 2015-07-28 to 2015-07-30 at their initial screening visit and then reports taking cough syrup from 2015-07-28 to 2015-07-31 at their re-screening visit, you will want to ask the Data Manager or site team to clarify and clean these data if they are in fact the same event. In the example below, subject RHO-001-001 reported a HYSTERECTOMY in the raw Medical History data as happening in 2004. After failing to meet all screening requirements, the subject returned for a repeat screening attempt, was assigned the SUBJID value of RHO-001-002, and reported a HYSTERECTOMY on July 2010.

ID	MHSCAT	MHTERM	MHSTDAT_RAW
RHO-001-001	Genito-urinary	HYSTERECTOMY	UN UNK 2004
RHO-001-002	Genito-urinary	HYSTERECTOMY	UN JUL 2010

Table 1. Example SDTM MH data

Shown below is what the MH data listing would look like if the data was not cleaned before the records for the subject were combined under their final SUBJID value.

Listing: 16.2.6
Listing of Medical History
Safety Population

Subject ID	Treatment Group	Start Date/ Stop Date/ Ongoing	Body System	Condition
120-040-2	TRT	2008/ Ongoing	CARDIOVASCULAR	HYPERTENSION
		2004/ 2004	GENITO-URINARY	HYSTERECTOMY
		2010JUL/ 2010JUL	GENITO-URINARY	HYSTERECTOMY

Figure 3. Example Medical History Listing with Duplicates

Hopefully, the data manager will be able to query the site to get this data point corrected. Not all of these seemingly duplicate data points will be truly duplicates but it's a good idea to work with your study team to address the issues that can arise with the Event domain data collection at multiple screening visits.

Another domain that may be affected by duplicate data reporting is the DM domain. Subjects may not report certain values the exact same way if data is collected at two different visits. An obvious place to check is the Specify Other Race field. Again, discussing these issues with your larger study team is recommended.

IMPLEMENTATION

Unless there are additional screening visit values captured in the raw data as part of the protocol and schedule of events, implementing an additional screening EPOCH is a good solution for mapping re-screened subjects. Keeping one Screening VISIT and using multiple screening EPOCH values will allow you to have multiple screening visit results captured in the Disposition Events in the SDTM Disposition (DS) domain. See the example SDTM DS data for subject RHO-001-001. The subject had an Informed

Consent on 2015-03-13 and then an initial screening visit on 2015-05-19. The subject failed due to Inclusion/Exclusion criteria. The subject returned for another Informed Consent and another screening attempt. This screening attempt was successful. Instead of having one SCREENING EPOCH for the trial, we have designated an INITIAL SCREENING and REPEAT SCREENING EPOCH in order to completely capture the subject's study path. Subjects that only had one screening would only have INITIAL SCREENING in their SDTM data. Subjects that had an additional screening attempt would have a REPEAT SCREENING record in their SDTM DS data.

USUBJID	DSSEQ	DSTERM	DSDECOD	DSCAT	EPOCH	DSSTDTC
RHO-001-001	1	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	PROTOCOL MILESTONE		2015-03-13
RHO-001-001	2	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	PROTOCOL MILESTONE		2015-07-31
RHO-001-001	3	INCLUSION/EXCLUSION	INCLUSION/EXCLUSION	DISPOSITION EVENT	INITIAL SCREENING	2015-05-19
RHO-001-001	4	COMPLETED	COMPLETED	DISPOSITION EVENT	REPEAT SCREENING	2015-07-31
RHO-001-001	5	RANDOMIZED	RANDOMIZED	PROTOCOL MILESTONE		2015-08-11
RHO-001-001	6	COMPLETED	COMPLETED	DISPOSITION EVENT	DOUBLE BLIND	2016-02-02
RHO-001-001	7	COMPLETED	COMPLETED	DISPOSITION EVENT	OPEN LABEL	2016-08-10

Table 2. Example SDTM DS data

If your data has more than one subject identifier value for a subject, we recommend retaining the latest value in SUBJID and USUBJID and keep the previous subject identifier value(s) in SUPPDM. In the example below, the previous SUBJID value is kept in the SUPPDM data with QNAM = "SUBJOLD" and QVAL = previous screening SUBJID value.

