

Standard Implementation (SI06): Who is Subject X

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The Speakers



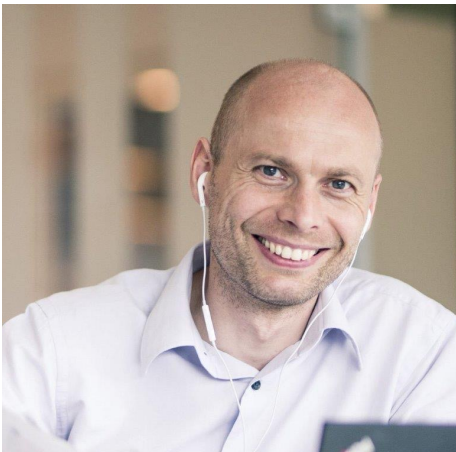
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Vicky Poulsen

Principal Standards Specialist, Novo Nordisk A/S

Joined Novo Nordisk A/S in 2015 after being a SAS consultant for a decade in the public health sector specialising in End-to-End BI solutions. She participated in the CDISC Implementation Project shortly after. In her present position, Vicky leads the standard programming strategy and development efforts that drive the SDTM Generation Framework for SDTM and define.xml automation.

Vicky holds an MPhil in Geographic Information Systems and Network Analysis from the University of Hong Kong.



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Statistical Programming Director, Novo Nordisk A/S

Henning has over 15 years of experience in the pharma industry. He holds a MSc in Physics and has previously worked as a researcher within the field of satellite orbit determination as well as consultant for SAS Institute supporting various industries including Pharma, Tele, and Supply Chain.

His main interest is currently the strategic clinical development of new indications and drugs for authority approvals and building up strong project teams across locations and organisations.

Disclaimer

“Views and opinions expressed are those of the speakers’ and not necessarily Novo Nordisk.”

Background

The Hurdles

A Standard End-to-end Solution

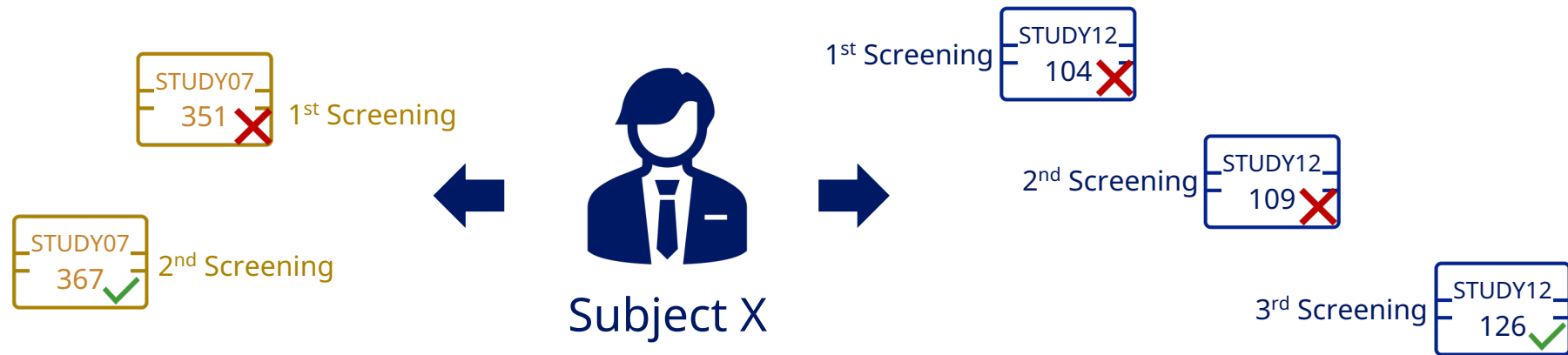
From Analysis Perspective

Key Take Away Messages

Agenda

Re-screening and cross-study participation have become more common practices in clinical studies for rare diseases and therapeutic areas that require more invasive diagnostic procedures to determine eligibility for participation.

How to represent instances of subject participation within and across studies in SDTM while maintaining **traceability**, **transparency**, **data friendliness**, and staying **compliant to standard and submission requirements**?



Unique Subject Identifier (USUBJID)

- It is a requirement to use USUBJID to uniquely identify individual subject in all studies within a submission
- There are clear definition in SDTM IG and guidance from FDA and PMDA

DM – Specification

dm.xpt, Demographics — Special Purpose, Version 3.3. One record per subject, Tabulation.

