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EPOCH in Reverse

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ABSTRACT

After supplying test data through the electronic gateway to the FDA, LEO Pharma was informed that the FDA required some updates to our SDTMs. For SDTM model version 1.2 we had completed all the Expected and Required variables but EPOCH was a Permissible variable and now we were being asked to supply EPOCH on every subject level SDTM and create SE. With datasets already created, tables finalised and reports written what challenges could a programmer face adding EPOCH to studies that have already completed.

INTRODUCTION

The FDA announced in December 2014 that it would only be accepting standardised format data including CDISC SDTMs and ADAMs from December 2016. In the run up to that process they allow companies submitting New Drug Applications (NDAs) to send test data to them in the form of SDTMs and ADAMs, pre-submission, to check the compliance of their data to FDA requirements.

In 2014 LEO Pharma prepared data for a US submission based on comments from the FDA on previously submitted data (in SDTM format) and using the OpenCDISC Validator® (www.opencdisc.org). The data from our chosen study was submitted through the FDA Gateway for test submission. All seven studies involved in our submission package had completed, our pooled data was ready, all Clinical Study Reports finalized (some of them years before) and the electronic Common Technical Document (eCTD) was in its final stages of completion. Four weeks later we received an email with the FDA feedback on our test submission.

Along with comments suggesting updates to our data based on a newer version of the OpenCDISC Validator than we had used and the use of the Reviewers Guides as available through the PhUSE website, we were suggested to include the EPOCH variable in subject level domains to facilitate the review process. As EPOCH is a Permissible variable according to the CDISC Implementation Guide it was not a variable that LEO Pharma studies generally populated: indeed only one of the studies involved in our submission package contained EPOCH. We had limited experience in populating this variable!

As we started to write programs to add EPOCH to each study we came across scenarios in the data that required special attention. I will look at some of these situations and what implications they can have on the EPOCH variable as you look to add EPOCH in Reverse (i.e. to study SDTMs after the study has completed).

SETUP OF LEO PHARMA DERMATOLOGY STUDIES

Dermatology products by LEO Pharma are applied to the skin. The first application is usually completed by the investigator at site once the subject has been randomised (or treatment assigned in an Open Label) in a trial. On some studies this may be the only application of study drug applied. The date of first dose is not always captured on the CRF as it is expected to be the same date as the randomisation visit. If there are multiple applications to be applied by the subject following first application then it is protocolled that the subject would apply these at home. For most of the trials involved in this paper the SDTMs were outsourced to CROs.

A common trial setup will involve a screening visit followed by a visit where the subject will be randomised and have the first or only application of study drug applied. This will then be followed by numerous visits to determine the endpoints of the trial. In studies where the subject applies multiple applications of the study drug at home it is protocolled and expected that the last dose will be applied the day before the last on-treatment visit. At the last of these visits LEO Pharma collects all the relevant study end information on the subject including when the last dose was applied. In some of the trials referenced in this paper the subjects were supplied with a diary on which to record the dates they applied medication at home.

In this paper there are a few types of studies referenced.

- Completed studies had data in SDTM format and a completed CSR.

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- Active studies were still being built and/or in the reporting phase where the CSR was not yet completed.

EXPECTATIONS FOR DERIVING EPOCH

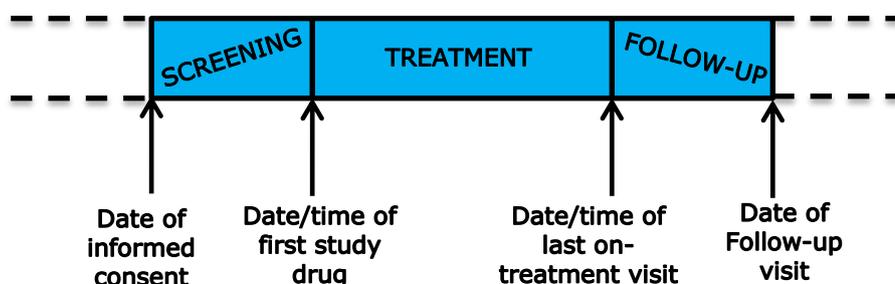
The expected progression of a subject in a simple study:

