PP30

Ensuring USUBJID is Unique for an Individual within an Application

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Introduction

- FDA identified issues with implementation of USUBJID in applications
- PhUSE Working Group formed March 2014 to investigate, brainstorm solutions, and draft a White Paper to describe the best practice for handling USUBJID

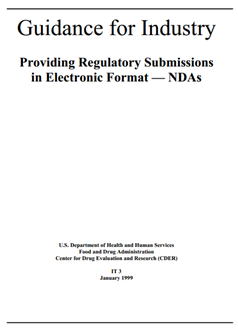
Objective

Develop a recommendation for ensuring a unique USUBJID value for each individual in an application, both within and across studies

Background: History behind USUBJID

(1) 1999 Guidance on Providing Regulatory Submissions in Electronic Format – NDAs, Section 4.k.6

"Each subject should be identified with a single, unique number for the entire application. The unique number needs to be provided in each dataset. This is essential for joining different datasets."


Guidance for Industry

Providing Regulatory Submissions in Electronic Format — NDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

IT 3
January 1999

(2) SDTM IG v3.2, Section 4.1.2.1

"To identify a subject uniquely across all studies for all applications or submissions involving the product, a unique identifier (USUBJID) should be assigned and included in all datasets… USUBJID values must be unique for each trial participant (subject) across all trials in the submission. This means that no two (or more) subjects, across all trials in the submission, may have the same USUBJID. Additionally, the same person who participates in multiple clinical trials (when this is known) must be assigned the same USUBJID value in all trials."

(3) December 2014 Technical Conformance Guide, Section 4.1.1.2 on USUBJID

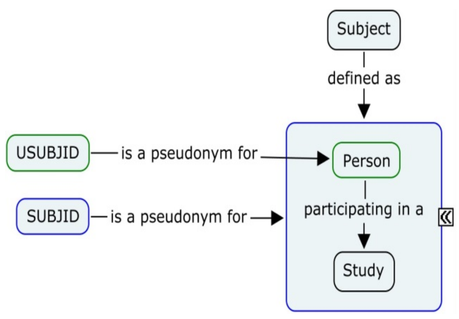
"Each individual subject should be assigned a single unique identifier across the entire application… An individual subject should have the exact same unique identifier across all datasets, including between SDTM and ADaM datasets. Subjects that participate in more than one study should maintain the same USUBJID across all studies…Improper implementation of the USUBJID variable is a common error with applications and often requires sponsors to re-submit their data."

Problem Statement

Sponsors are required to ensure a consistent single USUBJID value is assigned to each individual with data in an application

Important Considerations

(1) The word "subject" is often used to mean two related but different constructs:
   a. Individual person
   b. Participant in a clinical trial



(2) Relationship of USUBJID to SUBJID
   a. At the time USUBJID was defined, it was anticipated there would be a 1:1 relationship of USUBJID to SUBJID within a study
   b. In reality, there is often a 1:many relationship of USUBJID to SUBJID (e.g., when a screen failure rescreens in the same study)

(3) Characteristics of the SDTM DM domain
   a. Topic variable is SUBJID (specifies the focus of the observation)
   b. Record structure of the SDTM DM domain is "one record per subject"
      i. "Subject" is not overtly defined as a unique individual, nor as a trial participant
      ii. Practical implementation has been to define "one record per subject" as "one record per USUBJID"

(4) Technical Conformance Guide, December 2014, Section 4.1.1.2 on SUBJID

"If the same subject is screened more than once in a trial, then the subject's SUBJID should be different."

Key Rationale

PhUSE USUBJID Working Group recommendations are predicated on the concept that the key structure of the SDTM DM domain, "one record per subject", can be defined as "one record per SUBJID" .

- DM domain key structure currently documented as STUDYID, USUBJID.
- This could be changed to STUDYID, USUBJID, SUBJID if the Working Group's recommendations are adopted.