SDTM IG 3.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format ¹	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	DM	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product. This must be a unique number, and could be a compound identifier formed by concatenating STUDYID-SITEID-SUBJID.	Req
SUBJID	Subject Identifier for the Study	Char		Topic	Subject identifier, which must be unique within the study. Often the ID of the subject as recorded on a CRF.	Req

PMDA: Technical Conformance Guide on Electronic Study Data Submissions

USUBJID has been prepared as a variable for storing the unique ID assigned to each individual subject across the entire application. It enables the data of one subject in multiple studies, for example, in a phase III study and the subsequent long-term study, to be summarized. Therefore, consideration should be given to ensure that each subject has the same USUBJID across all the studies in the application to the extent possible.

FDA: Study Data Technical Conformance Guide

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 product²⁵. 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).

Subject Identifier (SUBJID)

- SUBJID is a unique identifier within a study
- It is unclear how to represent individuals that are screened/enrolled more than once in a study
- FDA requires that SUBJID to be different for each screening or enrolment within a study

DM – Specification

dm.xpt, Demographics — Special Purpose, Version 3.3. One record per subject, Tabulation.

SDTM IG 3.3

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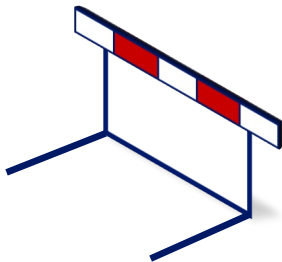
FDA: Study Data Technical Conformance Guide

Subject Identifier (SUBJID)

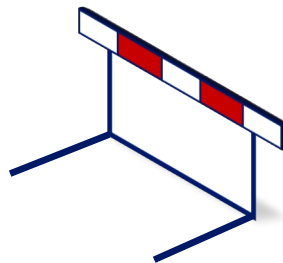
The variable SUBJID uniquely identifies each subject that participates in a study. If a single subject is screened and/or enrolled more than once in a study, then the subject's SUBJID should be different for each unique screening or enrollment. For a study with multiple screenings and/or multiple enrollments per subject, SUBJID should be included

The Hurdles

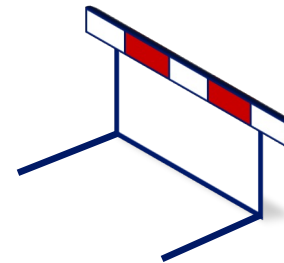
SUBJID is a
Topic Variable
and can be
used only in
DM domain



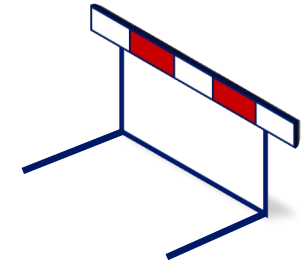
USUBJID and
SUBJID must
be 1:1



Use of
POOLDEF
reduces data
friendliness



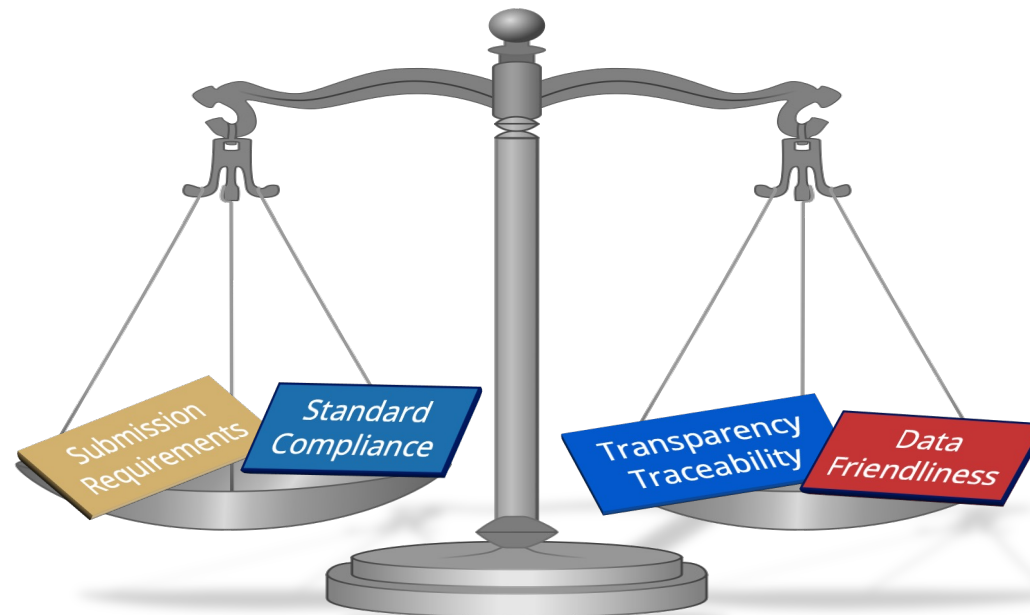
Traceability/
Transparency
not supported