- Informed consent should have been the same date/time as first visit or earlier
- Screening should have been before or the same date/time as randomisation (or treatment assignment)
- The first dose should have been the same date/time as randomisation (or treatment assignment) or later.
- The last dose should have been before the last on-treatment visit
- Visit dates are not expected after a subject's death

Assume for the duration of this paper that there are two consistent rules regarding EPOCH at LEO Pharma:

- 1) Date/time of first dose of any study drug was the start of Treatment EPOCH.
- 2) Date/time of last scheduled visit following treatment was the end of Treatment EPOCH

SIMPLE STANDARD FOR AN EPOCH MODEL



This is based on the CDISC Model¹. In general, most subjects will follow this pattern. In small studies with one or two sites the expected pattern will almost certainly be followed. In larger studies there may be special case subjects that did not follow the expected pattern. What discrepancies did we encounter? How did we deal with them?

START OF TREATMENT ISSUES

Conflict in collected information arose with studies where the first dose is administered by the investigator and the date is based on the subject visit (it is expected not collected). Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS) may have a conflicting date to the subject visit hence the issue. Sometimes IVRS/IWRS isn't functioning and there may be workaround allowing the site to still dispense drug.

The Comments dataset (CO domain) is a good starting position for investigating these situations; investigator's often write comments if they have had to intervene in a study proceeding. Also a deviation domain (DV) or log may exist to help determine if this was reported on during the study by the study team. Where additional information from CO or DV existed we used it to determine our approach to the start of Treatment EPOCH. Where no additional explanation was given then we reviewed the subject visit domain (SV), any dispensing information (DA) and the expectations from the Protocol. If no further insights could be taken we took the conservative approach that the earliest date should be used for the start of the Treatment EPOCH which in turn assumed the subject took drug for longer than they may have done. In all cases the resolution was noted in the Study Data Reviewer's Guide.

Date/time of randomisation after randomisation visit

On one study a subject had the following timeline:

- Randomisation visit - 2012-06-27
- First application expected at randomisation visit
- Exposure start date - 2012-06-28
- Randomisation according to IWRS - 2012-06-28
- Drug dispensed - 2012-06-28

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The expected date of first drug at the subject's randomisation visit was earlier than other application information so the date of randomisation according to IWRS was used as date of first drug application and hence the start of the Treatment EPOCH.

On another study a subject:

- Randomisation visit (visit number 2) - 2013-07-31
- First application expected at randomisation visit
- Exposure start date - 2013-07-31
- Randomisation according to IWRS - 2013-08-08
- First drug dispensed - 2013-07-31
- Visit 4 for the subject - 2013-08-08

The Investigator did not add any comments explaining what happened. We used the date of randomisation visit rather than IWRS date of randomisation for beginning of Treatment EPOCH taking the approach that we were at worst increasing the time the subject was exposed to the medication.

Date/time or visit of first dose Randomisation



In an Open Label study a subject had their recruitment visit on 2012-10-01. Subjects could only apply medication for 3 days. Their last dose was stated as 2012-10-04. In this instance we had an investigator comment about the first/last dose. The investigator had to assess the subject the day after their last dose yet was unavailable on that day so delayed the start of treatment to suit them.

“DRUG DISPENSED ON 1ST OCT, 2012 ON SCREENING DAY DRUG HAS BEEN GIVEN TO THE PATIENT TO START ON 2ND OCT”

We amended the date of first dose on the completed study to be the 2012-10-02 in our EX data and used this as the start of Treatment EPOCH.

Date/time of first treatment is before the date/time the subject is dispensed medication

In another blinded study we came across this data:

- Randomisation visit – 2013-08-16
- First application expected at randomisation visit
- Subject randomised - 2013-08-19
- First drug dispensed - 2013-08-16

According to a comment the subject returned to site for randomisation following a washout period. All subjects in this trial were guaranteed entry if they completed their washout. IWRS had completed randomisation and could not be opened at that time. The investigator intervened and the data was captured as such.

