SmPC 5.1 - What does good look like?

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EFSPI Workshop – September 2024

Disclaimer

The contents of this presentation are my personal opinion. My remarks do not necessarily reflect the official view of FIMEA, EMA, or any associated working party or committee.

What is SmPC?

A document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively.

Section 4.1: Indication

Section 4.8: Undesirable effects

Section 5.1: Pharmacodynamic properties

Relevant vs Reliable

- Positive B/R starting point for discussion of 5.1
- Statistical assessors job is to ensure that the information in 5.1 is reliable
- We are not the experts in defining what is relevant
- Relevant endpoints may have been collected and/or analysed in an unreliable way and are, hence, not suitable for 5.1
- Patients, treating physicians and the common public are free to use the information without further understanding of methodology

  → Unreliable endpoints are not included
- My plea to industry statisticians:

Make sure the relevant data is also reliable!

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Study design

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Data collection and analysis methods aligned with the estimand

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Transparency

Pre-planned sensitivity and supplementary analyses

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Composite estimand -
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Drop-out	30%	5%
Rescue medication	20%	15%
AE leading to withdrawal	0%	10%

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	Placebo	Active
Proportion of responders	20%	50%
Proportion of non-responders	80%	50%
Clinical non-responder	20%	40%
Rescue medication	60%	10%

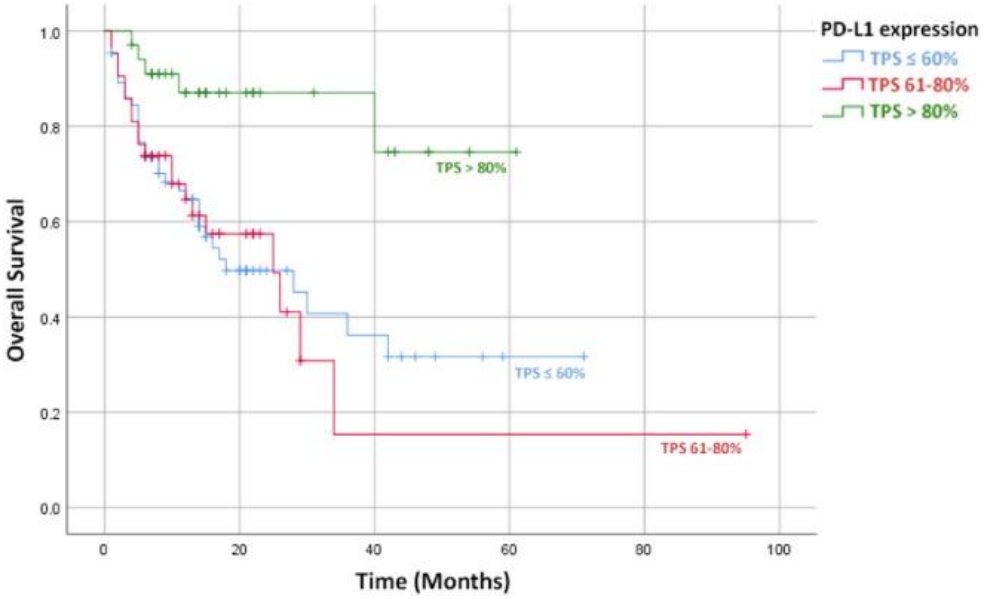
Time-to-event with early drop out – ICEs carry patient relevant information

"…10% of patients in the active arm withdrew from the study due to treatment related infusion reactions during the first 3 weeks…"

"…for 10% of patients in the active arm CAR-T -therapy was not successfully manufactured…"

"…10% of patients in the control arm withdrew from the study immediately after randomization…" ???