SDTM data model does not support representation of multiple instances
of subject participation within a study

A Standard End-to-end Solution

- Traceable: Protocol >> CRF >> SDTM >> ADaM >> CSR
- Operational: Support standardized/efficient data collection, processing, analysis and reporting
- Transparent: Clearly depict relationship between screening/enrolment instances of a subject
- Data friendly: Simple to use and easy to understand
- Compliant to standard: Violate as few rules as possible
- Conform to submission requirements: Conform to as many requirements as possible



NN Standard QNAMs in SDTM

- Expand DM domain with two sets of standard QNAMs
 - For **re-screening**
 - PREVSUB: Subject ID of immediate previous screening instance, Collected on CRF
 - IUSUBJID: Individual Unique Subject Identifier, Derived



STUDYID	USUBJID	SUBJID	PREVSUBJ	IUSUBJID
STUDY12	STUDY12/101	104		STUDY12/126
STUDY12	STUDY12/109	109	104	STUDY12/126
STUDY12	STUDY12/126	126	109	STUDY12/126

Chain
all screening
instances

2. For **cross-study participation**

- PRVTRLID: ID of previous study, Collected on CRF
- PRVTSUBJ: Subject ID of last screening instance in previous study, Collected on CRF



STUDYID	USUBJID	SUBJID	PRVTRLID	PRVTSUBJ
STUDY12	STUDY07/367	126	STUDY07	367

Data collection: NN Standard Forms

Rescreening

DM=Demographics

V1			
Rescreening		(Rescreening) - [RESCREENING] - Non-repeating	
Study ID: NNXXXX-XXXX			
Integration			
*	Is this a rescreening?	☐ No ☐ Yes NOT SUBMITTED PREVSUBJ in SUPPDM Previous subject number: NXXXXXX	

Previous study participation

DM=Demographics

V1			
Previous study participation - (Prev study)		[PREV_STUDY] - Non-repeating	
Study ID: NNXXXX-XXXX			
Integration			
In case of rescreening(s) during previous study participation, please provide the latest Subject no.			
Did subject participate previously in any of the listed Novo Nordisk studies?		☐ Yes ☐ No Study ID: <Study ID 1> <Study ID 2> <Study ID 3> PRVTRLID in SUPPDM Subject No. of previous study: N6 PRVTSUBJ in SUPPDM	

Look up re-screened subjects

IUSUBJID QNAM definition

Derived IUSUBJID QNAM, USUBJID of last screening instance, for each subject by looping through the chained screening instance reported in PREVSUBJ QNAM

