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POINTS TO CONSIDER ON MISSING DATA

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Note:

Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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POINTS TO CONSIDER ON MISSING DATA

1. INTRODUCTION

Missing data are a potential source of bias when analysing clinical trials. Interpretation of the results of a trial is always problematic when the number of missing values is substantial. This problem is only partially covered in ICH E9 (Statistical Principles of Clinical Trials) and there is no regulatory guidance currently available on this issue.

There are many possible sources of missing data, affecting either complete subjects or specific items. There are many possible reasons for missing data (e.g. patient refusal to continue in the study, treatment failures or successes, adverse events, patients moving) not all of which are related to study treatment. Different degrees of data incompleteness can occur, i.e. measurements may be available only at baseline, or may be missed for one or several follow-up assessments. Even if the study protocol is completed, some data may remain simply uncollected.

Missing data violate the strict ITT principle: measurement of all patient outcomes regardless of protocol adherence and analysis performed by treatment assigned regardless of which treatment patients actually received. Full set analysis generally requires the imputation of values for the unrecorded data. Actually, even the per protocol analyses might also require the use of some imputation. This process can have, depending upon the amount and type of missing data, a crucial influence on the final results of a clinical trial.

The extent to which missing values lead to biased conclusions about the size and existence of any treatment effect is influenced by many factors. Among these are the relationship between missingness, treatment assignment, and outcome; and the type of measure employed to quantify the treatment effect (e.g. an absolute vs. a relative measure).

The types of bias that affect interpretation will depend upon whether the objective of the study was to show a difference or demonstrate equivalence/non-inferiority.

It should be noted that the strategy employed to impute missing values might in itself provide a source of bias.

2. THE EFFECT OF MISSING VALUES ON DATA ANALYSIS AND INTERPRETATION

If missing values are handled by simply excluding any patients with missing outcomes from the analysis, the following problems may affect the interpretation of the trial results.

2.1 Power and Variability

The sample size and the variability of the outcomes affect the power of a clinical trial. Power is greater the larger the sample size and the smaller the variability.

A reduction in the number of valid cases available for analysis due to incompleteness of data may result in a reduction of the statistical power –the greater the number of missing values the greater the likely reduction in power-.

In addition, non-completers might be more likely to have extreme values (treatment failure leading to dropout, extremely good response leading to loss of follow-up). Therefore, the loss of these non-

completers could lead to an underestimate of variability and hence artificially narrow the confidence interval for the treatment effect.

2.2 Bias

Bias is the most important concern resulting from missing data and may affect:

- The estimation of the treatment effect.
- The comparability of the treatment groups.
- The representativeness of the study sample in relation to the target population.

While the reduction of the statistical power is mainly related to the number of missing values, the risk of bias in the estimation of the treatment effect depends upon the relationship between missingness, treatment and outcome:

- In principle missing values will not be expected to lead to bias if they are only related to the treatment (an observation is more likely to be missing on one treatment arm than another) but not to the real value of the unobserved measurement (poor outcomes are no more likely to be missing than good outcomes).
- Conversely, if the unmeasured observation is related to the real value of the outcome (e.g. the unobserved measurements have an higher proportion of poor outcomes), this will lead to bias even if the missing values are not related to treatment (i.e. missing values are equally likely in all treatment arms).
- Missing observations will lead to bias if they are related to both the treatment and the unobserved outcome variable (e.g. missing values are more likely in one treatment arm because it is not as effective).

In most cases it is difficult or impossible to elucidate whether the relationship between missing values and the unobserved outcome variable is completely absent. Thus it is sensible to adopt a conservative approach, considering missing values as a potential source of bias.

3. HANDLING OF MISSING DATA

In the design and conduct of a clinical trial all efforts should be directed towards minimising the amount of missing data likely to occur. Despite these efforts some missing values will generally be expected. The way these missing observations are handled may substantially affect the conclusions of the study.