RDOMAIN	USUBJID	QNAM	QLABEL	QVAL
DM	RHO-001-001	IECHECK	Inclusion/Exclusion Eligibility Check	N
DM	RHO-001-001	IECHECK2	Inclusion/Exclusion Eligibility Check2	Y
DM	RHO-001-001	PROTVER	Protocol Version	3.0
DM	RHO-001-001	RFICDTC2	Informed Consent Date 2	2015-07-31
DM	RHO-001-001	SUBJOLD	Old Subject ID	001-222

Table 3. Example SDTM DM data

From here, any other findings data that are collected at INITIAL SCREENING and at REPEAT SCREENING will need special attention as well. For example, all laboratory records for a subject will be mapped to the LB domain but the INITIAL SCREENING records will be linked to the previous subject identifier value under which the data was collected in SUPPLB. In the example below, we linked the INITIAL SCREENING records for a subject with the SUBJID that the data was initially collected under using LBSEQ and SUPPLB.QNAM = "SUBJOLD". Notice that laboratory data collected at INITIAL

SCREENING and at REPEAT SCREENING will have the same VISIT/VISITNUM values but these records will be differentiated by EPOCH value and date.

USUBJID	LBSEQ	LBTESTCD	VISIT	EPOCH	LB DTC
RHO-001-001	1	ALB	Screening	INTSCREEN	2015-03-13
RHO-001-001	2	ALB	Screening	RPTSCREEN	2015-07-31
RHO-001-001	3	HGB	Screening	INTSCREEN	2015-03-13
RHO-001-001	4	HGB	Screening	RPTSCREEN	2015-07-31
RHO-001-001	5	RBC	Screening	INTSCREEN	2015-03-13
RHO-001-001	6	RBC	Screening	RPTSCREEN	2015-07-31

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
LB	RHO-001-001	LBSEQ	1	SUBJOLD	Old Subject ID	RHO-001-222
LB	RHO-001-001	LBSEQ	3	SUBJOLD	Old Subject ID	RHO-001-222
LB	RHO-001-001	LBSEQ	5	SUBJOLD	Old Subject ID	RHO-001-222

Figure 4. Example SDTM LB and SUPPLB data

The SV domain will have a date range for the VISIT/VISITNUM used for Screening. SVSTDTC will be equal to the start of the first screening attempt for a subject. SVENDTC will be equal to the final screening attempt for a subject. The example below represents the SV data for the subject shown in the DS domain above. Notice VISITNUM = 1 is the only record where there is a date range for the visit.

DOMAIN	USUBJID	VISITNUM	VISIT	SVSTDTC	SVENDTC	SVSTDY	SVENDTY
SV	RHO-001-001	1	Screening	2015-03-13	2015-07-31	-151	-11
SV	RHO-001-001	2	Week 0/ Baseline	2015-08-11	2015-08-11	1	1
SV	RHO-001-001	3	Week 3	2015-09-02	2015-09-02	23	23
SV	RHO-001-001	4	Week 6	2015-09-22	2015-09-22	43	43

Table 4. Example SDTM SV data

CONCLUSION

There are certainly other ways to deal with the SDTM mapping for re-screened subjects. There are likely other ways that do not cause issues with regards to the FDA guidance and SDTM validation rules. For example, you could just create additional visit records for the additional screening records for the subjects that have them, but if there are more than one or two additional screening visits, the addition of all these extra visits could get confusing. Also, being able to have multiple Disposition Event records for the screening attempts using EPOCH in the DS domain adds value for the reviewer. In accordance with FDA guidance, you could also keep the multiple SUBJID values in your SDTM DM domain as long as the USUBJID remains consistent. But, of course, this diverges with the current SDTM Model when SUBJID is placed in domains other than DM. We argue that being able to see all study data for a subject using one SUBJID while retaining those previous IDs linked in SUPPLEMENTAL data is a more linear approach. With our approach, all data is together for the subject with the EPOCH values of INITIAL SCREENING and REPEAT SCREENING being the indicator to check the supplemental data for the previous SUBJID value if that information is needed. In the opinion of the authors, seeing results at a glance is more important than being able to see the previous SUBJID value at a glance. Also, keeping all data under one SUBJID may even be less complicated for programming and debugging.

RECOMMENDED READING

- <http://www.pinnacle21.net/blog/fda-final-guidance-webinar-ga>
- <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>
- <https://www.pharmasug.org/proceedings/2017/SS/PharmaSUG-2017-SS04.pdf>

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Charity Quick
Rho, Inc.
919-408-8000
charity_quick@rhoworld.com
<http://www.rhoworld.com/rho/>

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