“SUBJECT RETURNED FOR DAY 0 RANDOMIZATION ON 16AUG2013 AFTER A 2-WEEK WASHOUT PERIOD. ENROLLMENT CLOSURE OCCURRED ON 16AUG2013 ...THE STUDY COORDINATOR RANDOMLY PULLED AND ASSIGNED KIT # ... TO THE SUBJECT. ON 19AUG2013 THE SYSTEM WAS UNLOCKED AND ALLOWED RANDOMIZATION TO OCCUR FOR THIS SUBJECT...”

The derivation for the start of Treatment EPOCH used was the date of the randomisation visit.

Date/time of first dose Medication dispensed



A treatment diary is to enable capturing the information of when a subject applies medication and improve / indicate compliance to administering the drug. However it can also be an issue if the subject's data does not agree with the investigator entered CRF data. Take for example a study with the following 2 subjects.

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Subject 1:

- First dose application date according to investigator on CRF - 2013-07-03
- First dose application date according to treatment diary - 2013-07-04
- First dose in Exposure data (EX) - 2013-07-04
- First dose according to RFXSTDTC in DM - 2013-07-03
- Drug first dispensed - 2013-07-03
- No comment or deviation detailing the issue.

Subject 2:

- First dose application date according to investigator on CRF - 2013-07-09
- First dose application date according to treatment diary - 2013-07-13
- First dose in Exposure data (EX) - 2013-07-13
- First dose according to RFXSTDTC in DM - 2013-07-12
- Drug dispensed - 2013-07-09
- Comment confirming first date as 2013-07-12.

In both cases we updated the exposure data for the subject to include the start date as specified in the DM record. For the second subject the date of first application from the CRF was not used. The start of Treatment EPOCH was taken from the new date of first dose (2013-07-12) which had been confirmed in a comment.

Investigator recorded date/time of first dose

Patient diary date/time of first dose



END OF TREATMENT ISSUES

At LEO Pharma a collection of the date of last treatment is made on the end of study page. This may conflict with the compliance data collected at the last on-treatment visit, the date the subject completed the last on-treatment visit, or the collected date/time of treatment (if collected more than once), all of which we use to derive EPOCH. Additionally, treatment diaries can conflict with the CRF information as subject reported data cannot be subjected to the same data management queries as the rest of the CRF data. A review of the SV, CO, or DV domains may give light to these issues. In these instances the accompanying data determines the outcome of the end of Treatment EPOCH. This may result in some programming on a subject level which was noted in the Study Data Reviewer's Guide.

Two different treatment end dates

An example of a subject from a Blinded Trial:

- Diary last application date - 2013-09-11
- End of Trial form last application - 2013-09-10
- Final visit - 2013-09-11
- CRF response confirmed they had applied the medication as per protocol

We took the approach that the investigator data was more accurate and that the subject completed their treatment on 2013-09-10. The application on 2013-09-11 was programmed to be associated with the Follow-up EPOCH as it was inconsistent with other application information. We will not delete data where it has been supplied by the subject however this data was not subject to data management queries. The exposure, compliance, and drug accountability for the subject were checked against the study report. While the trial was active the study team had based their results on the date supplied on the CRF and not the diary date.

Date/time of last treatment after last recorded visit

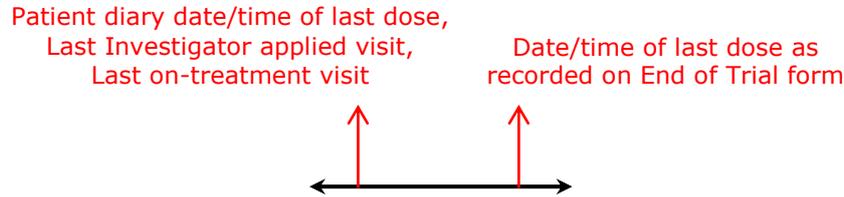
Another trial subject example:

- Last application date - 2013-08-14
- Last visit - 2013-08-13
- Subject lost to follow-up

We set the end of treatment EPOCH to be the date of last recorded dose on the CRF, not the last on-treatment visit for this subject. For most subjects the last on-treatment visit was the end of Treatment EPOCH; however for

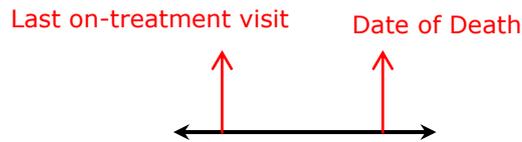
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some subjects who did not complete we considered other data such as their last treatment date to determine the end of Treatment EPOCH.