3.1 Complete case analysis

A possible approach to handling incomplete data is to ignore them and to perform the statistical analysis with complete data only (complete case analysis). Some problems associated with this approach are discussed in section 2. In light of these difficulties complete case analysis is not generally acceptable as the primary approach to data analysis, although it may be appropriate in certain circumstances.

- In exploratory studies, especially in the initial phases of drug development.
- In confirmatory trials as a secondary supportive analysis to illustrate the robustness of conclusions.

Complete case analysis violates the intention to treat principle. More importantly it is subject to bias, and thus cannot be recommended as the primary analysis in a confirmatory trial.

3.2 Imputation of missing data

3.2.1 Scope of imputation

As missing values may affect different types of variables, the process of imputation might consider not only the main variables, but also the secondary efficacy, safety variables, baseline variables, and covariates. In some cases the latter variables may be of importance, because excluding unrecorded data from analysis may lead to both bias and losses of power, especially in the presence of confounding variables.

3.2.2 Methods for imputation of missing data

The statistical analysis of a clinical trial generally requires the imputation of values to those data that have not been recorded. Many techniques have been used for the imputation of missing data, but none of them can be considered as the gold standard for every situation.

To cope with situations where response collection is interrupted after one point, one widely used method is last observation carried forward –LOCF-. This analysis uses the last measured response as an endpoint by itself, not necessarily attached to a particular study time point.

This method is likely to be acceptable if measurements are expected to be relatively constant over time. However in clinical situations where measurements are not expected to be constant over time, such as Alzheimer's disease where the patient's condition is expected to deteriorate over time, the method is less acceptable. In some cases, LOCF may provide an acceptably conservative approach depending on the rate and timing of missingness in each treatment arm. For instance, in depression, where the condition is expected to improve spontaneously over time, this method might be considered conservative if patients in the experimental group tend to withdraw earlier and more frequently due to safety reasons.

Factors that affect the acceptability of the LOCF method include differences between the treatment groups in the proportion and timing of withdrawals, the direction of any spontaneous changes over time, and the reason for the withdrawals.

Best or worst case imputation, assigning the worst possible value of the outcome to dropouts for a negative reason (treatment failure) and the best possible value to positive dropouts (cures), is another approach that may be considered, provided it is applied conservatively. These techniques may be useful to assess a lower bound of efficacy as a demonstration of robustness.

Another simple approach for imputing missing data is to replace the unobserved measurements by values derived from other sources. Possible sources include information from the same subject, from other subjects with similar baseline characteristics, a predicted value from an empirically developed model, historical data, etc.

Most methods face the risk of biasing the standard error downwards by estimating a central value and ignoring its uncertainty. This risk can be avoided by some techniques based upon maximum-likelihood methodology and with multiple imputation methods. Maximum-likelihood methods have been proposed for the imputation of missing values, as have multiple imputation methods. The maximum-likelihood based strategies fit a model by an iterative process (e.g. the Expectation Maximisation algorithm). Multiple imputation methods generate multiple copies of the original data set replacing missing values by randomly generated values, and analyse them as complete sets.

Some statistical approaches are less sensitive to the presence of missing data. Mixed effects models have been proposed for use in a variety of situations, such as when the outcome is measured repeatedly over time and the time of measurement may be considered as a random variable; these models may estimate a slope to summarise each patient's response. When the outcome measure is time to event, survival models which take into account censored observations may be used. However, these approaches assume that there is no relationship between treatment and the missing outcome, and generally this cannot be assumed.

4. GENERAL RECOMMENDATIONS

Unfortunately, there is no universally accepted methodological approach for handling missing values. Nevertheless there are some rules which should be considered when handling missing data.

4.1 Avoidance of missing data

Several major difficulties arise as a result of the presence of missing values and these are aggravated as the number of missing values increases. Thus, it is extremely important to avoid the presence of unobserved measurements as much as possible, by favouring designs that minimise this problem, as well as strengthening data collection regardless of the patient's adherence to the protocol and encouraging the retrieval of data after the patient's drop-out.

