BBS Workshop, October 2023

ESTIMANDS IN EARLY DEVELOPMENT – AN EXTERNAL PERSPECTIVE

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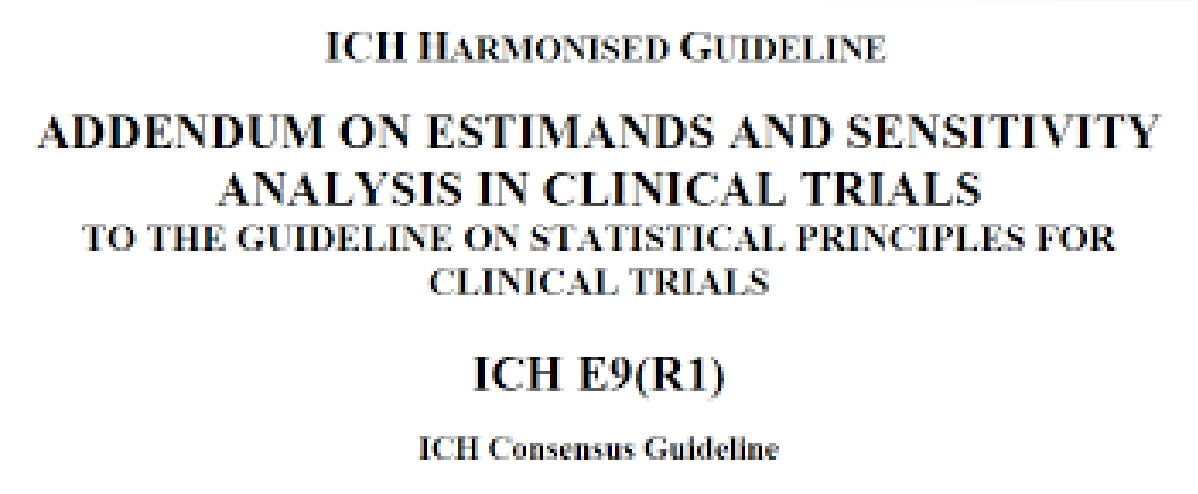
Consilium Salmonson and Hemmings

PREACHING TO THE CONVERTED?

ICH E9(R1) _ SCOPE

- Applies any time an effect of treatment is to be estimated.
- Any comparison (even indirect) of outcomes under different treatment conditions
  - Includes e.g., dose-response
- Always helpful to consider which data are relevant to estimation, and why.



ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

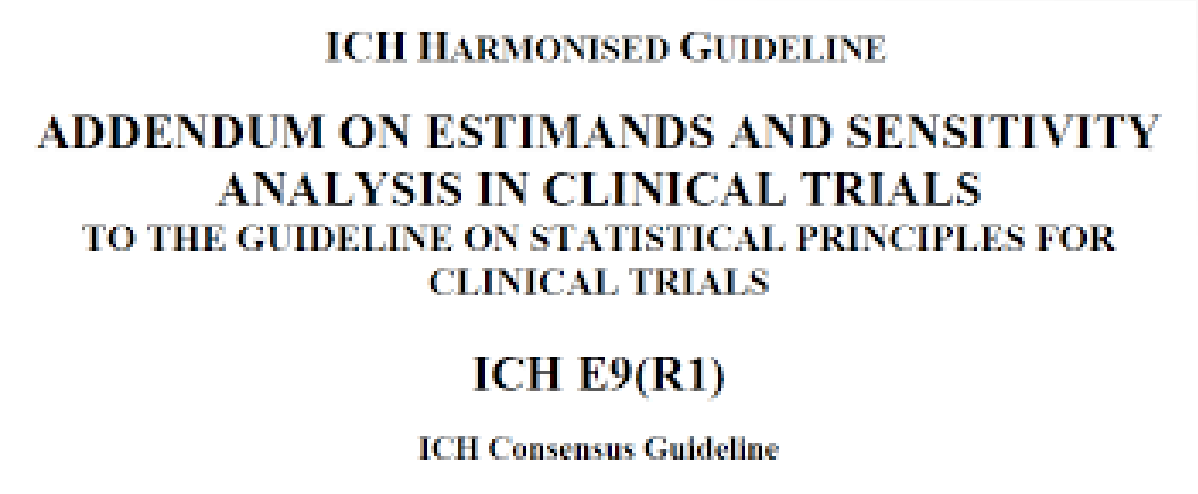
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

ICH E9(R1)

ICH Consensus Guideline

ICH E9(R1) _ SCOPE

- Less important for early phase studies because study conditions are more carefully controlled (fewer intercurrent events)??
  - Patients carefully selected and more closely monitored; treatment administration on site…



