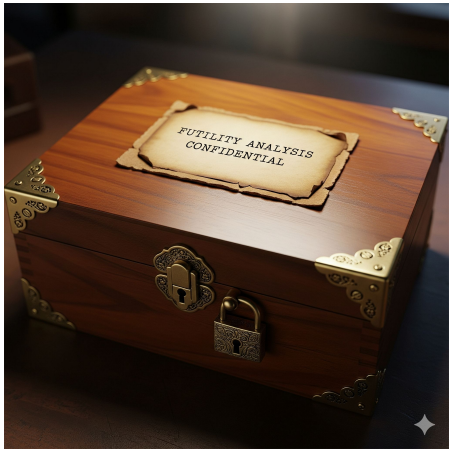
Surprises matter!



Limiting broad disclosure of futility analysis criteria to preserve trial integrity

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Perspectives on Futility Analysis

Futility analysis is a strategic tool that enables one to set objective criteria to stop a trial early when accumulating data suggests that there is little chance that it will read out positive in the end.

It reduces:

- patient exposure to ineffective drugs
- the expected sample size and trial duration if a drug does not perform
- significant costs and resources if implemented at the portfolio level.

Futility analysis is generally a sponsor's risk as it would never result in a decision to stop and file.

Care must be taken in any interim analysis to protect the integrity of the trial in the event that it continues.

Keep details of Futility analysis in interim SAP to prevent…

mhmhm, I prefer to wait and **enrol my patients after the futility analysis only.**

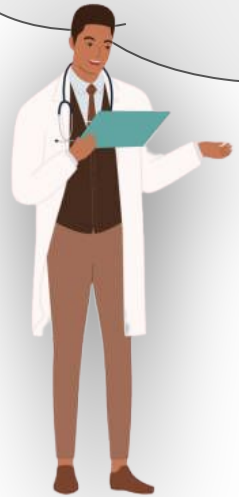
delayed enrolment

The trial passed the futility analysis. I will **start enrolling my patients who are less fragile**

Population shift

Keep details of Futility analysis in interim SAP to prevent…

The trial passed the futility analysis.
My patient who has some adverse events, is likely receiving the new drug.
If I ask him to **do again the walking test** he will walk faster & improve his disability score.



Change in efficacy/safety assessment

The trial passed the futility analysis with a very high bar.
This new drug likely works!
My patient, who is not doing well, is certainly on placebo.
I am going to **withdraw him from the trial.**

study retention issue

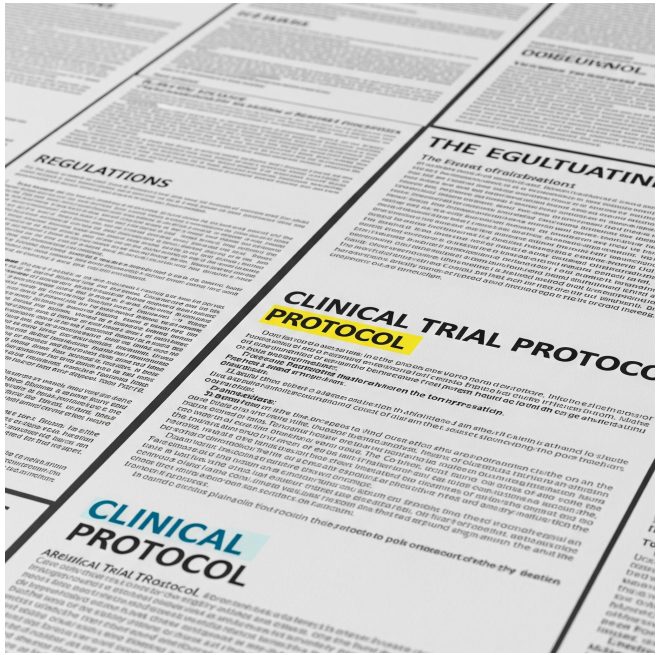
Proposed Protocol Language

The Sponsor may choose to introduce a futility interim analysis.

