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Practical benefits of EC: building a comprehensive exposure story

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ABSTRACT

Since the inclusion of EC in SDTM, exposure data can be entered in the database as it is collected in the e-source/(e)CRF. EC enables us to document an accurate, traceable and clearly structured exposure story in situations where the exposure data and its provenance would otherwise be unclear and ambiguous. The derived EX can be kept clear and concise, aimed at analysis.

These real-life case studies are discussed:

- Capturing relevant exposure information without cluttering EX/SUPPEX.
- Factual data entry by site personnel (crucial when using e-source).
- Unblinding in an orderly fashion.
- Per dose traceability.
- Multiple dose medications.
- Complex dosing schemes.
- Using ECMOOD to document scheduled and performed exposures.

Our shared experience with using EC to document the exposure in a comprehensive manner can help others to use EC to accurately and clearly capture the whole story behind trial exposures in very diverse situations.

INTRODUCTION

The Exposure domain model (EX) records the details of a subject's exposure to protocol-specified study treatment. As EX is ultimately used for the statistical analysis, it should be concise and easily analyzable. However, if EX is the only exposure capturing domain, it can become too cluttered (by adding too much detail) or miss essential information (by making it too concise). Evidently, we don't want EX to be the only exposure capturing domain.

To facilitate the accurate capturing of the exposure data, the EC Domain was introduced. Since the inclusion of EC in SDTM, as of SDTM IG 3.2, exposure data can be collected as it is present in the esource or the (e)CRF. The EX dataset is derived afterwards from the EC dataset and other relevant data sources (like for example from the randomization data, medication logs ...).

At SGS Life Sciences, we have implemented EC since it was included in the SDTM standard. The usage of EC enabled us to document an accurate, traceable, and clearly structured exposure story in situations where the exposure data and its provenance would otherwise have been unclear and ambiguous

CASE STUDIES

To illustrate how EC can help in creating an accurate, traceable and clearly structured exposure story, the following real-life case studies are discussed:

- Unblinding in an orderly fashion.
- Capturing relevant exposure information without cluttering EX/SUPPEX.
- Factual data entry by site personnel (crucial when using e-source).
- Per dose traceability.
- Multiple dose medications.
- Complex dosing schemes.
- Using ECMOOD to document scheduled and performed exposures

UNBLINDING IN AN ORDERLY FASHION

One of the obvious advantages of using EC is the unblinding in an orderly fashion.

In the blinded dataset, the exposure term (ECTRT) is a general placeholder. All Data Management activities are performed on the blinded dataset. Once the data is unblinded, we can derive EX, based on the EC dataset and the information in the randomization log. EC remains untouched at the time of unblinding. The derivations of EX is tested during the quality control phase of the setup of the database using dummy data and dummy unblinding data. In the derived dataset EX, EXTRT is updated from ECTRT to contain the actual treatment. The actual dose is also recalculated based on the placebo/active ingredient status. The usage of EC ensures a stable dataset and a tested derivation of EX. Without EC, updates would be necessary to the actual data-capturing EX domain at unblinding; a crucial time at which data stability is a definite requirement.

Example 1: Placebo-controlled trial

ECTRT	ECDOSE	ECDOSU		EXTRT	EXDOSE	EXDOSU
TRT OR PLACEBO	150	mg	→	TRT	150	mg
TRT OR PLACEBO	150	mg		PLACEBO	0	mg

Table 1: Placebo-controlled trial. ECTRT is a general term. ECDOSE contains the theoretical dose. After unblinding, EX is derived. EXTRT is specified correctly and EXDOSE is recalculated.

As you can see in the datasets, the EC dataset contains a general placeholder ECTRT and the theoretical dose. After unblinding, the EX dataset is derived from the EC datasets and the unblinding information. EXTRT is specified correctly and the dose is recalculated

Example 2: Double dummy trial

ECTRT	ECDOSE	ECDOSU		EXTRT	EXDOSE	EXDOSU
TRT A OR TRTB OR PLACEBO	1	TABLET	→	TRT A	150	mg
TRT A OR TRTB OR PLACEBO	1	TABLET		PLACEBO	0	mg
TRT A OR TRTB OR PLACEBO	1	TABLET		TRT B	250	mg

Table 2: Double dummy trial. ECTRT, ECDOSE and ECDOSU are general terms. After unblinding, EX is derived. EXTRT is specified correctly and EXDOSE and EXDOSU are recalculated as required, taking the different treatments, dosages and placebo into account.