Predictive factors – Prognosis is relevant to patients



Similar efficacy was observed in all relevant subgroups

Patients with PD-L1 status >80% have a better prognosis than patients with PD-L1 status ≤80%, however, a positive benefit/risk was observed across all PD-L1 levels

https://doi.org/10.1016/j.cllc.2023.04.010

Study design – clear study objectives are key

- Placebo controlled RCT for a chronic disease, approved indication
- Primary endpoint: response rate at week 52, composite estimand
- Protocol: patients in both arms may move to double dose of active treatment after week 22 in the “absence of benefit” (≠ responder)
  → Misalignment with primary objective
  → Study not designed to study the B/R of double dose
- 40% of placebo patients switch to double-dose
  → “ICE” has a large impact on results
- Double dose not included in SmPC due to lack of reliable evidence
- Not possible to communicate primary endpoint without ICEs
- Double dose is off-label use
  → Results not included in 5.1

Take home messages

- Statistical assessor is the filter to ensure that only methodologically reliable information is included in SmPC Section 5.1
- Whether something is reliable is not black and white
  → scientific assessment
- Unreliable endpoints may be included in the EPAR

The burden of the proof is on the side of the industry

→ Regulators include in 5.1. what we know is reliable and relevant
→ And not what we cannot be sure of being unreliable or irrelevant
→ Please, be proactive, transparent and communicate the results in a reliable manner

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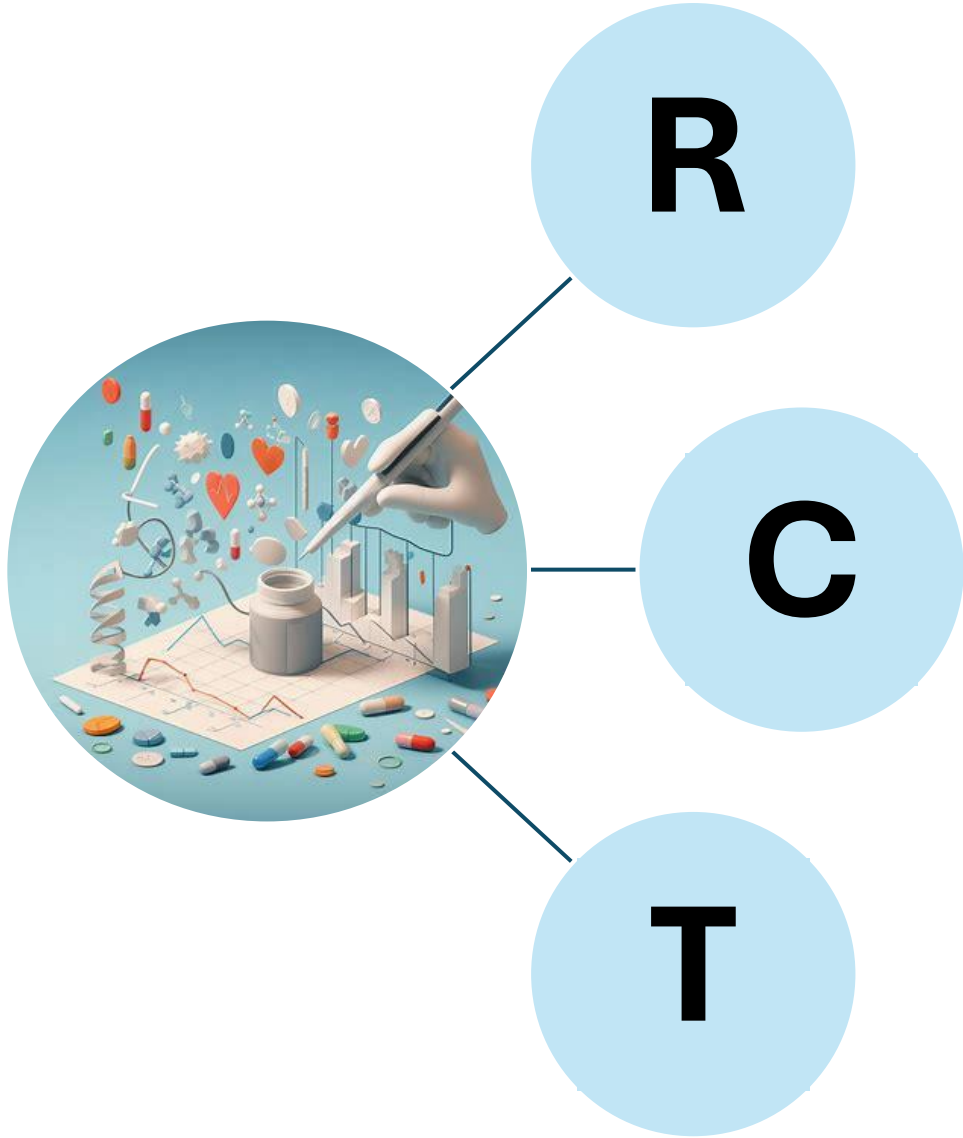
- We often implicitly or explicitly compare to the gold-standard for evidence generation: Randomized Clinical Trial



