Statistical details in the protocol: how much is enough?

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Why discuss statistical details in the protocol now?

Protocol content is being standardized through the implementation of ICH M11, including the harmonized protocol template

ICH E6(R3), E8(R1), E9/E9(R1), and EU-CTR all touch on statistical content in protocols, but guidance remains relatively high-level, leaving room for interpretation

- ICH E6(R3) recommends a 'clear and concise protocol'

Appropriate level of statistical detail in the protocol has direct implications for:

- trial integrity, including assessment of pre-specification,
- whether later changes require a protocol amendment vs. a SAP amendment, and
- clarity and conciseness of protocol

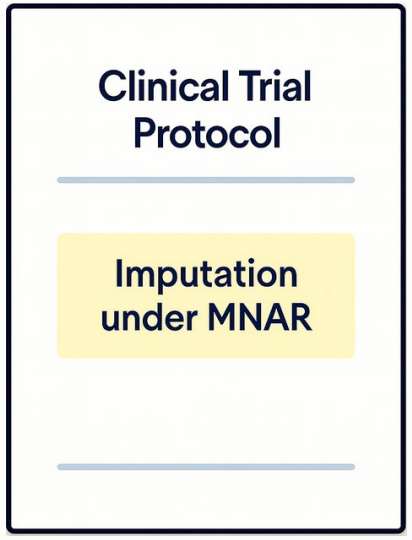
➢ **Need for clearer guidance on which statistical details are essential for the protocol and which are more appropriately documented in the SAP.**

Motivating example: multiple imputation in the primary analysis

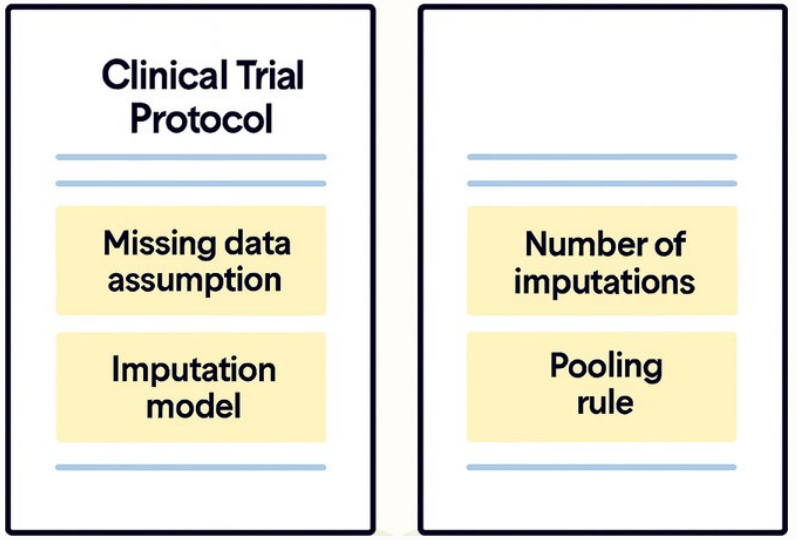
Multiple imputation is frequently used in primary analyses, but a fully specified approach requires considerable detail

Clinical trial teams have encountered differing regulatory expectations for the same type of analysis

High-level strategy is sufficient
(e.g., "imputation under MNAR")



Request for full pre-specification
in the protocol



Questions for the panel

1. **Which principles should guide the level of statistical detail included in a clinical trial protocol (vs. the SAP)?**

2. **Applying those principles to a primary analysis using multiple imputation for missing data, which of the following aspects should be specified in the protocol, as opposed to the SAP?**
   - Analysis model applied to each completed dataset
   - Missing data assumption (e.g., MAR or jump-to-reference)
   - Method for pooling results across completed datasets (e.g., Rubin's rule)
   - Imputation model (e.g., multivariate normal imputation, fully conditional specification), including covariates, prior distributions, and related implementation details
   - Number of imputations

3. **Which aspects of the statistical analysis need to be justified, and where should they be documented (protocol versus SAP)?**

Thank you

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Backup

Definition of protocol and SAP

Protocol: “A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol usually also gives the background and rationale for the trial [...]” ICH E6(R3)

SAP : “A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.” ICH E9

ICH E6 (R3): level of statistical detail in prtocol

B.10	**Statistical Considerations**
B.10.1	A description of the statistical methods to be employed, including timing and purpose of any planned interim analysis(ses) and the statistical criteria for the stopping of the trial.
B.10.2	The number of participants planned to be enrolled and the reason for the choice of sample size, including reflections on or calculations of the power of the trial and clinical justification.
B.10.3	The level of significance to be used or the threshold for success on the posterior probability in a Bayesian design.
B.10.4	The selection of participants to be included in the planned analyses, a description of the statistical methods to be employed and procedures for handling intercurrent events and accounting for missing, unused and spurious data. These should be aligned with the target estimands, when defined (see ICH E9(R1)).
B.10.5	Statement that any deviation(s) from the statistical analysis plan will be described and justified in the clinical trial report.