In a double dummy trial, the subject is exposed to either one of two treatments or to the placebo. Once again, the ECTRT is a general placeholder showing all the possible exposures. The dose is shown as a general placeholder as well. For double dummy trials, both the subject and the site personnel usually need to remain blinded, so the drugs and the placebos are provided in an identical formulation (e.g. the same tablet shape, color ...). Here an extra derivation has to be performed to get the correct dosing information in the EX dataset. The extra information for derivation is documented in the protocol or the randomization log, and if wanted could be recorded in the database as well; e.g. in SUPPEC.

CAPTURING RELEVANT EXPOSURE INFORMATION

EC can also be used to capture relevant exposure information without cluttering up EX and/or SUPPEX. This can even be interesting for open label trials. The information captured in EC can document why the concentration in EX is not as expected, or it can document errors in exposure which might not be visible in EX.

Example 1: Dosing inconsistency for an IV exposure

USUBJID	EXTRT	EXDOSE	EXDOSU		USUBJID	ECTRT	ECDOSE	ECDOSU	ECPSTRG	ECPSTRGU
1001	TRT	150	mg	←	1001	TRT	100	mL	1.50	mg/mL
1002	TRT	147	mg		1002	TRT	98	mL	1.50	mg/mL

Table 3: Identifying the origin of a dosing inconsistency by using EC. In this example, the origin of the calculated EXDOSE discrepancy for subject 1002 can be traced back to an incorrect volume administered, rather than an incorrect solution concentration. Be aware that the EC domain is on the right side in this table.

The amount of drug in the body due to IV exposure is dependent on the volume administered and the concentration of the solution. In case of aberrations from the expected dose of 150 mg, as seen in the example shown in Table 3, EX only provides the end result information (i.e. 147 mg). It is not clear from EX whether the error occurred during the preparation of the solution (i.e. a solution with an incorrect concentration), or if the total volume of 100 mL was not provided correctly. In this example, the origin of the calculated EXDOSE discrepancy for subject 1002 can be traced back to an incorrect volume administered, rather than an incorrect solution concentration.

By using EC, specifically the ECDOSE/ECDOSU information combined with the Pharmaceutical Strength (ECPSTRG) information, we can document in the EC domain why the resulting amount of medication was not as expected per protocol. ECPSTRG and ECPSTRGU are parameters which indicate the amount of an active ingredient expressed quantitatively per dosage unit, volume, or weight.

Example 2: Documenting errors in exposure for weight-dependent exposures

USUBJID	EXTRT	EXDOSE	EXDOSU
1001	TRT	15.8800	mg
1002	TRT	15.0400	mg
1003	TRT	15.1632	mg

←

USUBJID	ECTRT	ECDOSE	ECDOSU
1001	TRT OR PLACEBO	0.2	mg/kg
1002	TRT OR PLACEBO	0.2	mg/kg
1003	TRT OR PLACEBO	0.2016	mg/kg

Table 4: Identifying incorrect dose per weight by using EC. In this example, the concentrations documented in EX look perfectly acceptable. However, the information in EC identifies an incorrect dose/kg for subject 1003. Be aware that the EC domain is on the right side in this table.

Table 4 shows that the 3 subjects received a dose based on their weight. It is impossible to clean the dose information without knowledge of the expected dose per kilogram, the weight of the subject, and, to facilitate the cleaning process, the calculated actual dose per kilogram. In the EC table, we can now see that, although everything looked acceptable in the EX dataset, the actual dose per kg for subject 1003 was incorrect.