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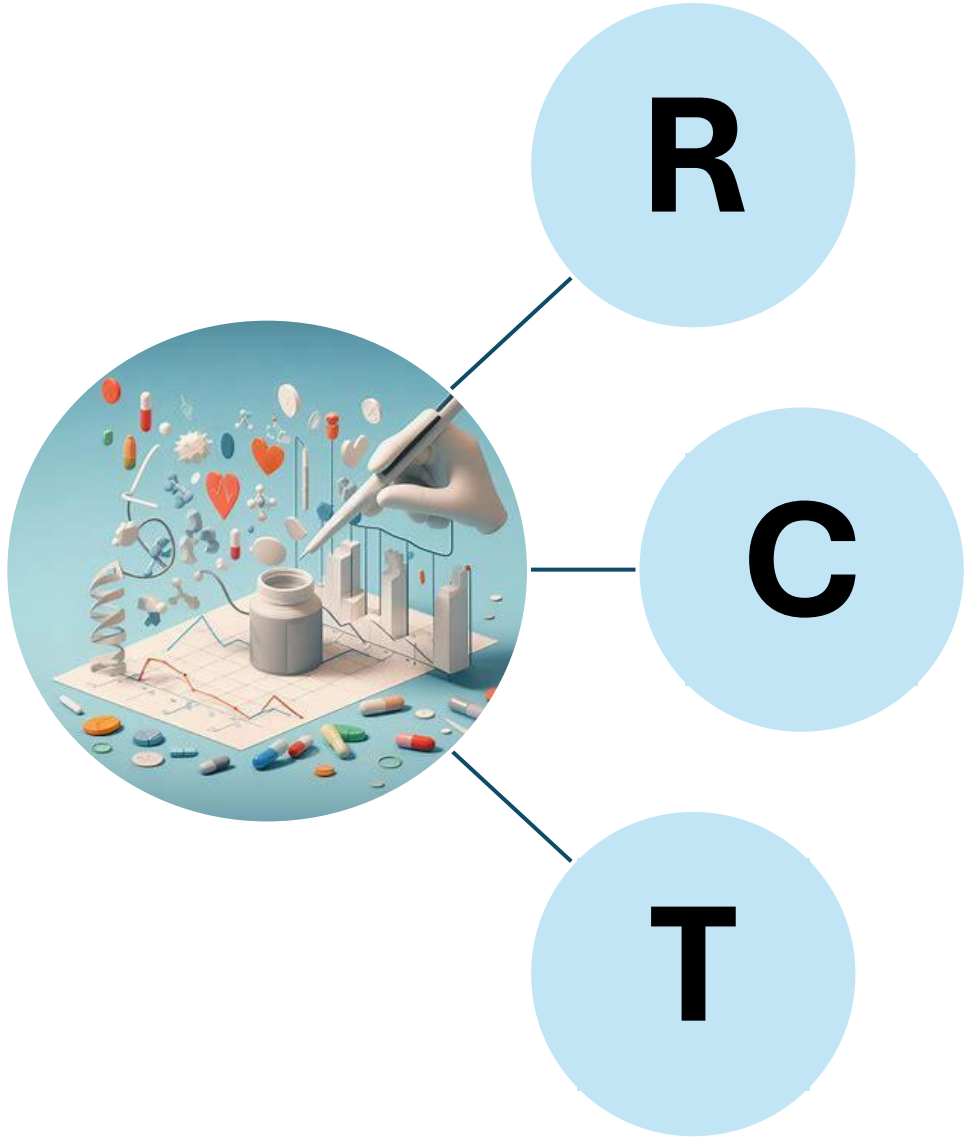
- What makes an analysis ‘reliable’?
- We often implicitly or explicitly compare to the gold-standard for evidence generation: Randomized Clinical Trial
  - Enables estimation of the causal effect of treatment assignment
  - In the absence of missing data + mild assumptions: “association = causation”



