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MISSING DATA: THE POINT OF VIEW OF ETHICAL COMMITTEES

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Reporting and Ethics

- The reporting of research is not a purely objective task
- Numerous reporting techniques (such as statistical analysis techniques) present numerous options
- Some options are more scientifically valid and ethical than others

Missing data: concerns of the EC

- Whether the available data would be biased
- Whether the study will have sufficient power

Reference documents

- ICH E9 guidelines Statistical Principles for Clinical Trials (1998)
- CPMP points to consider on missing data and recommendation for the revision (2001, 2007)
- A Standard for the Scientific and Ethical Review of Trials - ASSERT statement (2005)
- Consolidated Standards of Reporting Trials - CONSORT statement (2001)

ASSERT and CONSORT statements

Table 5. **Information Required To Document the Flow of Participants through Each Stage of a Randomized, Controlled Trial**

Stage	Number of People Included	Number of People Not Included or Excluded	Rationale
Enrollment	People evaluated for potential enrollment	People who did not meet the inclusion criteria People who met the inclusion criteria but declined to be enrolled	These counts indicate whether trial participants were likely to be representative of all patients seen; they are relevant to assessment of external validity only, and they are often not available
Randomization	Participants randomly assigned		Crucial count for defining trial size and assessing whether a trial has been analyzed by intention to treat
Treatment allocation	Participants who received treatment as allocated, by study group	Participants who did not receive treatment as allocated, by study group	Important counts for assessment of internal validity and interpretation of results; reasons for not receiving treatment as allocated should be given
Follow-up	Participants who completed treatment as allocated, by study group Participants who completed follow-up as planned, by study group	Participants who did not complete treatment as allocated, by study group Participants who did not complete follow-up as planned, by study group	Important counts for assessment of internal validity and interpretation of results; reasons for not completing treatment or follow-up should be given
Analysis	Participants included in main analysis, by study group	Participants excluded from main analysis, by study group	Crucial count for assessing whether a trial has been analyzed by intention to treat; reasons for excluding participants should be given

ICH E9: 1.2 Scope and Direction (continued)

- The principles … primarily relevant to clinical trials conducted in the later phases of development, many of which are confirmatory trials of efficacy … (but) should be applied as far as possible to all phases of clinical development.
- … the principles … deal with minimizing bias and maximizing precision.

ICH E9: 1.2 Scope and Direction

- … it is important to evaluate the robustness of the results and primary conclusions of the trial … the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis.
- …(This) implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches.

ICH E9: 2.3 Design Techniques to Avoid Bias

- Bias can also be reduced at the design stage by specifying procedures in the protocol aimed at minimizing any anticipated irregularities in trial conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems and to handle the problems that do occur in the analysis of data.

ICH E9: 3.3.2 Trials to Show Equivalence or Non-inferiority (continued)

- The equivalence (or non-inferiority) trial is not conservative in nature, so that many flaws in the design or conduct of the trial will tend to bias the results towards a conclusion of equivalence. For these reasons, the design features of such trials should receive special attention and their conduct needs special care.
- For example, it is especially important to minimize the incidence of violations of the entry criteria, noncompliance, withdrawals, losses to follow-up, missing data, and other deviations from the protocol, and also to minimize their impact on the subsequent analyses.

ICH E9: 3.3.2 Trials to Show Equivalence or Non-inferiority

- There are also special issues in the choice of analysis sets. Subjects who withdraw or drop out of the treatment group or the comparator group will tend to have a lack of response; hence the results of using the full analysis set may be biased toward demonstrating equivalence.

ICH E9: 3.5 Sample Size

- Using the usual method for determining the appropriate sample size, the following items should be specified: … the approach to dealing with treatment withdrawals and protocol violations.
- Sample size calculations should refer to the number of subjects required for the primary analysis. If this is the full analysis set, estimates of the effect size may need to be reduced compared to the per protocol set. This is to allow for the dilution of the treatment effect arising from the inclusion of data from patients who have withdrawn from treatment or whose compliance is poor. The assumptions about variability may also need to be revised.

ICH E9: 5.1 Prespecification of the Analysis

- The statistical analysis plan may be written as a separate document to be completed after finalizing the protocol. In this document, a more technical and detailed elaboration of the principal features stated in the protocol may be included …
- The plan should be reviewed and possibly updated as a result of the blind review of the data and should be finalized before breaking the blind. If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment.

ICH E9: 5.2 Analysis Sets (continued)

The protocol should:

- specify procedures aimed at minimizing any anticipated irregularities in study conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values …
- consider ways both to reduce the frequency of such problems and to handle the problems that do occur in the analysis of data.

