

Imputing Partial Dates

Introduction

"Missing values represent a potential source of bias in a clinical trial. Hence, every effort should be undertaken to fulfil all the requirements of the protocol concerning the collection and management of data. In reality, however, there will almost always be some missing data. A trial may be regarded as valid, nonetheless, provided the methods of dealing with missing values are sensible, and particularly if those methods are pre-defined in the protocol. Definition of methods may be refined by updating this aspect in the statistical analysis plan during the blind review. Unfortunately, no universally applicable methods of handling missing values can be recommended. An investigation should be made concerning the sensitivity of the results of analysis to the method of handling missing values, especially if the number of missing values is substantial." ICH E9 Statistical Principles for Clinical Trials.

General Problem

A partial date is simply any date where the date is incomplete, but not wholly missing. This may be the day or month or year or any combination of two of these. More commonly in clinical trials, the day and/or month are missing. In these cases, we may be asked to impute a reasonable date or time.

Partial dates are most common in variables where the date is historical information (e.g. prior medication, medical history). This is a general problem as the subject understandably does not recall a wholly accurate start date for a medication they have been taking for a number of years, or when a particular medical event occurred during childhood.

For current dates, there are several measures which can be put in place at the point of data collection to minimise the occurrence of incomplete data. This is especially the case with the increased use of electronic Case Report Forms (eCRFs) where the data is entered directly into the database by the subject or investigator and point of entry checks can be put in place to reduce the number of partial dates.

Where it has not been possible to eliminate the occurrence of partial dates, it is imperative that they are handled correctly to retain the integrity of the data. In the previous examples of longstanding medication use or childhood disease, it is unlikely to impact data integrity if a date is imputed which is a month away from the actual date; but it does still need to be handled correctly.

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However, if a missing date is the end date of a prior medication which could potentially have a long half-life, it could impact on the interpretation of efficacy of the study drug. In this situation, making the most appropriate approximation for the missing information is more important.

Imputation Rules

How you impute often depends on the type of date. For example, if you have a month and year but no day, you might want to impute the day to be the first of the month, the middle of the month, or the last of the month.

Assume the worst / make the most conservative judgment when imputing Adverse Event and concomitant medication start dates.

The purpose of imputing a start date is to help define whether the AE/Medication started while taking study drug.

Adverse Event / Concomitant Medication

Partial/Missing Start Date	Missing day – Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date
	Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date
	Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
	When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or med.

Make the most conservative judgment when imputing end dates. Duration of AE/med should not be derived using imputed dates.

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Adverse Event / Concomitant Medication

Partial/Missing Start Date	Missing day - Impute the last day of the month unless month is same as month of first dose of study drug then impute last dose date Missing day and month – impute 31st December unless year is the same as first dose date then impute last dose date Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present / medication is still being taken (i.e. do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.
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When to Impute Imputation Flags

When dates and times are imputed, a flag should be provided to show that this is an imputed rather than actual date. CDISC ADaM has some rules to follow for both date and time imputations.

- Date imputation flags should have the name suffix –DTF and contain “D” for day, “M” for month, or “Y” for year. Note that “M” implies both day and month are imputed, and “Y” implies day, month, and year are all imputed.
- Time imputation flags should have the name suffix –TMF and contain “S” for second, “M” for minute, or “H” for hour. Note that “M” implies both second and minute are imputed, and “H” implies second, minute and hour are all imputed.