Moving away from a ‘perfect RCT’

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Ann Intern Med. 2013 Oct 15; 159(8): 10.7326/0003-4819-159-8-201310150-00709.
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Randomized trials analyzed as observational studies

Miguel A. Hernán,[1,2,3] Sonia Hernández-Díaz,[1] and James M. Robins[1,2]

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Randomized trials analyzed as observational studies

Miguel A. Hernán,[1,2,3] Sonia Hernández-Díaz,[1] and James M. Robins[1,2]

“What started as a randomized trial may effectively become an observational study that requires analyses that complement, but go beyond, intention-to-treat analyses. A key obstacle in the adoption of these complementary methods is a widespread reluctance to accept that overcoming the limitations of intention-to-treat analyses necessitates untestable assumptions. Embracing these more sophisticated analyses will require a new framework for both the design and conduct of randomized trials.”

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- Nuanced language to express scientific questions of interest
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- Nuanced language to express scientific questions of interest
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- Framework that helps us to discuss ‘relevance’ as well as ‘reliability’

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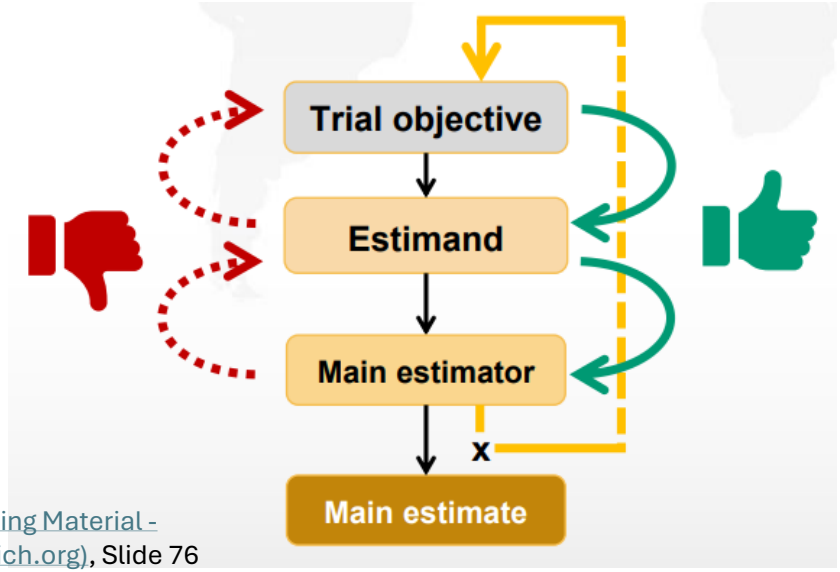