Populate QLABEL/QORIG

```

data sdtmrawt.supdm;
  if _n=0 then set sdtmrawt.supdm sdtmrawt.supdm(keep=usubjid rename=(usubjid=_id));
  call missing(of _all_);

  if _n=1 then do;
    %*** Loop through all PREVSUBJ QNAMs to find linked USUBJID ***;
    declare hash h1(dataset:'sdtmrawt.supdm(where=(qnam eq "PREVSUBJ") rename=(usubjid=_id))');
    h1.defineKey('qval');
    h1.defineData('_id');
    h1.defineDone();

    declare hash h2(dataset:"gcmd.cd_list_val(rename=(sdtm_qnam_qorig=qorig cd_val_lb=qlabel cd_val=qnam)
                                                where=(cd_list_id eq 'SDTM_QNAM' and cd_list_val_status eq 'A'
                                                and qnam eq 'IUSUBJID'))");
    h2.defineKey('qnam');
    h2.defineData('qorig','qlabel');
    h2.defineDone();
  end;
  set sdtmrawt.supdm
    sdtmrawt.dm (in=b keep=studyid domain dmupid usubjid subjid
                  rename=(domain=rdomain dmupid=idvarval subjid=_subjid));

  %*** Append IUSUBJID QNAMs ***;
  if b then do;
    idvar='DMSPID';
    qval=_subjid;
    if h1.find() = 0 then do;
      %*** Loop through all PREVSUBJ QNAMs to find chained USUBJID ***;
      _qval=scan(_id,2,'/');
      do until (_rc ne 0);
        _rc=h1.find(key:_qval);
        if _rc=0 then _qval=scan(_id,2,'/');
      end;
      qval=_id;
    end;
    else qval=usubjid;
  end;

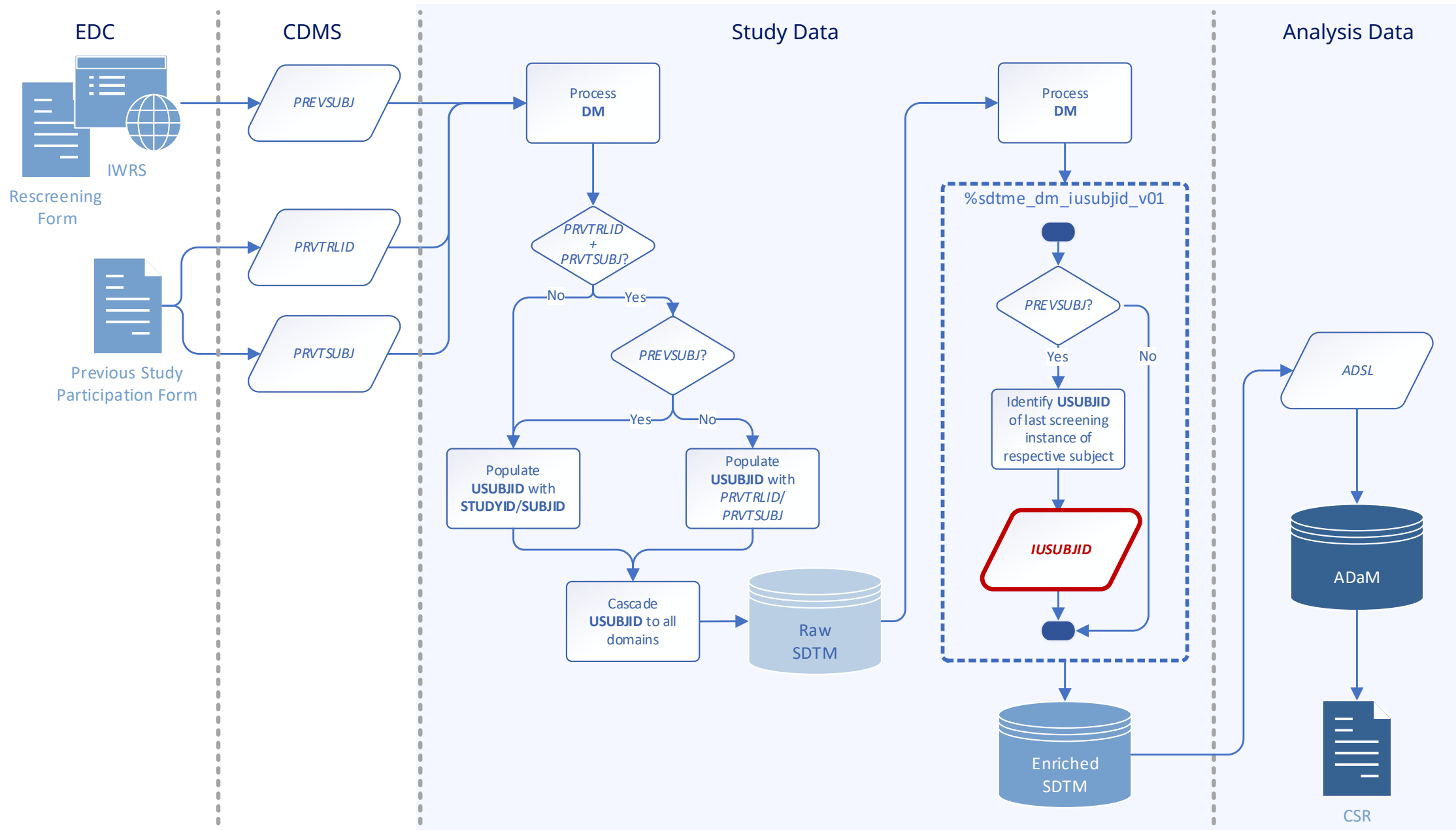
  %*** Populate IUSUBJID QNAM attributes based on GCMD ***;
  qnam='IUSUBJID';
  _rc1=h2.find();

end;
drop _;;
run;