ICH E9: 5.2 Analysis Sets

- Possible amendments to the way in which the analysis will deal with protocol violations should be identified during the blind review.
- Decisions concerning the analysis set should be guided by the following principles: (1) to minimize bias and (2) to avoid inflation of Type I error.

ICH E9: 5.2.1 Full Analysis Set (continued)

- Special problems arise in connection with subjects withdrawn from treatment after receiving one or more doses who provide no data after this point, and subjects otherwise lost to follow-up, because failure to include these subjects in the full analysis set may seriously undermine the approach.
- Imputation techniques, ranging from the carrying forward of the last observation (LOCF) to the use of complex mathematical models, may also be used in an attempt to compensate for missing data.

ICH E9: 5.2.1 Full Analysis Set

- Other methods employed to ensure the availability of measurements of primary variables for every subject in the full analysis set may require some assumptions about the subjects' outcomes or a simpler choice of outcome (e.g., success/failure). The use of any of these strategies should be described and justified in the statistical section of the protocol, and the assumptions underlying any mathematical models employed should be clearly explained.
- Because of the unpredictability of some problems, **it may sometimes be preferable to defer detailed consideration of the manner of dealing with irregularities until the blind review of the data at the end of the trial**, and, if so, this should be stated in the protocol.

ICH E9: 5.3 Missing Values and Outliers

- A trial may be regarded as valid, nonetheless, provided the methods of dealing with missing values are sensible, particularly if those methods are predefined 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.

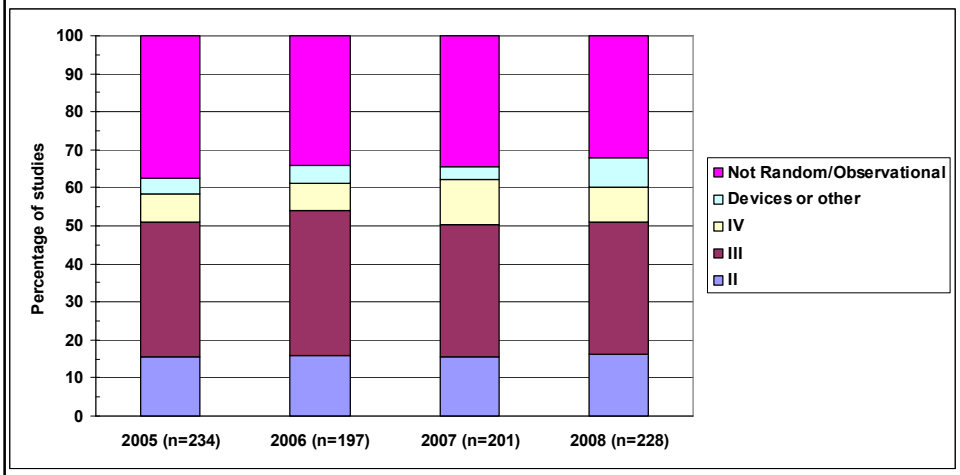
CPMP points to consider on missing data

- Power is greater the larger the sample size and the smaller the variability.
- A reduction in the number of valid cases … due to incompleteness of data may result in a reduction of statistical power.
- … non completers might be more likely to have extreme values … leading to an underestimate of variability and hence narrow the confidence interval for the treatment effect.