End of Trial date is after death date

The data in SV should contain all visits where the subject positively saw or spoke to the investigator and should not include the dates that the investigator entered the information onto the CRF. Our End of Trial forms were expected to be entered at study completion visit and we included a section to capture the date that this form was completed. Initially, this date was included in the SV domain and used in the derivation of EPOCH. However, we subsequently removed this date from the SV domain after finding a few occasions where the SV domain had the End of Trial form date after a subject had died which in turn was being used in the calculation of EPOCH. At this point we realised that for some subjects the End of Trial date could be the date the form was completed and not necessarily the date of last visit. Ensure that fatal adverse events and comments that may mention fatalities / death are looked into before finalising the capture all of a study's essential time points.



Medication returned after last visit

- When is the end date of a subject on a study?
- Can we assume that it was the subject who returned the medication at the site post study?
- Can we assume that the subject continued using the drug after their intended time in the study?
- Can we assume that because the subject did not return all dispensed medication that they continued to use it post study?

These were questions that we considered when deriving EPOCH. We decided that the return of medication could not be counted as a true subject visit beyond their last scheduled or follow-up visit as there was no guarantee that the subject had seen the investigator, that it was the subject who returned the medication, or that a subject would have used any remaining medication beyond their agreed time in the study. Therefore it was decided that the date of return of medication would not contribute to deriving the subject's last date in a study EPOCH.