```

⚠ Expect PREVSUBJ is correct

A Standard End-to-end Solution



Scenario 1: Study allowing rescreening of subjects

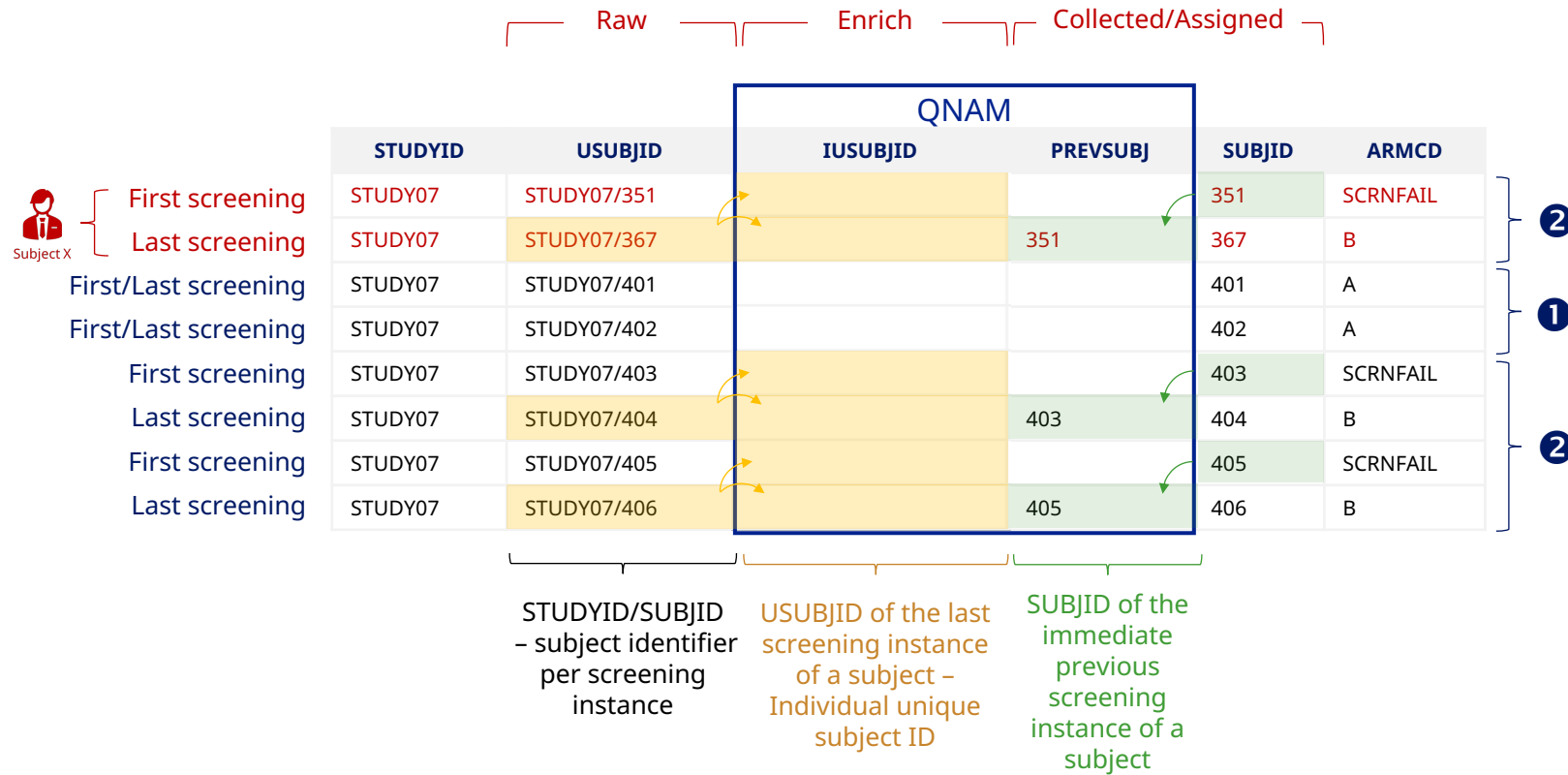
- Protocol allows rescreening of subjects who failed screening or due to other reasons
- Subject signs informed consent and will be assigned a new Subject No. (SUBJID) for each screening instance

6.4 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. A screen failure session must be made in the IWRS.

Individuals who do not meet the criteria for participation in this trial may be re-screened once within the limits of the recruitment period. In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated.