When the decision to conduct the optional futility interim analysis is made, the decision along with the rationale, timing, and statistical details for the analysis will be documented in the SAP or a designated futility iSAP, and finalized before the data snapshot date for the futility analysis.

*The trial will **not be stopped for positive efficacy** as a result of an interim analysis for futility. The futility analysis will be **non-binding**. The analysis will be conducted by an external statistical group and reviewed by the **iDMC** to preserve trial integrity.*

Regulations demand inclusion of details in protocol



- ICH E9, ICH E6(R1) and ICH E20 (draft)
- EU CTR Annex I, paragraph D17(u)

Member states cite these regulations when requesting inclusion of futility analysis details in study protocols

Questions

Can the futility analysis details be included in the SAP, not the protocol?

Can the protocol include optional futility language in the protocol, with **details specified in a separate statistical analysis plan** finalized before any interim analysis to protect trial integrity?

Under what circumstances should the details of a futility analysis be shared broadly prior to its conduct?

What references should sponsors provide when member states request

1) the details of the futility analysis be included in the protocol

2) disclosure of data / interim results even though the trial is ongoing?

Backup

Selected Regulatory Perspectives

ICH E9	Interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to the formal completion of a trial… Because the number, methods and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol.
EU CTR Annex I, paragraph D17(u) & GCP ICH E6(R1), Section 6.9	The protocol shall at least include a description of the statistical methods to be employed, if relevant: • timing of any planned interim analysis and the number of subjects planned to be enrolled; • criteria for the termination of the clinical trial;
CHMP/EWP/2459 /02	Executive summary – In all instances the interim analysis and the type of the anticipated design modification (change of sample size, discontinuation of treatment arms, etc.) would need to be described and justified in the study protocol. Adaptations to confirmatory trials introduced without proper planning will render the trial to be considered exploratory.
ICH E20 (draft)	The protocol should contain the core elements, including the trial objectives and corresponding estimand(s), and the principal features of the trial design, conduct, and statistical analysis, including all adaptive design elements and their rationale. (lines 922-924) In some cases, details of the anticipated adaptation rule should be reserved for specific documents with access restrictions, rather than the protocol, to maintain trial integrity (926-928)

Selected Case Examples

Protocol Text	Regulator(s) Feedback (paraphrased)
Interim analyses to evaluate futility, safety, or adequacy of the safety database for longer-term Drug X exposure will be conducted by an external statistical group and reviewed by the iDMC. The iDMC may recommend increasing the overall sample size to ensure sufficient data … or stopping the trial early. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter. The timing and statistical details for interim analysis will be specified in the Statistical Analysis Plan…prior to the conduct of any interim analysis.	RFI feedback ■ Fully prespecify interim analyses in the protocol; otherwise, the trial will be considered exploratory ■ SAP is not relevant because NCAs don't receive SAPs
Optional interim analysis (3 protocols): To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis. 1. Sponsor kept blinded, analyses done by an independent statistical group (IDCC), IDMC charter, dedicated interim SAP sent to the relevant HA 2 months prior to IA.The study will not be stopped for positive efficacy as a result of the interim analysis. Criteria for stopping for futility will be written in the IDMC charter. Futility analysis will not take place prior to at least 50% of information is accumulated 2. Sponsor kept blinded, IDMC charter and interim SAP to contain the threshold and decision criteria for the futility analysis. 3. Sponsor blinded, IDMC charter and interim SAP, The study will not be stopped for positive efficacy as a result of the interim analysis.	1 HA requested the interim SAP 2 One HA requested inclusion of futility analysis details in the protocol. Sponsor sent interim SAP instead. 3 HA requested clarifications the control of alpha, the sponsor clarified that it will be a futility analysis only, trial will not be stopped for positive efficacy, therefore no need to adjust the alpha for the futility analysis 4 one HA requested to clarify that the futility analysis is non-binding