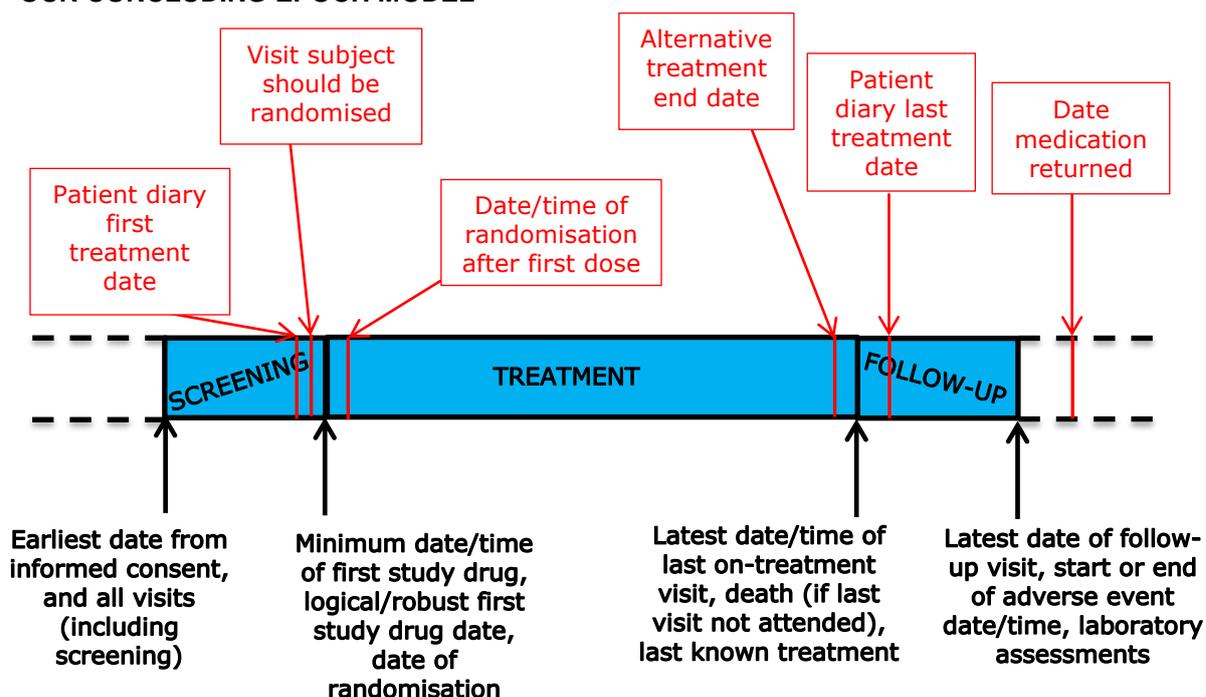
RESOLVING THE ISSUES

To derive EPOCH in a completed study we had to interrogate and understand the data for subjects to a greater extent than may usually be done during reporting a study. Comments were often a good starting place to see what happened. Often an investigator wrote a comment about the subject's course through the study, particularly if there had been a deviation. A review of the study deviations was included; often they had information related to subject data discrepancies. CRF data is subject to data management queries where often patient diaries are more difficult to validate. Hence CRF data was usually assumed to be more robust and reliable than diary data. Considering the confirmed data points for a subject such as the SV or DA domain also helped to derive EPOCH.

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After reviewing all the available data related to subjects who did not fit the elementary model, careful programming and sometimes the implementation of additional assumptions were included to finalise the EPOCH model for a study. For start times of epochs the minimum of selected dates was used to determine the subject's status in EPOCH time. For EPOCH end times the maximum of selected dates was used. Decisions and anomalies were noted in the Study Data Reviewer's Guide.

OUR CONCLUDING EPOCH MODEL



MORE COMPLEX STUDY DESIGNS

Cross-over designs and studies which mix models of blinded, open-label, and cross-over study types have some additional issues. Deciding what model should be used or how it should be constructed needs careful thought of how the data will fit.

On one occasion a suitable EPOCH model was derived for a study but after applying and reviewing the outcome against the study report it was decided that a less complex model would be better applied to meet the decisions and outcome of the study as it was written then. In a second study we applied a standard EPOCH design to a model that in the process of reviewing Adverse Event tables we realised a more complex structure was required to ensure the EPOCH values were in line with what was reported in the CSR.

When deriving EPOCH in a completed study ensure that tabular results and any assumptions, created as part of the study results, are involved in the derivation. Care should be taken that any changes to SDTMs do not result in a change in the study results.

Tables of Adverse Events within particular treatment timings

Adverse events were assigned to relevant specific time point(s) in a study and the start of each adverse event can only be attributed to one EPOCH. In a study with completed study reports decisions had already been taken about the best way to handle the data. Some adverse events were connected with multiple time points whereas others are attributed to one.

An adverse event which occurred on the start date of the 2nd treatment period was originally programmed as part of an EPOCH derivation to be in the 2nd treatment period of a cross over design but in the study tabulations it was associated with the 1st treatment period as assumed to occur before the start of the second treatment. The event

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likely fell into the washout for the 1st treatment and agreed while the study was active; the programming for EPOCH was updated to reflect this.

An adverse event started in the 1st treatment period but worsened and was still active in the 2nd treatment period hence it is counted in both tables of the treatment periods. The event could only associate with one EPOCH which was decided to be the 1st treatment EPOCH. We had to ensure that when reviewing the outcome of EPOCH against the study tables this was taken into consideration when counting occurrences.

CONCLUSION

During an active study, EPOCH should be determined and programmed prior to database lock to allow any issues to be investigated. It is best to know and understand the data in order to resolve EPOCH issues while data and the study team can still be queried. Applying EPOCH prospectively to active studies is the ideal method.

In the instance of a study where the report has been completed, the addition of EPOCH to SDTMs should not change the results of the study. Applying EPOCH to any study, particularly a completed study, requires constant attention to understand each subject's timeline. Additional checking to ensure that study results are unaffected by adding EPOCH to the study data is necessary. In short, careful programming is required when applying EPOCH in Reverse.

REFERENCES

¹ CDISC Study Data Tabulation Model (Version 3.1.2)

CONTACT INFORMATION

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