Scenario 1: Study allowing rescreening of subjects



Scenario 2: Study including subjects from other NN studies

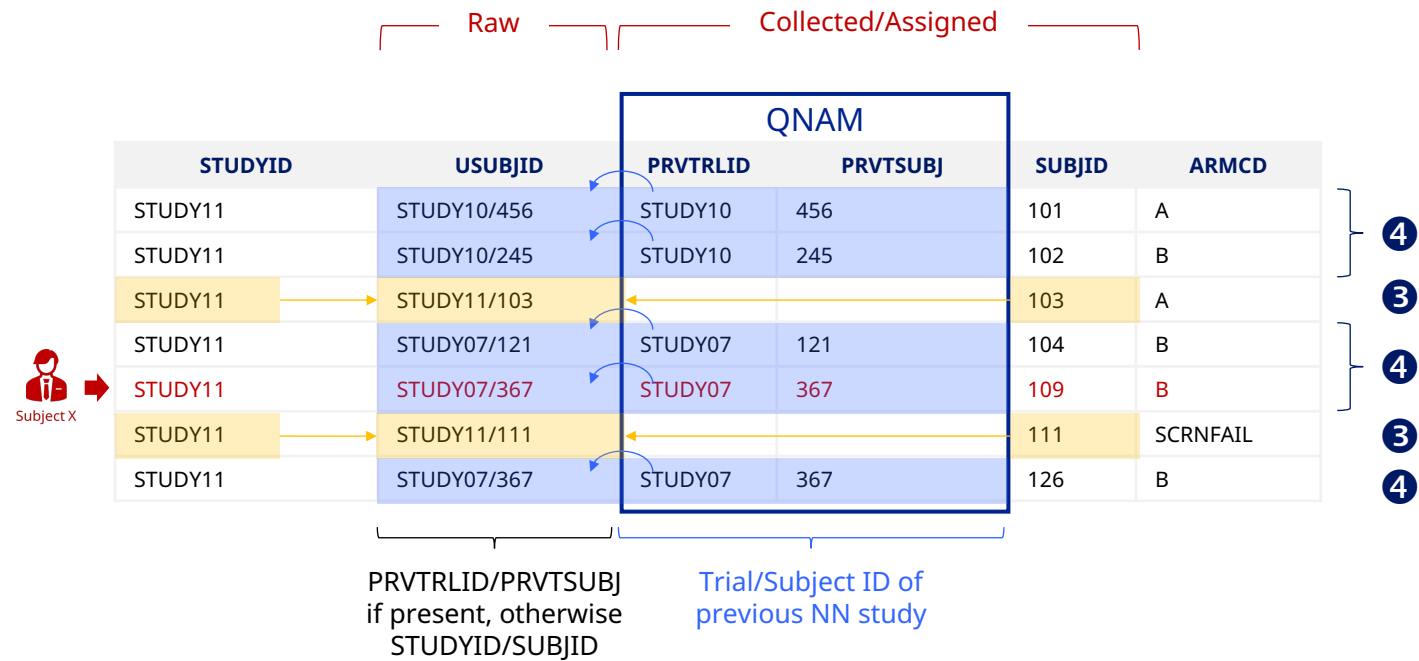
- Protocol explicitly states the **scope** of and **criteria** for inclusion of subjects from other NN studies

6.1 Inclusion criteria

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent from the patient or the child's parent/LAR obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male patients of all ages with the diagnosis of severe congenital haemophilia A (FVIII activity <1%) based on medical records
3. On-going participation in the Phase 2 trials Study 07 (Pilotstudy1), or Study 10 (Pilotstudy4) at the time of transfer
4. The patient or child's parent/LAR is willing to follow one of the defined turoctocog alfa pegol prophylaxis regimens
5. The patient and/or caregiver is capable of assessing a bleeding episode, capable of home treatment of bleeds and otherwise able to follow trial procedures

Scenario 2: Study including subjects from other NN studies



Scenario 3 : Study including subjects from other NN studies and allowing rescreening at the same time