It may be useful to anticipate the number of missing values likely to be observed in the trial. There is no rule regarding the maximum number of missing values that could be acceptable. It may be affected by a number of factors: a) the nature of the outcome variable. The occurrence of missing values is expected to be lower when the outcome variable is mortality (e.g. cardiovascular trials), than when the outcome is more difficult to assess and requires the active participation of patients and/or sophisticated methods of diagnosis. b) The length of the clinical trials: the longer the follow up the greater the likelihood of missing values. c) Missing values are more frequent in those diseases where the adherence of patients to the study protocol is usually low (e.g. Psychiatric disorders). d) The treatment modalities (e.g. surgical versus medical treatment).

4.2 Design of the study. Relevance of predefinition.

There is no universally applicable method of handling missing values, and different approaches may lead to different results. As such it is essential to pre-specify the selected methods in the statistical section of the study protocol. This section must include a detailed description of the selected method and a justification of why the method to be applied is expected to be optimal. Furthermore, an estimate of the foreseen and acceptable amount of missing data is highly recommended: firstly because this may have repercussions for the sample size calculation, and secondly because the reliability of imputation procedures becomes more uncertain as the number of missing values increases. The final report must include documentation of any deviation from the expected number of missing values and a discussion of whether the pre-defined analysis is still defensible.

It is considered of particular importance to ensure that the selected method is a conservative approach and does not favour the study's working hypothesis (intentionally or unintentionally). For instance, missing data handling in non-inferiority trials should avoid underestimation of differences between treatments. Similarly, the method of handling missing data in superiority trials should avoid an overestimation of differences between treatments.

Because of the unpredictability of some problems, it may be acceptable to allow in the study protocol the possibility of updating the strategy for dealing with missing values in the statistical analysis plan, or during the blind review of the data at the end of the trial. Relevant deviations from and amendments of the pre-specified plan should be clearly documented and justified. In addition, the time-point at which these deviations and amendments were decided and implemented in relation to the blinding of the data must be clearly identified. Methods for the documentation of these changes can be found in ICH E9.

4.3 Analysis of missing data

It might be useful to note whether there is any indication that the proportion and the time of appearance of missing values differ among the treatment groups. Analyses that investigate missing data imbalance in all relevant factors and whether patients with and without missing values have different characteristics at baseline might also be conducted.

4.4 Sensitivity analysis

Sensitivity analysis –a set of analyses showing the influence of different methods of handling missing data on the study results- will help to justify the choice of the particular method applied. These sensitivity analyses may be presented as additional support to the main analysis.

Some simple ways of performing a sensitivity analysis are:

- To compare the results of two analyses, one assigning the best plausible outcome to all missing values in both groups, and the other assigning the worst possible outcome to all missing values in both groups.
- To compare the results of two analyses, one assigning the best possible outcome to missing values in the control group and the worst possible to those of the experimental group, and vice-versa.
- To compare the results of the full set analysis to those of the complete case analysis.

Each sensitivity analysis should be designed to assess the effect on the results of the particular assumptions made in imputation. The sensitivity analysis should be planned and described in the protocol and/or in the statistical analysis plan and any changes must be documented and justified in the study report.

If the results of the sensitivity analyses are consistent and lead to reasonably similar estimates of the treatment effect this provides some assurance that the lost information had little/no effect on the overall study conclusions. In this situation the robustness of the results is clear and the missing values will not generally be considered to be a serious source of concern. Conversely, if a sensitivity analyses raises inconsistent results, their repercussions on the conclusions of the trial must be discussed. In certain circumstances, when the missing may be considered as a source of concern, the validity of the trial might be compromised.

4.5 Final report

A detailed description of the pre-planned methods to be used for handling missing data and any amendments of that plan should be included in the statistical methods section.

A discussion of the number, time, pattern and possible implications of missing values in efficacy and safety assessments should be included in the clinical report. Imputed values must be listed and identified.

As stated before, a sensitivity analysis can give robustness to the conclusions of a study.