

Avoiding a REL-WRECK; Using RELREC Well

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ABSTRACT

Everything that happens to a single subject in a clinical trial is interrelated. Most points of data can be reported and processed in isolation, but not all. When two or more points of data in two or more CDISC Study Data Tabulation Model (SDTM) domains require reporting their relationship, there is a Special-Purpose domain, RELREC (Related Records) for this purpose. Although employed for accidental (or inexplicit) relationships where data destined for two domains is collected on one CRF page; an explicit relationship between data reported in two domains is also possible. A subject who takes a concomitant medication to treat an adverse event has an explicit relationship between two records in the CM and AE domains. An adverse event which causes a dose-delay or titration (AE & EX), a lab value which indicates a change in dosing epoch (LB & DS) and a substance usage report which results in study termination (SU & DS) are other examples of related records. Careful consideration of what types of explicit relationships are expected and how they will be reported can prevent RELREC from turning into a RELWRECK. In this paper, we demonstrate our method of avoiding the re-mapping of entire SDTM domains and risking mismatched relationships in your final submission data.

INTRODUCTION

Designated as a Special-Purpose domain in the CDISC Study Data Tabulation Model (SDTM), the Related Records (RELREC) domain can be used to identify numerous relationships between records in two (or more) domains. For direct relationships, they are usually comprised of a direct one-to-one relationship. For relationships that are not directly collected, the recording of the relationships between records becomes more complicated and requires more attention to detail. Relationships that are used can have numerous cross-references between datasets and without careful consideration can turn into a nightmare and easily turn RELREC into REL-WRECK. One can easily work to avoid a related mess through careful pre-planning.

In practical terms, employing RELREC well requires planning and preparation. We present here six steps which we have found helpful for implementing RELREC. Five of these steps will be illustrated with examples.

1. Identify, in advance, all combinations (typically pairs) of domains which could logically generate RELREC records and then pare this list down in consultation with your statistician, safety physician and clinical scientist.
2. Identify the key variables in each domain which will appear in the IDVAR in the RELREC domain. These variables will be the key variables employed to merge the information from the two domains and must be in both; typically –SPID, –GRPID or –REFID.
3. Identify if only a portion of the records in these domains will be reported in RELREC. For example, all concomitant medications can be linked to the adverse event for which the subject takes them, however, often is it just serious or severe adverse events (SAE) which are linked to their concomitant medications.
4. Develop a plan for identifying and reporting unified start and end dates. A concomitant medication will not normally start coincidentally with the adverse event, may end sooner, or may end later.
5. Decide how to programmatically create the RELREC domain from the source domains; the logic needs to be clear and written down, normally recorded in program notes.
6. Add an extra cycle of programming review for the RELREC domain to avoid reporting unnecessary links into the CSR.

PRE-IDENTIFY ALL LOGICAL PAIRS OF DOMAINS FOR RELATED RECORDS

In many clinical trials, smoking is contraindicated. For a variety of experimental medications it is totally forbidden. The protocol may even include a test for checking smoking non-compliance at every visit; subjects who violate this prohibition may be forcefully terminated from the study. If this is the case, then linkage via RELREC of the substance

usage (SU) and disposition (DS) domains may be appropriate. Since, the SU domain has no reference ID variable, the SUSPID will be employed as the IDVAR for that domain's record and either the DSSEQ or DSREFID should serve for the disposition record.

Example 1:

SU (Substance Use) Domain [partial]:

USUBJID	SUSPID	SUTRT	SUCAT	SUDOSTOT	VISIT	SUSTDTC	SUENDTC
XXX-XXX-22-0510	1	CIGARETTES	TOBACCO	0 Pack/Day	2		
XXX-XXX-22-0510	2	CIGARETTES	TOBACCO	1 Pack/Day	3		

Table 1. Subject's smoking status went from '0 Pack/Day' to active or '1 Pack/Day' on visit 3

DS (Disposition Status) Domain [partial]:

USUBJID	DSREFID	DSTERM	DSDECOD	VISIT	DSDTC	DSSTDTC
XXX-XXX-22-0510	1	Violated Participation Criteria	EARLY TERMINATION	2		

Table 2. Subject was discontinued from the study, mid-trial, on visit 3 for violation of participation criteria

RELREC (Related Records) Domain [partial]:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
SU	XXX-XXX-22-0510	SUSPID	2	ONE	SUDS-001
DS	XXX-XXX-22-0510	DSREFID	1	ONE	SUDS-001

Table 3. Linking subject study status with the reason for discontinuation from the study

Since, in this example, we are considering smoking to be strictly forbidden, this linkage might be retained for each DS record, as the subject proceeds through each epoch of the study. The date of the test whether by direct questioning, staff report, urinalysis or blood draw would coincide with the start date of the new epoch.

IDENTIFY KEY VARIABLES WHICH WILL LINK VIA IDVAR

Employing a common variable found in each domain, --GRPID or --REFID, minimizes the required number of records in the dataset. In this example, commonly related domains PC (Pharmacokinetic Concentrations) and PP (Pharmacokinetic Parameters) are employed to demonstrate RELREC in the relationship of which calculates parameter records. Through careful consideration and communication with the programmers involved with the parameter calculations, establishing an ID that minimizes the number of RELREC records saves time in data review. Since a majority of the parameter calculations are derived from multiple concentration records collected, multiple concentrations can employ more than one parameter, it is key to assign values for the variables used in IDVAR to delineate which concentrations are employed and which ones are excluded in the calculation of the parameters.

Example 2:

PC (Pharmacokinetic Concentration) Domain [partial]:

USUBJID	PCSEQ	PCGRPID	PCTEST	PCSPEC	PCORRES	PCORRESU	PCTPT
XXX-XXX-01-0001	1	DRGA_DY5-101	DRUG A	Plasma	9	ug/mL	Hour 1
XXX-XXX-01-0001	2	DRGA_DY5-011	DRUG A	Plasma	15	ug/mL	Hour 2

USUBJID	PCSEQ	PCGRPID	PCTEST	PCSPEC	PCORRES	PCORRESU	PCTPT
XXX-XXX-01-0001	3	DRGA_DY5-111	DRUG A	Plasma	21	ug/mL	Hour 3
XXX-XXX-01-0001	4	DRGA_DY5-110	DRUG A	Plasma	13	ug/mL	Hour 4

Table 4. Concentrations from four separate time points used in parameter calculations following a pre-defined –GRPID

PP (Pharmacokinetic Parameter) Domain [partial]:

USUBJID	PPSEQ	PPGRPID	PPTTEST	PPCAT	PPORRES	PPORRESU
XXX-XXX-01-0001	1	DRGA_DY5-100	TMAX	DRUG A	2.95	h
XXX-XXX-01-0001	2	DRGA_DY5-010	CMAX	DRUG A	21.8	ug/L
XXX-XXX-01-0001	3	DRGA_DY5-001	AUC	DRUG A	234.8	h*mg/L

Table 5. Three different parameters which are calculated from different concentration records and following a pre-defined –GPRID value for a parameter

RELREC (Pharmacokinetic Concentration) Domain [partial]:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
PC	XXX-XXX-01-0001	PCGRPID	DRGA_DY5-101	MANY	PCPP-001
PC	XXX-XXX-01-0001	PCGRPID	DRGA_DY5-011	MANY	PCPP-001
PC	XXX-XXX-01-0001	PCGRPID	DRGA_DY5-111	MANY	PCPP-001
PP	XXX-XXX-01-0001	PPGRPID	DRGA_DY5-001	ONE	PCPP-001

Table 6. Linking a parameter record with the concentration records used in calculation

We can see concentration samples were collected on Day 5 of the trial for Drug A at different time points. Implementing the pre-defined –GRPID (i.e. DRGA_DY5-###) allows the ability to reference the appropriate concentration records to the associated parameters as a result of the calculations. Using the third digit of the number found in –GRPID, using binary code a ‘1’ means the record was used in the calculation, the records are placed into a Many-to-One relationship making the review of the data easier to follow and verify in the review process.