FACTUAL DATA ENTRY

ECTRT	ECDOSE	ECDOSU
TRT OR PLACEBO	1	SYRINGE
TRT OR PLACEBO	1	SYRINGE

→

EXTRT	EXDOSE	EXDOSU
TRT	150	mg
PLACEBO	0	mg

Table 5: Factual recording of a blinded syringe exposure and unblinded EX. EC is entered factually correct without making unknown assumptions. EX is then derived based on additional information (in this case the randomization list and the apothecary medication log).

This is especially important when working with an esource system on site, because no processing of exposure information can be done in between the source data and the CRF. The site personnel cannot enter exposure data in the system of which they do not have accurate knowledge. The exposure data is entered as performed on site, without making assumptions on the type and the concentration of the medication.

The example in Table 5 shows a trial where the subjects were exposed with a solution given orally using a syringe. The color of the solution would have been unblinding, so the syringes themselves were blinded using dark tape. Because of this, the nurses could not ascertain the volume given. As you can see, the treatment information on dosing (ECDOSE/ECDOSU) collected in the EC dataset was 1 SYRINGE. To be able to derive the EX datasets, specific data was gathered from the randomization list (active vs placebo) and the apothecary medication log (dose and concentration). Joining this information together enabled us to derive EX while keeping EC valid, accurate and factual.

PER DOSE TRACEABILITY

USUBJID	ECTRT	ECDOSE	ECDOSU	ECPSTRG	ECPSTRGU	SUPPEC.QNAM	SUPPEC.QVAL
1001	TRT A	1	TABLET	100	mg/tablet	CODE	AABB01
1001	TRT A	1	TABLET	100	mg/tablet	CODE	AABB02
1001	TRT A	1	TABLET	100	mg/tablet	CODE	AABB03

↓

USUBJID	EXTRT	EXDOSE	EXDOSU
1001	TRT A	300	mg

Table 6: Per dose traceability. Dose codes are traced in EC, but total dose is recalculated in EX.

For some trials, the individual tables or capsules are coded and this information should remain present in the database. However, this information is often not important for the actual analysis. The example in the table above, shows a situation where a subject was given 3 coded tablets at a single visit. In EC the three records are present, together with a custom SUPPEC link to the code of the tablet. In this case, the codes were not necessary in the analysis of the data and were therefore not expected in EX. Because of this, we could join the records together and present the EX data in a concise and easily analyzable EX dataset.

MULTIPLE DOSE MEDICATIONS

USUBJID	EC TRT	EC DOSE	EC DOSU	EC PSTRG	EC PSTRGU
1001	TRT A	1	TABLET	25	mg/tablet
1001	TRT A	1	TABLET	50	mg/tablet
1001	TRT A	2	TABLET	100	mg/tablet

↓

USUBJID	EXTRT	EXDOSE	EXDOSU
1001	TRT A	275	mg

Table 7: Multiple dose medications. Exposures with different dosages can be entered in EC as separate entries, but are combined in EX to facilitate the analysis.

In Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) trials different dosages need to be prepared. To simplify the manufacturing process, the doses can be prepared by combining tablets with different concentrations. Exposures with different dosages can be entered in EC as separate entries and combined in EX as a single entry, to facilitate the analysis.

COMPLEX DOSING SCHEMES

ECTRT	ECDOSE	ECDOSU	VISIT
DEVICE 1	2	INHALATION	VISIT3
DEVICE 2	6	INHALATION	VISIT3
DEVICE 1	2	INHALATION	VISIT4
DEVICE 2	6	INHALATION	VISIT4

→

EXTRT	EXSCAT	EXDOSE	EXDOSU	VISIT
COMPOUND 1	DEVICE 1	200	mg	VISIT3
COMPOUND 2	DEVICE 1	20	mg	VISIT3
PLACEBO	DEVICE 2	0	mg	VISIT3
COMPOUND 1	DEVICE 1	200	mg	VISIT4
COMPOUND 2	DEVICE 1	20	mg	VISIT4
COMPOUND 1	DEVICE 2	600	mg	VISIT4
COMPOUND 2	DEVICE 2	60	mg	VISIT4

Table 8: Complex dosing scheme. Two types of inhalation devices are used. The exposure is recorded in EC (left) as inhalations. Each inhalation contains 2 active compounds or a placebo. The active compounds are a compound (COMPOUND 1) with a dose of 100 mg/inhalation and a compound (COMPOUND 2) with a dose of 10 mg/inhalation. EX is derived per device, on sponsor request.