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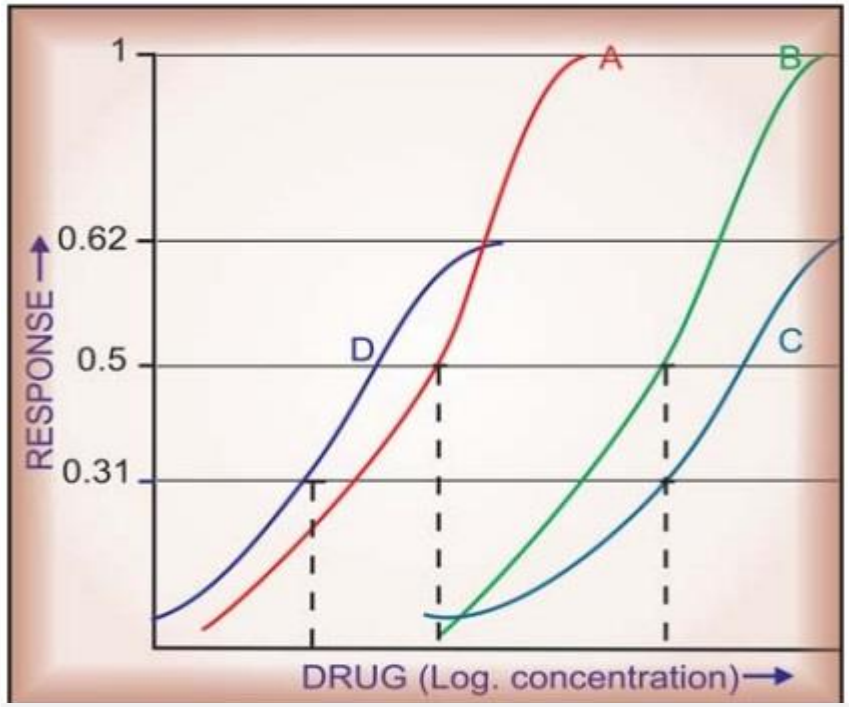
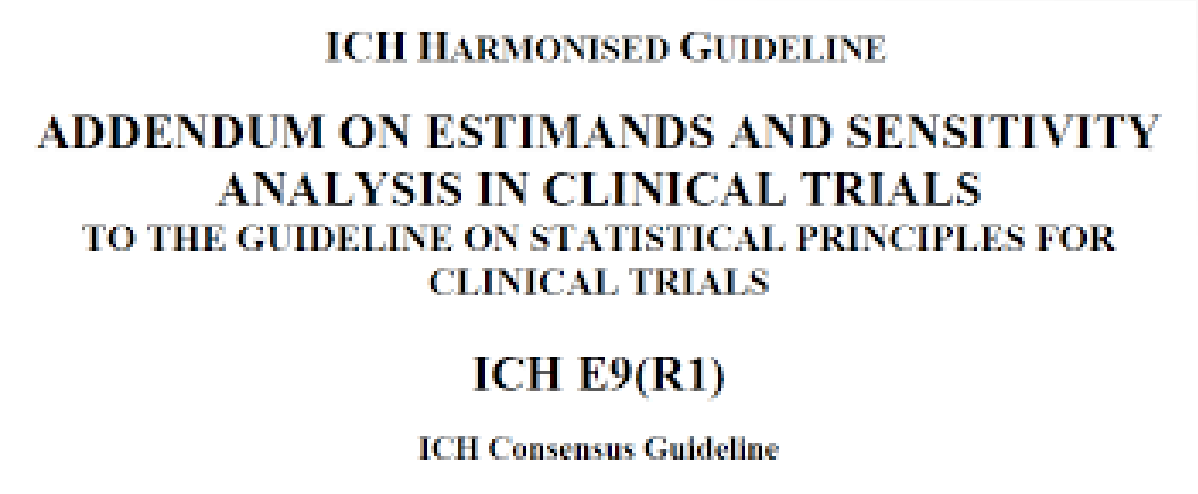
ICH E9(R1) _ WHY IMPORTANT?

- The effect of treatment across doses:
  - … if all patients adhere to treatment…
  - … regardless of adherence…
  - … regardless of rescue medication use … etc. etc.
- POC studies, non-clinical studies
- Contrasting and integrating safety and efficacy outcomes



ICH E9(R1) _ WHY IMPORTANT?

- Any study is better designed with a full understanding of the research question of interest (the quantity to be estimated).
- Any estimate is better interpreted with a full understanding of what is being estimated.



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ESTIMANDS IN EARLY PHASE TRIALS