E9(R1) Training Material - PDF_0.pdf (ich.org), Slide 76

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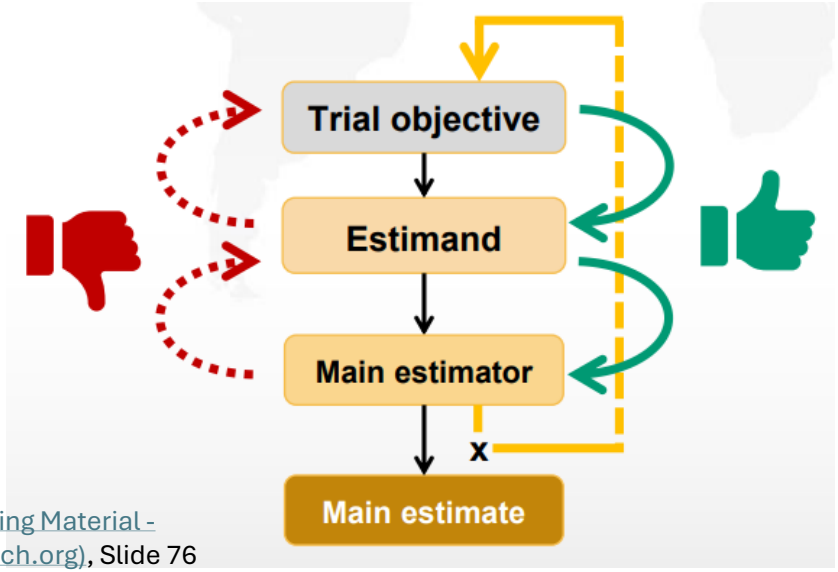

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- What is ‘relevant’ may not be ‘reliable’ and vice versa

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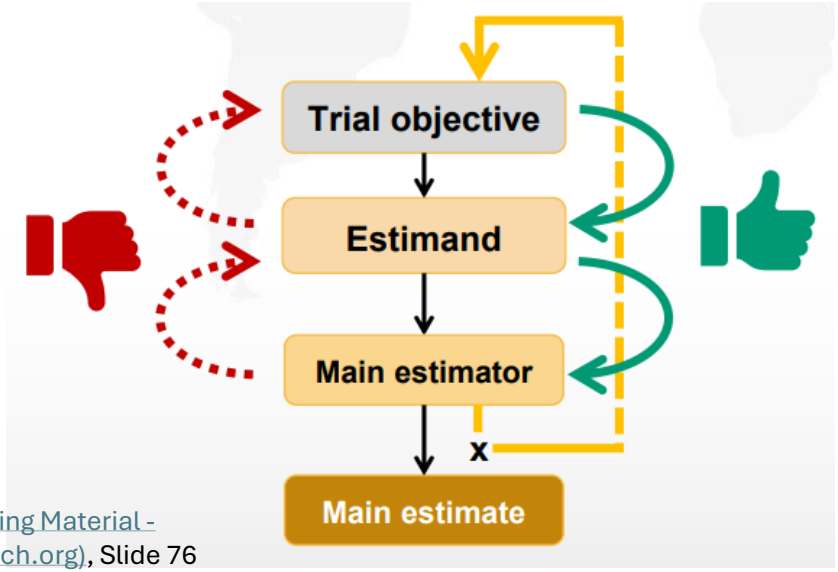

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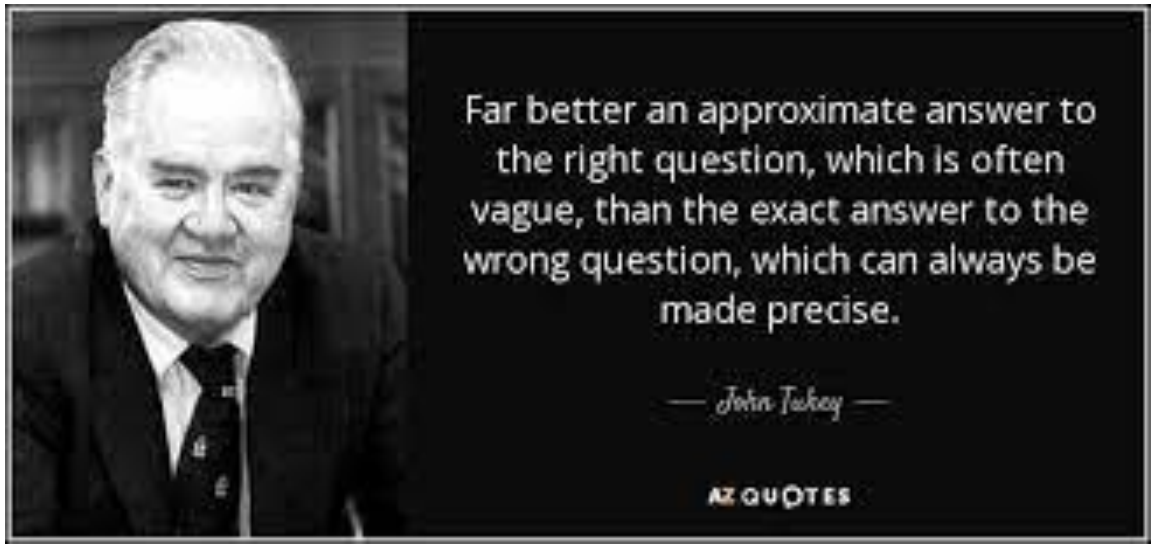