Using EC facilitates complex dosing schemes by enhancing the traceability between the recorded dosing in EC and the derived value in EX. For example, in trials where a combination of multiple active and placebo exposures are performed within the same exposure time point, we can establish an easily traceable link between the performed exposure, the randomization data and the derived data.

In the example above (Table 8), two types of inhalation devices are used. The exposure is recorded in EC (left) as inhalations. Each inhalation contains 2 active compounds or a placebo. The active compounds are a compound (COMPOUND 1) with a dose of 100 mg/inhalation and a compound (COMPOUND 2) with a dose of 10 mg/inhalation. EX is derived per device, as requested by the sponsor. We can see in EX how the inhalations are derived to the correct mg per compound per visit and per device. The unblinding is incorporated as well, differentiating between the active and placebo devices. The actual dose is also recalculated in EX based on the amount of inhalations.

ECTRT	ECDOSE	ECDOSU	VISIT
DEVICE 1	2	INHALATION	VISIT3
DEVICE 2	6	INHALATION	VISIT3
DEVICE 1	2	INHALATION	VISIT4
DEVICE 2	6	INHALATION	VISIT4

→

EXTRT	EXDOSE	EXDOSU	VISIT
COMPOUND 1	200	mg	VISIT3
COMPOUND 2	20	mg	VISIT3
COMPOUND 1	800	mg	VISIT4
COMPOUND 2	80	mg	VISIT4

Table 9: Alternative derivation of the EC used in Table 8 under the assumption device information is not important for the analysis.

The example above (Table 9) present a different derivation for the situation presented in Table 8. In this example, the device information is assumed to be irrelevant for the analysis and thus is dropped. We know from the

randomization list and the medication log that DEVICE 2 on VISIT 3 contains placebo. All other inhalations contain the active compounds. Deriving EX now gives a very concise overview of compounds 1 and 2 for each visit.

USING ECMOOD TO DOCUMENT SCHEDULED AND PERFORMED EXPOSURES

ECTRT	ECMOOD	ECDOSE	ECDOSU	ECPRESP	ECOCCUR	VISIT
TRT A	SCHEDULED	50	mg			1
TRT A	PERFORMED	50	mg	Y	Y	1
TRT A	SCHEDULED	100	mg			2
TRT A	PERFORMED	100	mg	Y	Y	2
TRT A	SCHEDULED	200	mg			3
TRT A	PERFORMED			Y	N	3

↓

EXTRT	EXDOSE	EXDOSU	VISIT
TRT A	50	mg	1
TRT A	100		2

Table 10: ECMOOD can be used to document both the scheduled and the performed exposures in EC. When deriving EX, only the performed records for which the occurrence is marked as Yes in EC will create a record in EX.

The ECMOOD parameter contains the mode or condition of the record specifying whether the intervention (activity) is intended to happen or has happened. ECPRESP defines whether an exposure is prespecified in the esource/(e)CRF; and the ECOCCUR then records whether or not a prespecified records occurred.

In the example above (Table 10), three scheduled exposures are listed, giving a clear overview of which exposures we would expect at those visits. The exposures that should be performed are present as prespecified records in which the dose and the occurrence are recorded. The first two exposures occur, the third does not. When deriving EX, only the occurred exposures and the actual dose are listed; once again creating a dataset which is easy to analyze. Even though EX is concise, all planned and actual exposure information is present in EC.

CONCLUSION

The usage of EC enables us to document an accurate, traceable, and clearly structured exposure story in situations where the exposure data and its provenance would otherwise have been unclear and ambiguous. In sharing our experience using EC to document the exposure in a comprehensive manner, we hope we can help other users to implement and use EC to accurately and clearly capture the whole story behind trial exposures in very diverse situations.

CONTACT INFORMATION

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