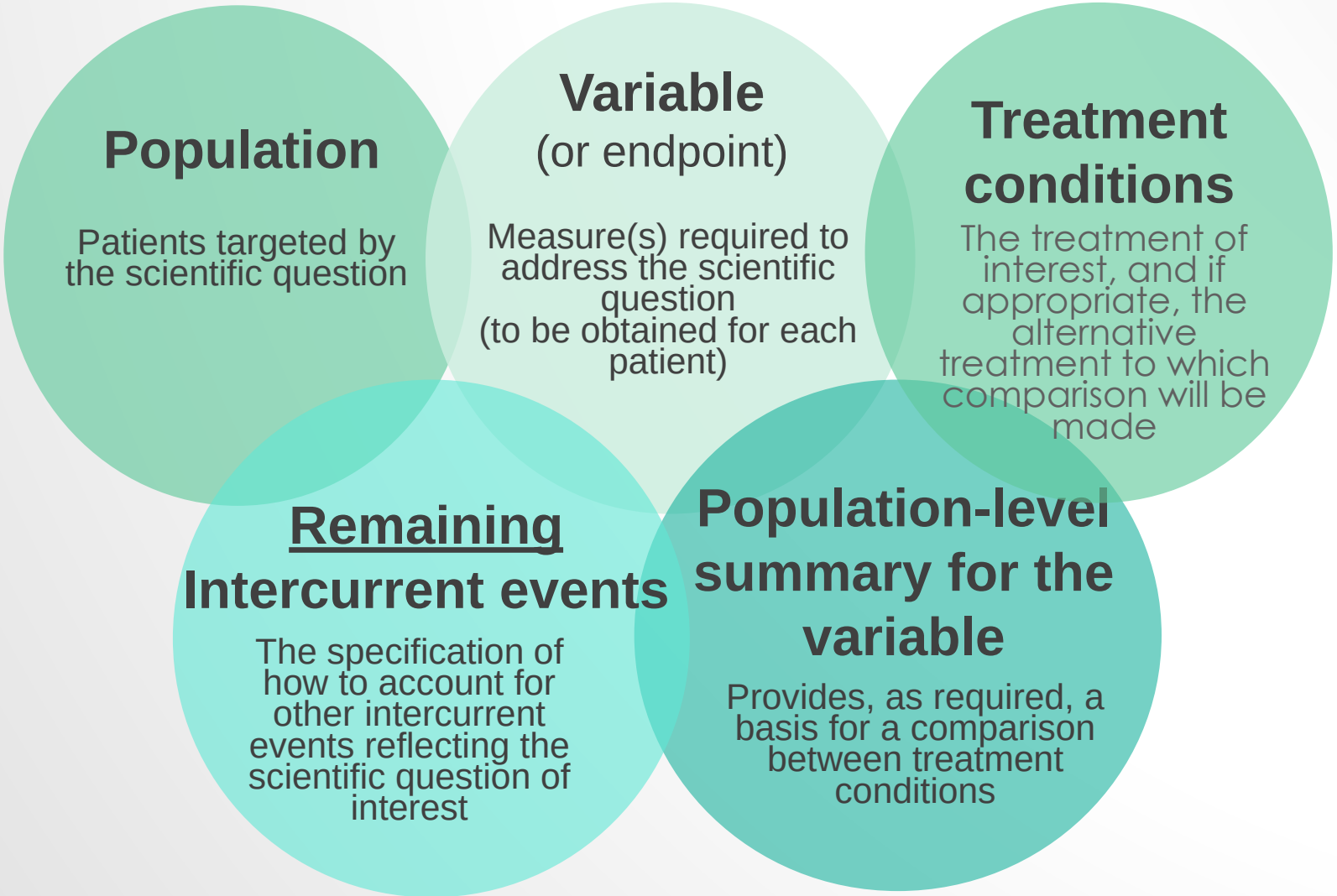
- Early phase trials are to inform us about the drug, not the outcomes of drug in practice?

- More scope for "hypothetical" questions related to patient outcomes? Consider:
  - AE leading to trt discontinuation
  - Need for rescue medication
  - Unrelated death

- Early phase trials are to inform the design of confirmatory trials?

- Reducing the "replication crisis"
  - Helping to explain why effect sizes in Phase 3 might differ
  - Better informed sample size calculations
  - … etc.

ESTIMAND ATTRIBUTES



ESTIMANDS IN EARLY PHASE TRIALS

- Present the estimates alongside the estimand

- Present the intercurrent events alongside the estimates

ESTIMANDS IN EARLY PHASE TRIALS _ REGULATORY CONSIDERATIONS

LESS PROMINENT IN COMPANY SUBMISSIONS

LESS PROMINENT IN REGULATORY FEEDBACK

JUST THE "SPONSOR'S RISK"?

DOES IT MATTER?

PERHAPS NOT IN A FULLY FUNCTIONING INTERNAL TEAM

REGULATORY INTEREST WOULD PROMOTE WIDER UPTAKE OF THE FRAMEWORK.

ESTIMANDS IN EARLY PHASE TRIALS _ INTERNAL CONSIDERATIONS

- Feedback that using the framework for Phase 3 promotes better conversations within clinical teams.
  - Statistician to Clinician
- Why not also in Phase 1, 2
  - Statistician and pharmacologist / pharmacometrician
- What is the target of interest, which data are relevant to that target, and what are appropriate methods in the absence of relevant data?

ESTIMANDS IN EARLY PHASE TRIALS _ INTERNAL CONSIDERATIONS

- When to implement in a sceptical organisation?

- When value can be demonstrated
  - Higher number / impact of intercurrent events, i.e., when the choice of estimand and analysis matters
  - Bigger discrepancy anticipated between early and late phase trials
- When you have rehearsed the conversation
- When you can deliver messages without jargon