What are the right questions to be answered in the SmPC?

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Need to also answer…

- How to get from ‘thumbs up’ to ‘user manual’?

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- How to get from ‘thumbs up’ to ‘user manual’?
- To which extent should a label reflect the estimand(s) of the confirmatory trial(s)?
  - When replacing an established clinical endpoint through a composite endpoint, how should the endpoint be labelled?
  - If a treatment is approved when using a treatment policy approach, what should be communicated in the label?

My view

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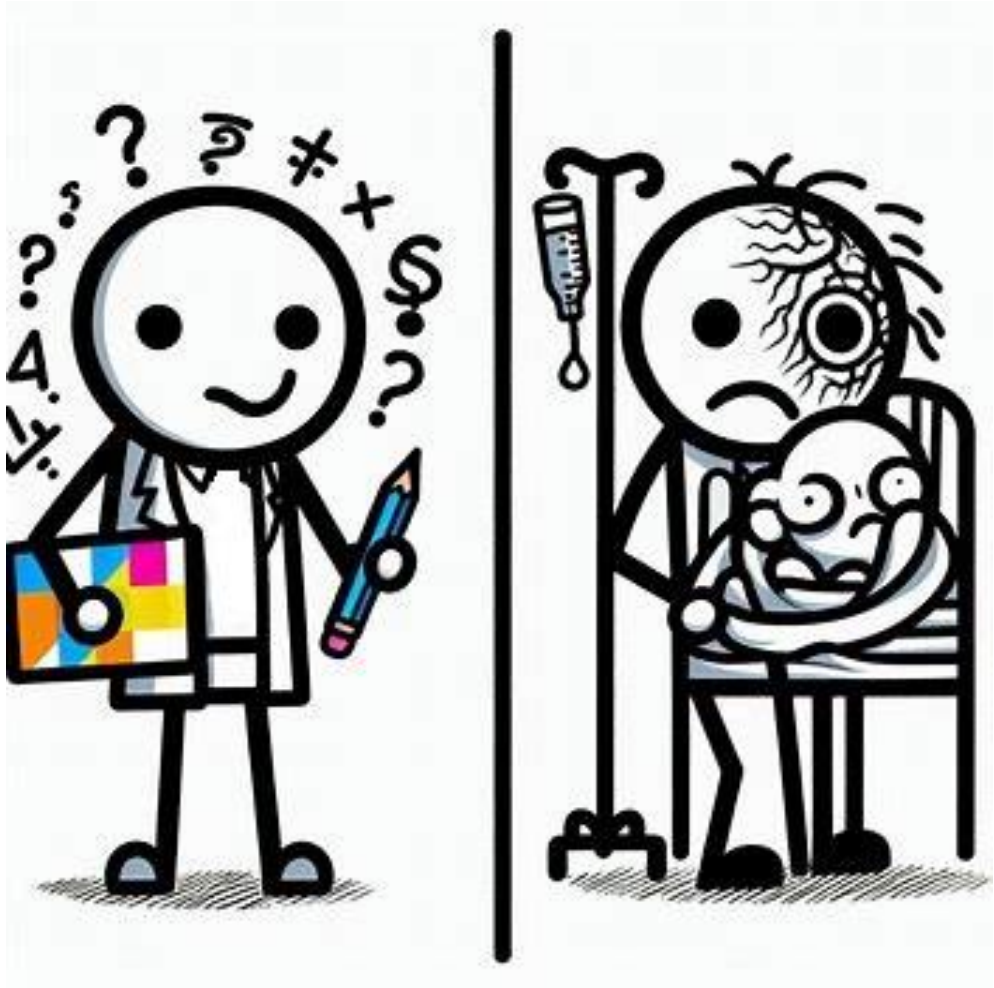
- Tension exists between
  - Mouna the statistician
  - Mouna the patient or caregiver



