Examples of opportunities to use the estimand framework in early Phase studies

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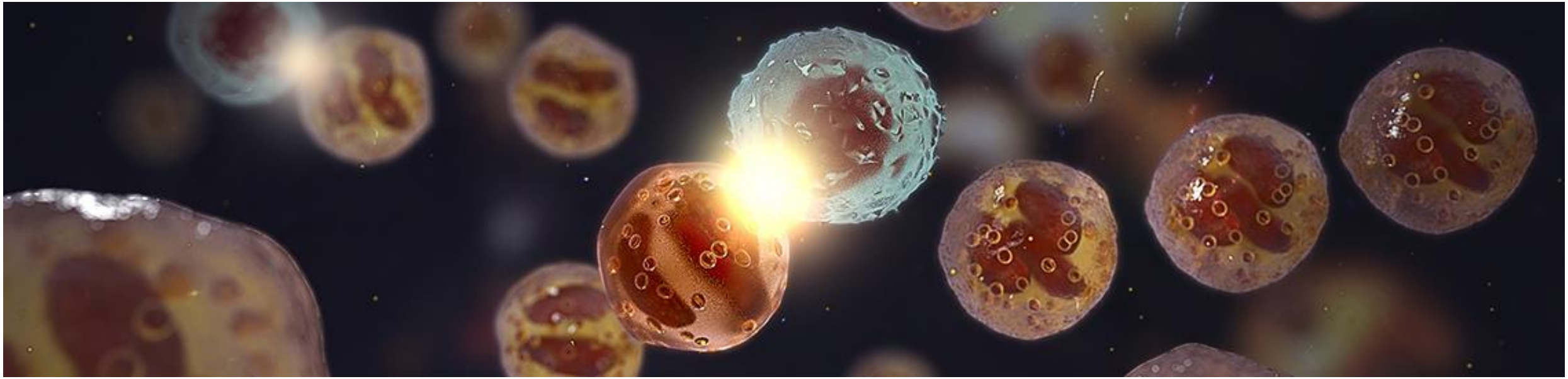

Contents

Introduction

- **What is the clinical question of interest?**
- **This is relevant to all clinical studies**
  - Hence the estimand framework can be used in early clinical development
  - I would go further and say at the very least the estimand thinking process should be used in all clinical development programmes (including the early phase part)
- **Issues/Misconceptions**
  - Image problem
    - Only for statisticians ×
    - Only for confirmatory studies ×
    - Adds no value in small early phase studies with few intercurrent events ×
  - Early Phase development is always the same ×
    - So leave it as it is - Why?
    - What about innovative approaches – if used can the same question be investigated as previously? Is the estimation as reliable or are more assumptions needed?

Time for a change in Mindset?

Easy/obvious use – Phase IIb

- Last chance to modify/choose population and choose dose(s) for Phase III
- If it is not clear what estimand is used in Phase IIb how can a decision be made whether or not to fund large Phase III clinical trials?
- Is it clear what population was studied and how big a change in population is being made between Phase IIb and Phase III?
- If using the same endpoint in Phase IIb and Phase III but for a shorter treatment duration what modelling has been done to predict likely longer-term efficacy?
- Or is a different endpoint used as a surrogate and if so has it previously been shown to be good surrogate?
- How will changes between Phase IIb and Phase III affect the occurrence and timing of intercurrent events that would be expected on active in Phase III?
- Has all of this uncertainty been adequately discussed and quantified?

Don’t work in silos

Medium – Phase IIa

- **Have you ever designed a study and not know if the aim is to characterize the dose response curve or find one or two doses to take forward to Phase IIb?**
- **Can you write down the estimand if the aim is to establish the shape of the dose response curve?**
- **Difference between dose finding, dose response curve and dose "optimization"**

Challenging

- **The further away from Phase III you get the lack of familiarity with the framework grows. So you need to front load conversations to justify changing the way things are done (not easy). More examples of why it matters are needed.**
- **But in fact being transparent about what is the aim is just good science.**
- **Acknowledge some areas need more work than others.**
  - See work on Duration of and time to response in Oncology clinical trials (Hans-Jochen Weber et al 2023 Pharm Stats https://onlinelibrary.wiley.com/doi/10.1002/pst.2340?af=R)
  - See work by Collignon et al Clinical Pharmacology and Therapeutics and on using estimands in Complex Innovation Designs such as Master Protocols and Platform trials https://doi.org/10.1002/cpt.2575

Conclusion

- **The estimand framework offers value throughout the clinical development process – including early phase**
- **Essential to use it in Phase IIb – can help reduce failures in Phase III**
- **Can be more complex in earlier trials but using the framework brings clarity and transparency that make decision making more straightforward**
- **More discussion of study and programme level estimands warranted**