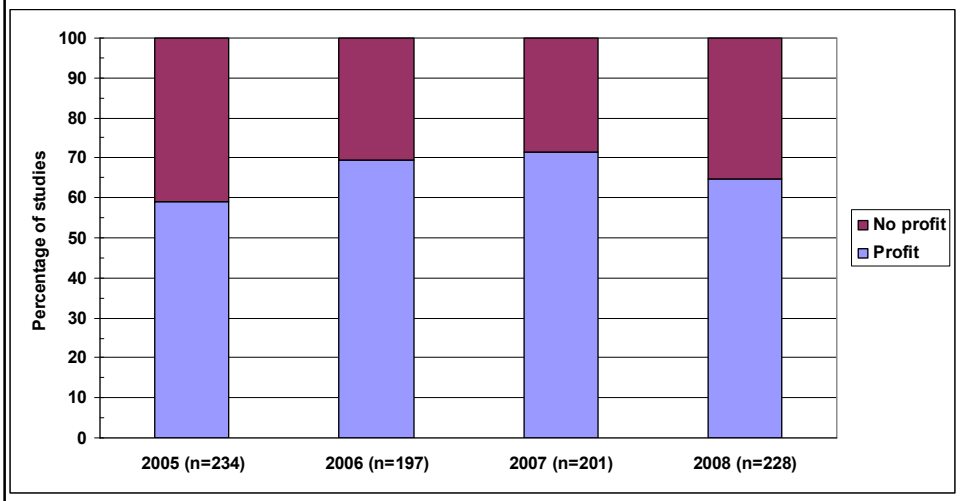
Relevance of pre-specification

- It is essential to pre-specify the missing values handling methods in the study protocol, including:
  - a detailed description of the selected methods
  - the justification of why the method is expected to be optimal
  - possibly, an estimate of the foreseen amount of missing data
- It is important that the selected method is a conservative one not favouring the hypothesis under study:
  - in a superiority trial, should avoid treatment effect overestimation
  - in a non-inferiority trial, should avoid treatment effect underestimation

The real world: studies presented at the University of Padua EC

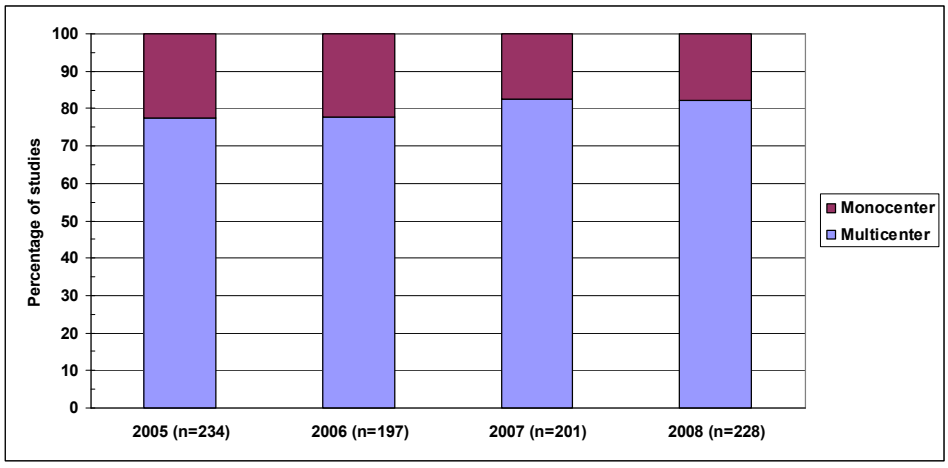


Sponsored research



Studies presented at the University of Padua EC in the year 2005-2008

Multicenter research



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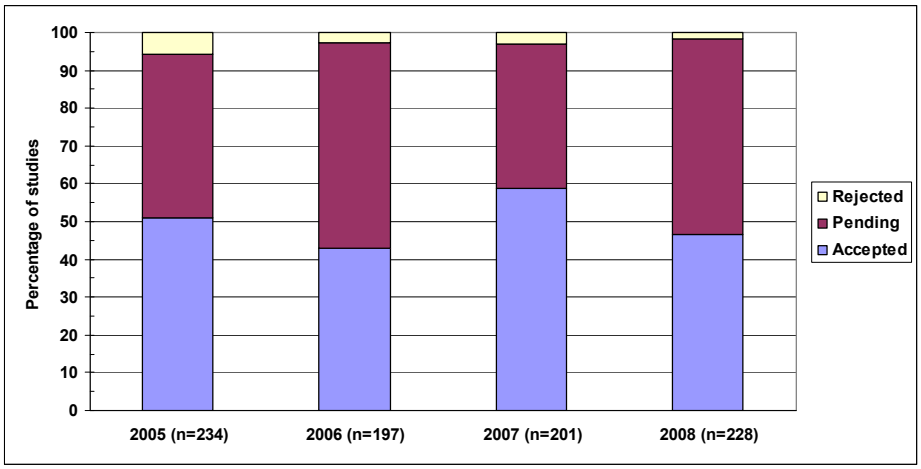
Protocol evaluation