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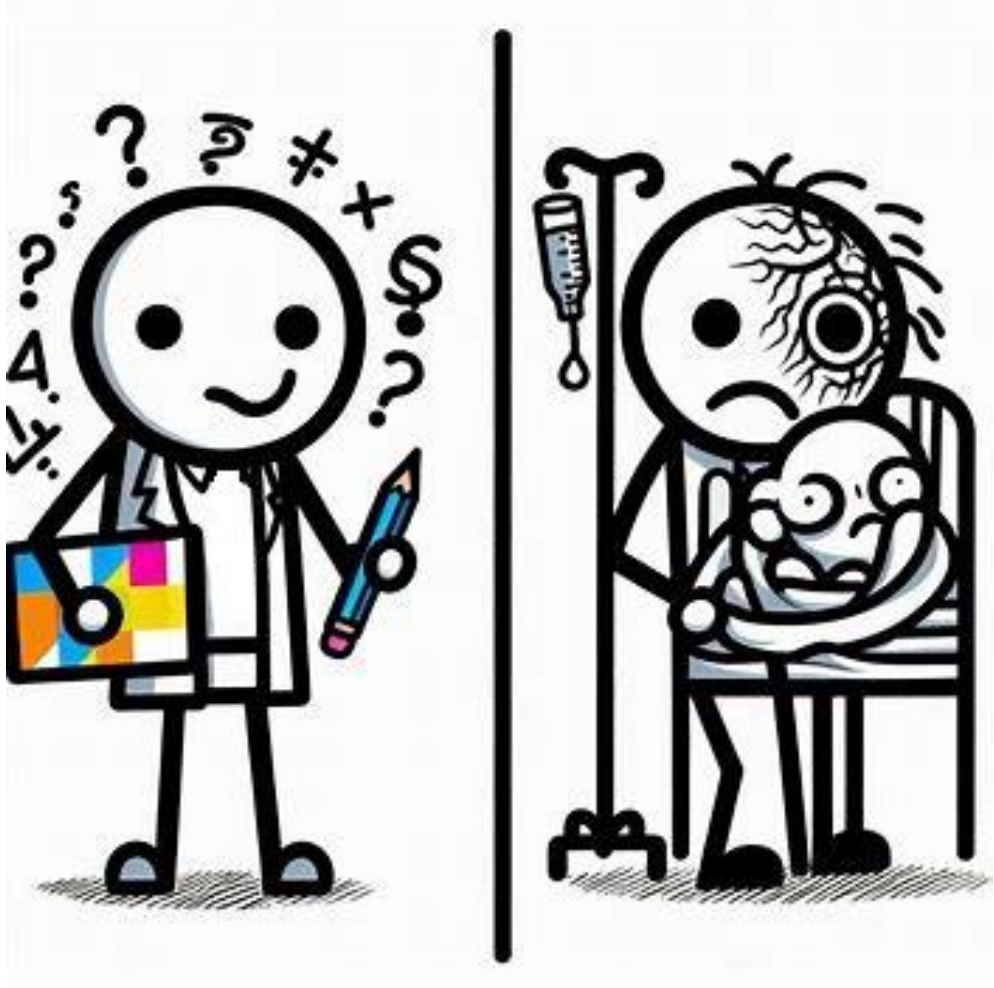
- We can do better, but it is not easy