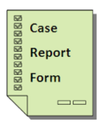
First Recommendation

Challenge: Identify individuals enrolled in more than one study, or individuals enrolled more than once in the same study

Recommendation 1: Design database to track previous enrollments

Typically use a Case Report Form (CRF)

Information needed:
- If previously enrolled in current study, SITEID and SUBJID of previous enrollment
- If previously enrolled in other study in the same application, STUDYID, SITEID, and SUBJID from other study/ies



Considerations

(1) CRF design needs to allow for multiple previous enrollments within the same study (e.g., re-screens)
(2) CRF design needs to allow for enrollments from multiple previous studies
(3) Data fields collected must be sufficient to identify whether individual has existing USUBJID

Second Recommendation

Challenge: Develop a proposal for the best way to record data in the SDTM DM domain when an individual has multiple enrollments in a single study

Recommendation 2: Create a new record in DM for each screening event

DM

…	USUBJID	SUBJID	…	RFICDTC	RFPENDTC	…	ARMCD	…
…	STDY1-3-201	3-001	…	2010-06-18	2010-06-23	…	SCRNFAIL	…
…	STDY1-3-201	3-101	…	2010-07-21	2010-07-26	…	SCRNFAIL	…
…	STDY1-3-201	3-201	…	2011-01-17	2011-08-15	…	ARM-A	…

Considerations

(1) Does not adhere to common practice

(2) PhUSE Working Group recommendation for interpretation of DM key structure "one record per subject" is "one record per SUBJID"

(3) Assumes different SUBJID for each screening event
   - Expectation per Dec 2014 Technical Conformance Guide

(4) Resulting DM domain easy to interpret
   - Allows unique record qualifiers for each record/enrollment

Third Recommendation

Challenge: Determine how to link assessments done during screening with the specific screening event data in the DM domain

Recommendation 3: Allow SUBJID as a permissible identifier variable on General Observation Class domains

VS

USUBJID	*SUBJID*	VSSEQ	VSTESTCD	VSDTC
STDY1-3-201	*3-001*	1	SYSBP	2010-06-18
STDY1-3-201	*3-001*	2	DIABP	2010-06-18
STDY1-3-201	*3-101*	20	SYSBP	2010-07-21
STDY1-3-201	*3-101*	21	DIABP	2010-07-21
STDY1-3-201	*3-201*	50	SYSBP	2011-01-17
STDY1-3-201	*3-201*	51	DIABP	2011-01-17

DM

…	USUBJID	SUBJID	…	RFICDTC	RFPENDTC	…	ARMCD	…
…	STDY1-3-001	3-001	…	2010-06-18	2010-06-23	…	SCRNFAIL	…
…	STDY1-3-001	3-101	…	2010-07-21	2010-07-26	…	SCRNFAIL	…
…	STDY1-3-001	3-201	…	2011-01-17	2011-08-15	…	ARM-A	…

- Allows link of assessments back to specific screening event
- Requires SUBJID to be unique to each screening event across all subjects in the study

Impact of Recommendations 2 and 3

(1) Would require change to SDTM
   - Ex: Include SUBJID in Table 2.2.4 as an available identifier variable
(2) Would require change to SDTM IG
   - Impact analysis needed for full assessment, but minimally a Section 4 assumption allowing SUBJID to be added as an available identifier variable
(3) Impact on other CDISC models considered out-of-scope for this Working Group

Discussion

(1) Key to the concepts presented within this Proposal for Best Practice, is that all of the CDISC and FDA documentation is consistent in the requirement of "**one record per subject**" in the DM domain, but "subject" is not overtly defined. In practice, industry implementation of this requirement has been to define "one record per subject" as one record per USUBJID in the DM domain, which has proven to be problematic.
(2) Sponsors should realize that the proposed solution may not accurately identify USUBJID for all individuals, as the solution often relies on the accuracy and validity of the data provided by screened subjects. this cannot prevent sponsors from performing **due diligence** in setting up a system that accurately identifies as many of these subjects as possible.
(3) The actual **submission of screen failure data** within an application should be a conscious decision based either on internal sponsor decision or through discussion with the regulatory agency responsible for reviewing the application.

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