Combination of scenario 1 & 2

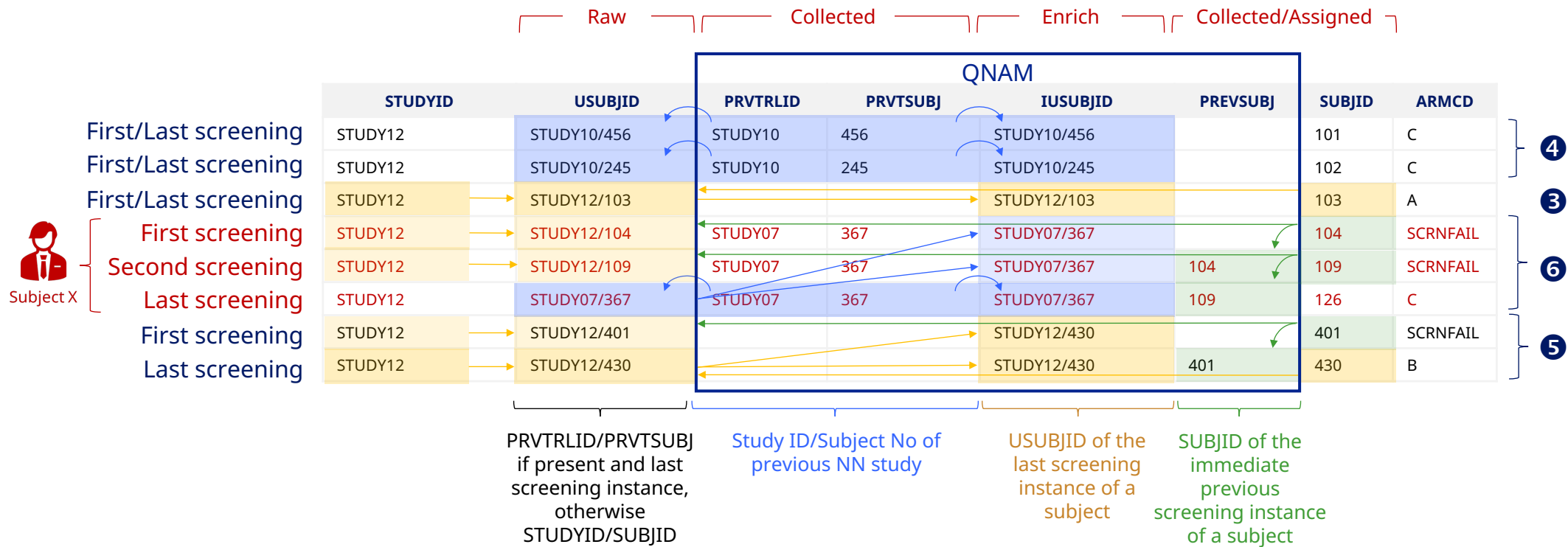
- Inclusion of subjects from other NN studies and rescreening of subjects failed screening or due to other reasons are explicitly stated in the Protocol
- Subject signs informed consent and will be assigned a new Subject No. (SUBJID) for each screening instance

Treatment arm 3:

Participants in the Phase 2 trials Study 07 (Pilotstudy1), or Study 10 (Pilotstudy4) were offered enrolment into arm 3. These patients continued compound1 PPX and had a combined visit 1 and 2.

Individuals who do not meet the criteria for participation in this trial may be re-screened twice within the limits of the recruitment period. In the event of re-screening, a new informed consent must be obtained and a new subject number must be allocated.

Scenario 3: Study including subjects from other NN studies and allowing rescreening at the same time



A Standard End-to-end Solution

- ✓ Traceable: Protocol >> CRF >> SDTM >> ADaM >> CSR
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How does it look from an analysis perspective?





Scenario 1: Re-screening of subjects

Analysis perspective

- ADaM: Include IUSUBJID only
→ Use that for counting instead

14.1.1 Subject disposition - overview - all subjects

	Active N (%)	Placebo N (%)	Total N (%)
Screened			286
Screening failures			191 (66.8)
Not assigned [1]			24 (8.4)
Randomised	47	24	71
Exposed	47 (100.0)	24 (100.0)	71 (100.0)
Analysis sets			
Full analysis set	47 (100.0)	24 (100.0)	71 (100.0)
Safety analysis set	47 (100.0)	24 (100.0)	71 (100.0)
Completed treatment [2]	41 (87.2)	23 (95.8)	64 (90.1)
(...)			

[1]: screened subjects who did not fail a specific in/exclusion criteria but were not randomised; [2]: subjects who completed treatment with trial product according to the end-of-trial form; N: number of subjects; %: proportion of randomised subjects.



