Reflections on the estimands addendum with a focus on the treatment policy strategy

David Wright

Head of Statistical Innovation, Early Biometrics & Statistical Innovation, DS&AI, BioPharmaceuticals R&D, AstraZeneca, Cambridge UK

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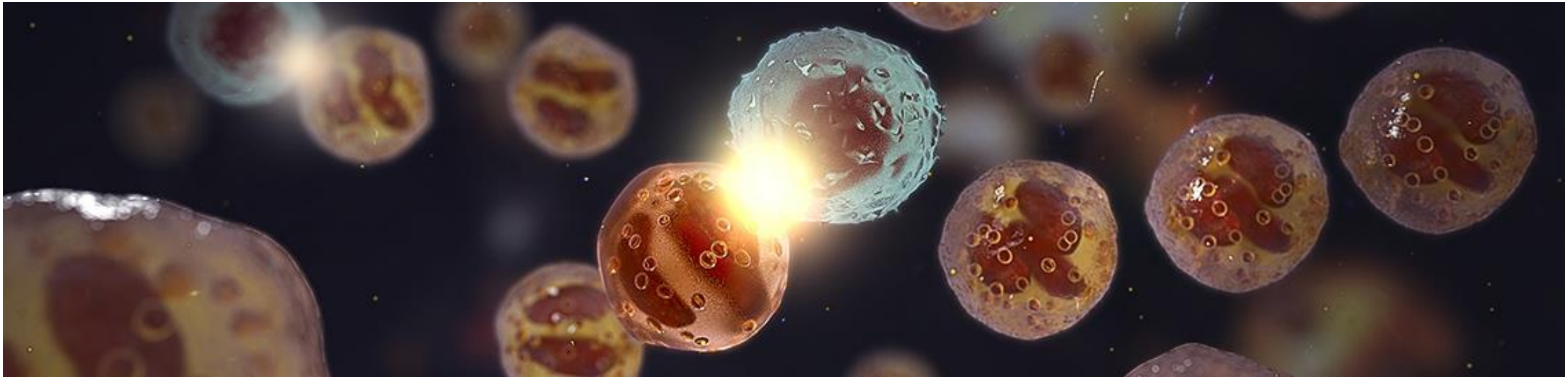

Disclaimer

- **These are my own personal views and do not necessarily represent the view of AstraZeneca.**

Acknowledgements

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Agenda

- **Why was an Addendum to ICH E9 necessary?**
- **Why isn’t ITT specific enough?**
- **New language needed**
- **Misconceptions – treatment policy estimation is easy**
- **What should be estimated when there are missing data?**
  - And which methods are best at targeting the treatment policy?
- **Conclusion**

Why was an Addendum to ICH E9 necessary?

- In 2010 The prevention and treatment of missing data in clinical trials was published by NAS.
- In 2011 The CHMP guideline on missing data in confirmatory clinical trials came into effect CHMP missing data guideline
- In regulatory submissions there was a lack of clarity about the main clinical question of interest and why a particular method of analysis had been chosen.
- It was not transparent what an “ITT analysis” really meant. Definition not consistent within E9. Has this led to different people thinking different things. See ICH training slides for a detailed discussion of this –ICH E9 R1 Training Slides
- Realization that the issue was not only a missing data problem.

What isn’t ITT specific enough

- **Issue with Longitudinal studies where an ITT analysis was presented as primary, *e.g.***
  - 1000 patients randomized
  - 600 patients took treatment they were allocated to for the whole treatment duration
  - 700 patients completed the study
  - 200 patients discontinued from the study prematurely (all discontinued treatment) [no data collected post study discontinuation]
  - 100 patients completed the study but all data at last visit was missing
  - 100 patients stopped taking assigned treatment and took another treatment subsequently
  - Of those 50 patients took a treatment specified in the protocol, 25 patients took a treatment not specified in the protocol, 25 took a treatment that was prohibited in the protocol.
  - primary analysis was change from baseline to end of study

What isn’t ITT specific enough

- How many patients should be included in the primary analysis?
- Should any data for those patients not be included in the primary analysis?
- How should missing data be handled? And does it depend on why the data were missing?

