Estimations – issues with Implementation

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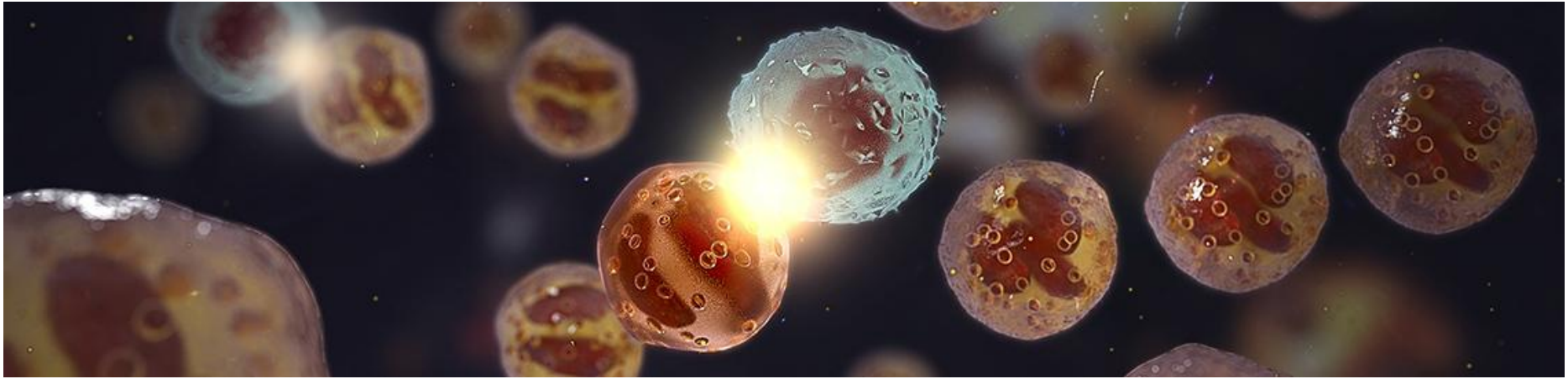

Contents

- Reminder of why was ICH E9 R1 written?
- Issues with recent publications
- Proposals for improvement

Why was ICH E9 R1 written?

- Realization that missing data was not the only challenge with interpreting the results from clinical trials
- Some so called “ITT analyses” did not include all randomized participants or some data from these participants
- Very poor description of the clinical question of interest

2025 Stats in Medicine paper Fleming et al

https://onlinelibrary.wiley.com/doi/full/10.1002/sim.70104

1. **Randomise**
2. **Control Arm** – SOC (not placebo withholding effective therapy)
3. **Endpoint** – Direct measure of how participants feel, function or survive
4. **Follow-up** – follow-up everyone until the end regardless of ICEs
5. **Primary analysis** – Treatment policy for treatment discontinuation and rescue, composite for death
6. **Sensitivity analyses** – referring to missing data

2025 NEJM paper “Statistics in Medicine – What’s in an Estimand?”

https://www.nejm.org/doi/full/10.1056/NEJMp2513633

- **ITT should remain the primary analysis** in randomized trials.
- **Estimands clarify the exact clinical question** being answered.
- **Trial-product estimands are hypothetical**, not directly observed effects.
- In **GLP-1 studies**, these hypothetical estimands may **overstate treatment benefit**.
- **Transparent reporting** of estimands and intercurrent events are essential.

Main messages from Commentary on Fleming paper by Keene, Fletcher and Wright (2025, Stats in Medicine)

https://doi.org/10.1002/sim.70453

1. **Treatment policy is not the only valid estimand strategy**
2. **Treatment policy estimates the effect of treatment assignment, not necessarily treatment received**
3. **All estimand strategies require assumptions, including treatment policy**

Main messages from Commentary on Fleming by Keene, Fletcher and Wright

4. Preserving randomization does not uniquely justify treatment policy

5. Clinical and real-world relevance depends on the question being asked. Real-world relevance is not unique to treatment policy.

Conclusion on Fleming and NEJM papers

1. It is disappointing to see the subtleties and richness that can be gained from utilizing the Estimand framework to better design and analyze clinical trials is not given sufficient credit in these papers.
2. I am not saying that treatment policy strategies are not often the best approach to handling some intercurrent events but a blanket message is dangerous and misleading.
3. Even the use of composite estimands creates a lot of issues in terms of feasibility, estimation and interpretation (it essentially creates a new endpoint) - in particular for continuous endpoints.

6 Proposals for improvement from EFPIA/EFSPI Estimation Implementation Working Group (EIWG)

https://eiwg.github.io/eiwg_webpage/

1. Clinical Question of Interest
2. Definition of intercurrent events
3. Determining which intercurrent events to identify
4. How to incorporate intercurrent events into estimand descriptions
5. Supplementary analyses
6. Analysis sets

Proposals for improvement

1. Templates are not the answer to everything – not an excuse for NOT clearly defining the clinical question of interest and why it is felt that the primary estimand is the best choice to provide evidence to answer that question.
2. Cross functional discussions on estimands are crucial – in particular the clinical question of interest should be clearly defined by clinicians.
3. Just because the results from different estimands lead to very similar treatment effect estimates in one case doesn't mean we should stop thinking about which estimand should be primary. This is important for both
    1. Scientific reasons – it is lazy science to not use the estimand that best targets the clinical question of interest
    2. Pragmatic reasons - under what circumstances might these estimates differ considerably in a future trial – important for choice of sample size at design stage)

Conclusions – A call to arms!

1. Estimands are not a discussion just for statisticians. Engage with your clinical colleagues to stress the importance of their full involvement in the process.
2. Find clinical champions and use them to spread the word with their clinical colleagues
3. The work to implement estimands has only just started. So much more to do.
4. If it helps don't use the word estimands in your discussions.
5. Share success stories where estimands were used and also situations where estimands could have helped but were not used.
6. Don't give up – together we can improve clinical trial design and improve the quality and relevance of summaries of these trials that are provided.