VIEWTABLE: Work.AdsI				
	USUBJID	IUSUBJID	SUBJID	ARM
1	STUDY07/101001	STUDY07/101005	101001	NOT ASSIGNED
2	STUDY07/101005	STUDY07/101005	101005	SCREEN FAILURE
3	STUDY07/109001	STUDY07/109001	109001	NOT ASSIGNED
4	STUDY07/109002	STUDY07/109002	109002	SCREEN FAILURE
5	STUDY07/117006	STUDY07/117022	117006	NOT ASSIGNED
6	STUDY07/117022	STUDY07/117022	117022	PLACEBO
7	STUDY07/117009	STUDY07/117024	117009	SCREEN FAILURE
8	STUDY07/117024	STUDY07/117024	117024	NOT ASSIGNED

```
if usubjid = iusubjid
and arm not in ("PLACEBO" "ACTIVE");
```

Scenario 3: Study including subjects from other NN studies and allowing rescreening at the same time

Analysis perspective

- ADaM: Use USUBJID = IUSUBJID for selection (as scenario 1)
→ Counting on USUBJID (or distinct IUSUBJID)

STUDY 12 disposition counts

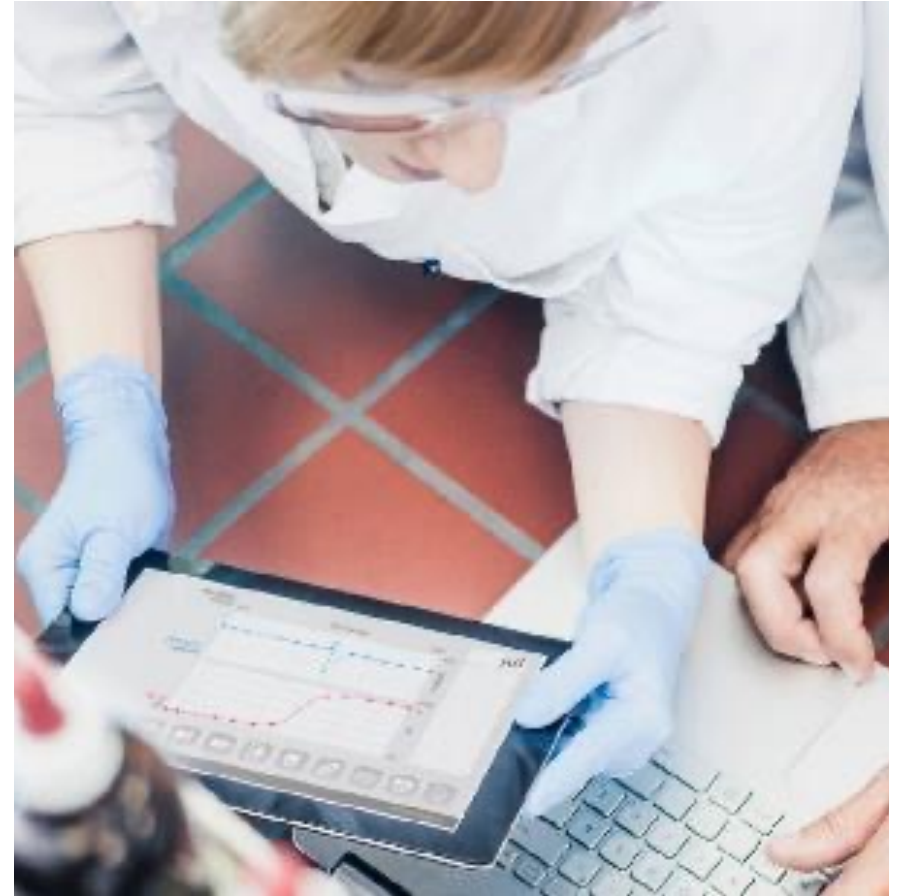
	STUDYID	USUBJID	IUSUBJID	ARMCD	
First/Last screening	STUDY12	STUDY12/775	STUDY12/775	SCRNFAIL	←
First/Last screening	STUDY12	STUDY10/245	STUDY10/245	C	←
First/Last screening	STUDY12	STUDY12/103	STUDY12/103	A	
First screening	STUDY12	STUDY12/104	STUDY07/367	SCRNFAIL	←
Second screening	STUDY12	STUDY12/109	STUDY07/367	SCRNFAIL	
Last screening	STUDY12	STUDY07/367	STUDY07/367	C	←
First screening	STUDY12	STUDY12/401	STUDY12/430	SCRNFAIL	←
Last screening	STUDY12	STUDY12/430	STUDY12/430	B	

Subject X

- Screening failure count
- Randomized counts
- One randomized count
- One randomized count

Key Take Away Messages

- A good standard is one that is operational
- Take data consumer's need into consideration
- Think end-to-end and out-of-the box
- Keep solution simple however still transparent!
- What's not to like? Seen from Biostatistics perspective...



Thank you for your attention



Contact

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