ANTICIPATE UNPREDICATABILITIES WITHIN THESE REPORTS

In our experience, all concomitant medications are taken for a reason, although few data management departments appear interested in recording that reason. This reason should always be recorded as an adverse event. While over the counter (OTC) medications may have little effect on the efficacy of study medications, concomitant medications taken for the most serious adverse events may have substantial efficacy implications. For this reason, the RELREC domain is frequently employed to link an adverse event (AE) domain record with concomitant medication (CM) domain records, especially for serious or severe adverse events (SAE).

Example 3:

AE (Adverse Events) Domain [partial]:

USUBJID	AEREFID	AETERM	AEDECOD	AEBODSYS	AESEV	AESTDTC	AEENDTC
XXX-XXX-01-0001	4	HEART ATTACK	410.21	Circulatory	Y		

USUBJID	AEREFID	AETERM	AEDECOD	AEBODSYS	AESEV	AESTDTC	AEENDTC
XXX-XXX-01-0001	5	HEART ATTACK (FU)	410.22	Circulatory	Y		

Table 7. Subject was reported of having an event of a heart attack along with a subsequent adverse event of heart attack on a follow-up (FU) visit

CM (Concomitant Medications) Domain [partial]:

USUBJID	CMSPID	CMTRT	CMDECOD		CMINDC	CMSTDTC	CMENDTC
XXX-XXX-01-0001	8	Retevase-tPA	B01AD07	Tissue Plasminogen Activator (tPA)	Heart Attack		

Table 8. Subject was given a concomitant medication for their adverse event of a heart attack

RELREC (Related Records) Domain [partial]:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
AE	XXX-XXX-01-0001	AEREFID	4	ONE	AECM-001
AE	XXX-XXX-01-0001	AEREFID	5	ONE	AECM-001
CM	XXX-XXX-01-0001	CMSPID	8	ONE	AECM-001

Table 9. Linking the subject's concomitant medication with the reason for administration

In this example, a subject has a heart attack (myocardial infarction MedDRA 410.21) with a period of follow-up care (410.22) and is treated with Retevase-tPA (tissue Plasminogen activator, ATC code B01AD07.) The AEREFID may be restricted to SAE reports (serious adverse events frequently involve an additional form beyond ordinary AEs) and may be a pre-printed number on a single line of this form. This would serve as the IDVAR for the AE domain record. For the CM domain record the CMSPID should be adequate. N.B. There is no variable available in the RELREC domain to identify that the AEs reported are only those with the serious AE (AESER) flag variable = 'Y'.

CHECK THE START AND END DATES FOR CONSISTENCY

Adverse events (AE) have been known to cause dose-delays or otherwise effect exposure (EX) to study medication. Although specific criteria for altering the dosing plan is seldom found in most study plans, a significant amount of investigator discretion is normally permitted; this is particularly true if the class of medications, in this example NSAIDs, is contraindicated during a particular illness, here common influenza. For the AE domain record the AESPID variable will typically be a pre-printed explicit line identifier on the AE case report form (CRF) page; for the EX domain record the EXSPID will also be an explicit line identifier on the exposure CRF page. Linking this is conceptually simple.

A relationship between the dates will not be as straightforward. The adverse event will, typically, be reported by the subject, either in person at a visit or, if unable to visit the clinic, by phone. This will leave the start date of the illness as moderately subjective. We find that rarely, is the infecting event reported. The first symptom, or the first day of diminished activity, is much more common as the date of the start of the event. The adjustment in exposure will only be based on the subject's instructions at the visit or by phone. There may be a delay. The modification to the exposure will normally continue until the next visit or clinic contact, either of which may vary significantly from the end of the reported illness. This lag may be confusing. A thorough review of the data, checking with the actual CRFs may be required.