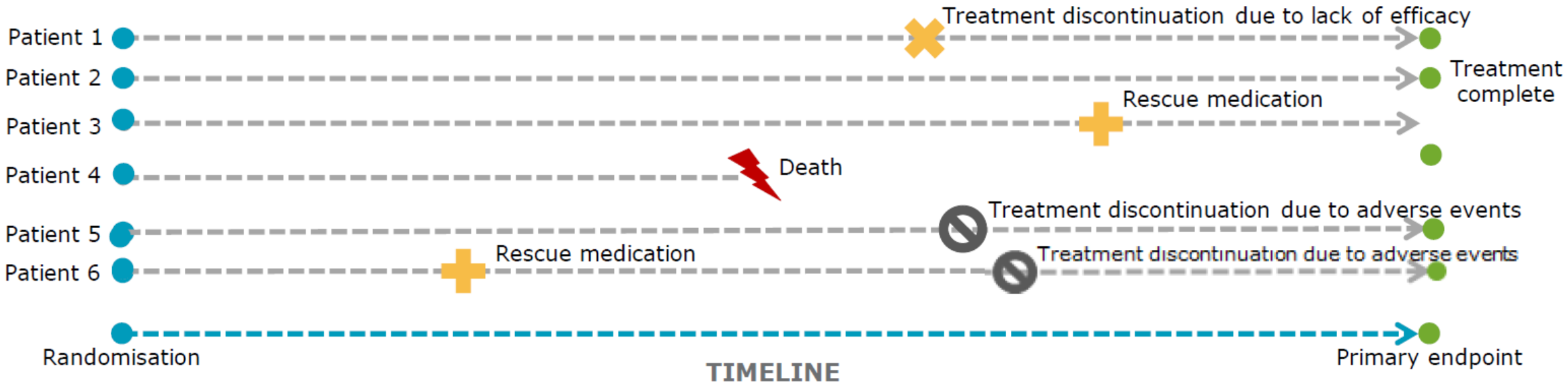
What isn’t ITT specific enough

- **Similar studies in the same indication – different sponsors were answering questions on previously slide differently. All specified ITT/mITT analysis as primary! Need for more clarity on**
  - What was the question on interest
  - What events after assignment to treatment affect the interpretation of the efficacy observed
  - The relationship between those events and the question of interest
  - See slide 47 of ICH E9 R1 Training Slides for more on lack of clarity in previous studies
  - Put altogether led to the birth of the estimand framework

New Language needed

- **Intercurrent events**
- **Treatment policy strategy – why is it called this. Do you have to define not just initially assigned treatment or also subsequent treatments and the order they should be given? *i.e.* is the definition precise enough?**
- **ITT – focuses on the HOW (estimation)**
- **Treatment policy – focuses on WHAT you are estimated.**

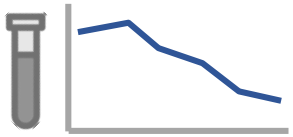
What is an intercurrent event?



The 5 estimand attributes

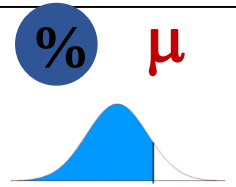
Target Population

Variable (Endpoint)

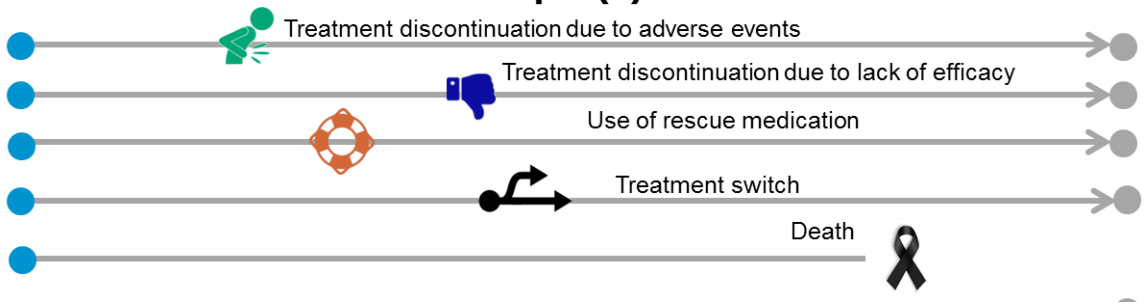


Treatments being compared

Population-level Endpoint Summary



***Intercurrent Event(s)* that can impact the above input(s)**



Treatment policy strategy is easy, right! - Wrong

- **With complete data collection for all patients in the study and no premature discontinuation from the study estimation of the treatment policy estimand is easy (well apart from what to do with subjects who die before the specified end of the study)**
- **So welcome to all long-term longitudinal studies ever conducted! – virtually all have some patients who discontinue from the study (missing data problem), most have some data missing for some patients (even though they stay in the study)**
- **Given this how do you estimate and interpret the treatment policy estimand in the presence of missing data?**
- **Some analyses that target a treatment policy estimand are easy but often don't account for all ICEs, *i.e.,* are they the most appropriate analysis approach, and are they biased?**

Which estimation method should you use when estimating a treatment policy estimand?

- **This is nearly the point I leave you in the capable hands of estimation experts.**
- **You will hear them discuss methods such as Maximum Likelihood, Multiple Imputation, Reference Based Imputation (such as Jump to Reference and Copy Reference) and Use of retrieved dropouts.**
- **All of these methods use unverifiable assumptions**
- **How should you choose the estimation method for the primary treatment policy estimand? Do you have to use the same estimation approach for all other analyses pre-specified in the trial (that target treatment policy estimands*) e.g.* subgroup analyses, analyses of different population summary measures, etc. ?**

Conclusion

- **This was deliberately a very gentle introduction to a complex topic!**
- **If you are not clear or don't know what you want to estimate there is little point in trying to estimate it!**
- **What is the best estimand for regulators to use for decision making?**
  - Are they regulating a treatment or a strategy?
  - If approval is based on a treatment policy approach should the label reflect the treatment strategy? And if so, how?
- **Is a treatment policy strategy for all ICEs the best approach?**
- **In situations when some missing data cannot be avoided assumptions are needed to estimate any estimand including a treatment policy estimand.**
- **There are more clinically relevant estimands than a blanket treatment policy approach in those settings – see next week's presentations for more on this.**
- **As you will see treatment policy estimation is far from straightforward when some data are missing! Enjoy the ride.**