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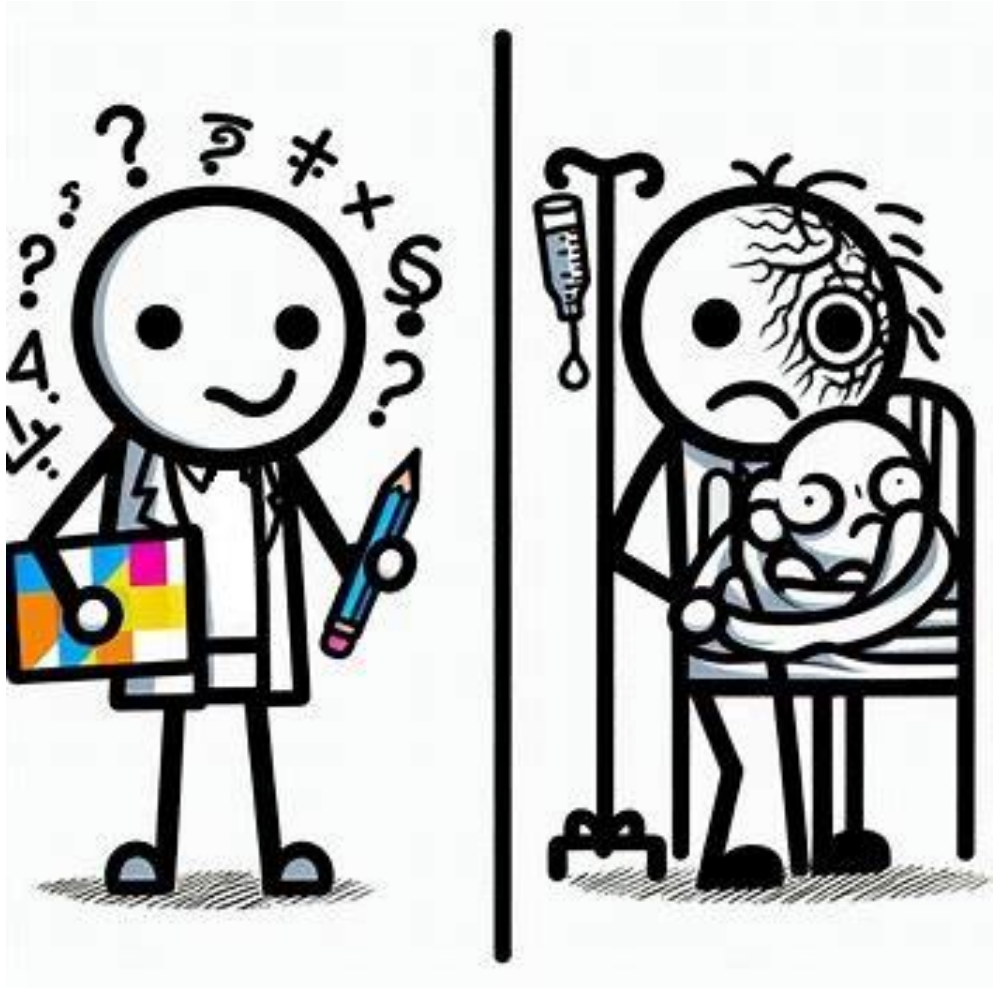
Potential part of a ‘solution’:

- Distinguish more clearly between testing and estimation
- Provide estimates for relevant questions if conclusions hold strong across a range of plausible assumptions
  - Pre-specification of plausible assumptions
- Collaborate with causal inference community (including role of designs)



Closing remarks

Let´s serve the patients by getting most out of clinical trial data

Things are not easy and straightforward and there is no clear rules

…but it´s worth the effort!

Thank you!