Example 4:

AE (Adverse Events) Domain [partial]:

USUBJID	AEREFID	AETERM	AEDECOD	AEBODSYS	AESEV	AESTDTC	AEENDTC
XXX-XXX-04-0027	515	INFLUENZA	487	Respiratory	N		

Table 10. Subject with a viral infection adverse event

EX (Exposure) Domain [partial]:

USUBJID	EXSPID	EXTRT	EXCAT	EXDOSFRM	EXDOSE	EXSTDTC	EXENDTC
XXX-XXX-04-0027	007	M01ae01 IBUPROFEN	Comparator 1	Tablet	0		
XXX-XXX-04-0027	008	N02BE01 PARACETAMOL	Comparator 2	Tablet	1		

Table 11. NSAID medication switched due to Reyes Syndrome risk with viral infection

RELREC (Related Records) Domain [partial]:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
AE	XXX-XXX-04-0027	AEREFID	515	ONE	AEEX-001
EX	XXX-XXX-04-0027	EXSPID	008	ONE	AEEX-001

Table 12. Linking the adverse event with the dosing change as a result of the AE

PROGRAMMATICALLY FILL IN VALUES

Many clinical trials involve a dosing titration or other adjustment to the dose. If multiple factors can affect a change in dosing (for example: multiple lab test values, one lab or length of time, length of time or investigator decision) then employ the RELREC to link the appropriate record with the record of either change in dosing epoch (DS) or change in exposure (EX). Illustrated here is a simple example of a lab test which triggers the change in dosing epoch.

The lab domain (LB) has an LBSPID variable which typically identifies a single line on the lab CRF page. This CRF page may either be standardized or custom for the clinical trial, but since we are assuming the hemoglobin (HGB) value triggers change in dosing regimen, this value should be quite prominent. The DS domain also has a DSSPID variable which can also be employed to link the change in dosing epoch.

Example 5:

LB (Laboratory Tests) Domain [partial]:

USUBJID	LBSPID	LBTEST	LBTESTCD	LBORRES	VISIT	LB DTC
XXX-XXX-29-0298	987	Hemoglobin	HGB	10.9	7	
XXX-XXX-29-0298	1051	Hemoglobin	HGB	14.6	8	

Table 13. Subject test records for Hemoglobin from samples taken

DS (Disposition Status) Domain [partial]:

USUBJID	DSSPID	DSTERM	DSDECOD	VISIT	EPOCH	DSDTC	DSSTDTC
XXX-XXX-29-0298	14	Treatment Milestone	Dosing Changed	8	Dose 2		

Table 14. Subject treatment milestone for change in dosing on visit 8

RELREC (Related Records) Domain [partial]:

RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
LB	XXX-XXX-29-0298	LBSPID	1051	ONE	LBDS-012
DS	XXX-XXX-29-0298	DSSPID	14	ONE	LBDS-012

Table 15. Linking the test record with the milestone used in dosing administration change

This type of change must be first anticipated, second the –SPID variables considered, third only the triggering events linked to the dosing changes, fourth the dates checked, fifth programmed and sixth reviewed. This RELREC domain can provide clear evidence of the events which trigger dosing changes.

BE AWARE THAT RELREC MAY REQUIRE INTELLIGENT INTERVENTION

RELREC is unlike most other domains in SDTM; its purpose is to highlight relationships across domains. Unlike the Adverse Events domain which reports all adverse events, every reported relationship in RELREC will be there because it is considered important to identify and report that relationship. Thus, a modicum of intelligent intervention to either add additional important relationships, or to delete ones of little reporting value, is required. The authors tend to err on the side of including information because brevity of presented information is rarely a criterion for considering that a clinical trial to be sufficiently reported, but completeness is.

CONCLUSION

We presented six considerations for building RELREC domains:

1. identify likely pairs of source domains for consideration to include in RELREC
2. select the key variable within each source domain for the identifying link between domains
3. subset the records in domains if appropriate
4. establish a system for insuring that dates are appropriate
5. clarify the programming logic
6. set aside extra time for a review of the RELREC records.

We have found these steps helpful in creating RELREC domains which highlight important relationships in clinical trial reporting and yet do not overwhelm downstream consumers of our data.

CONTACT INFORMATION

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