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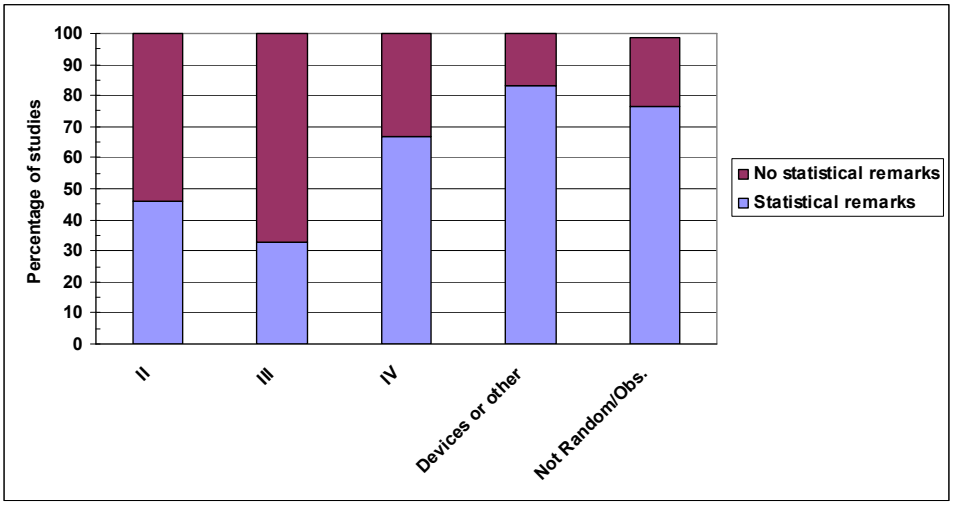
Statistical evaluation



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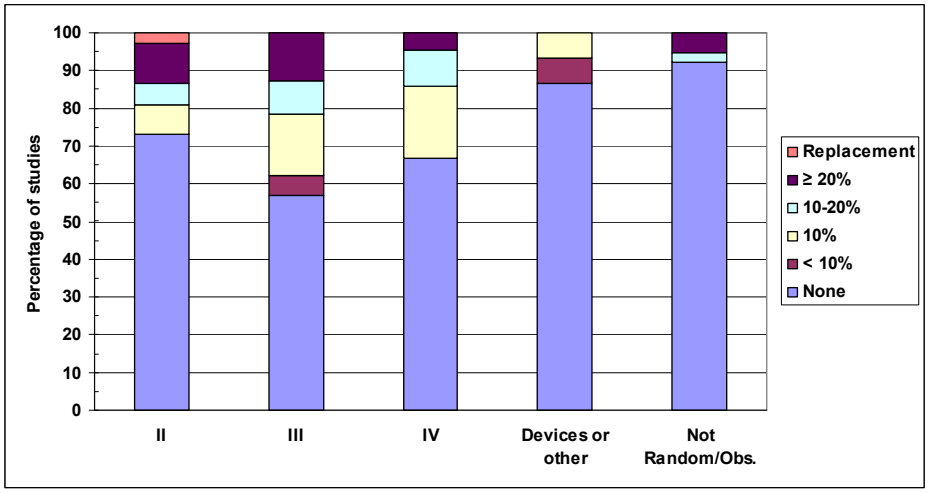
Sample size inflation for dropouts



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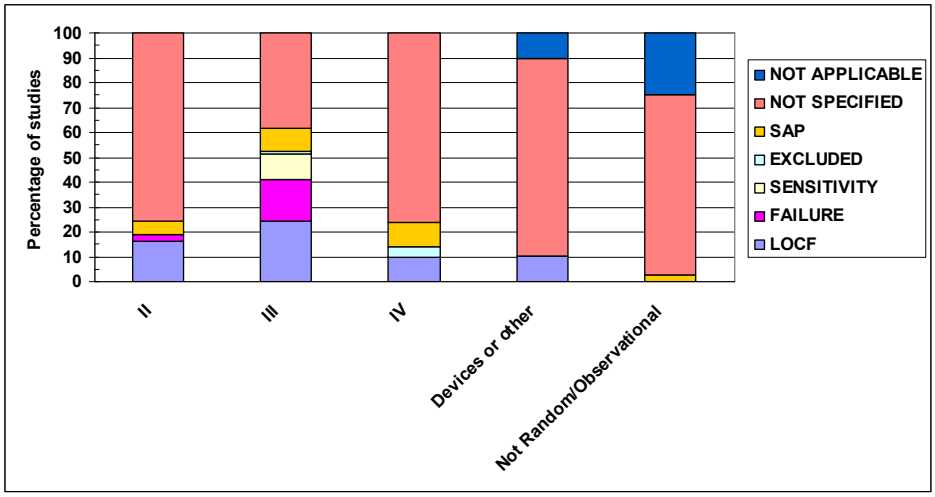
Missing data handling



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Conclusion

- Specify missing data handling in the protocol
- In doing that, consider:
  - the hypothesis under study (superiority, equivalence, non inferiority)
  - the set of patients planned for the analysis (per-protocol, intention-to-treat, safety, other)
  - the type of response variable
  - the expected type of missing data (completely at random, at random, not at random)
  - the opportunity of a sensitivity analysis