College ter Beoordeling
van Geneesmiddelen

Regulatory reflections on estimands implementation

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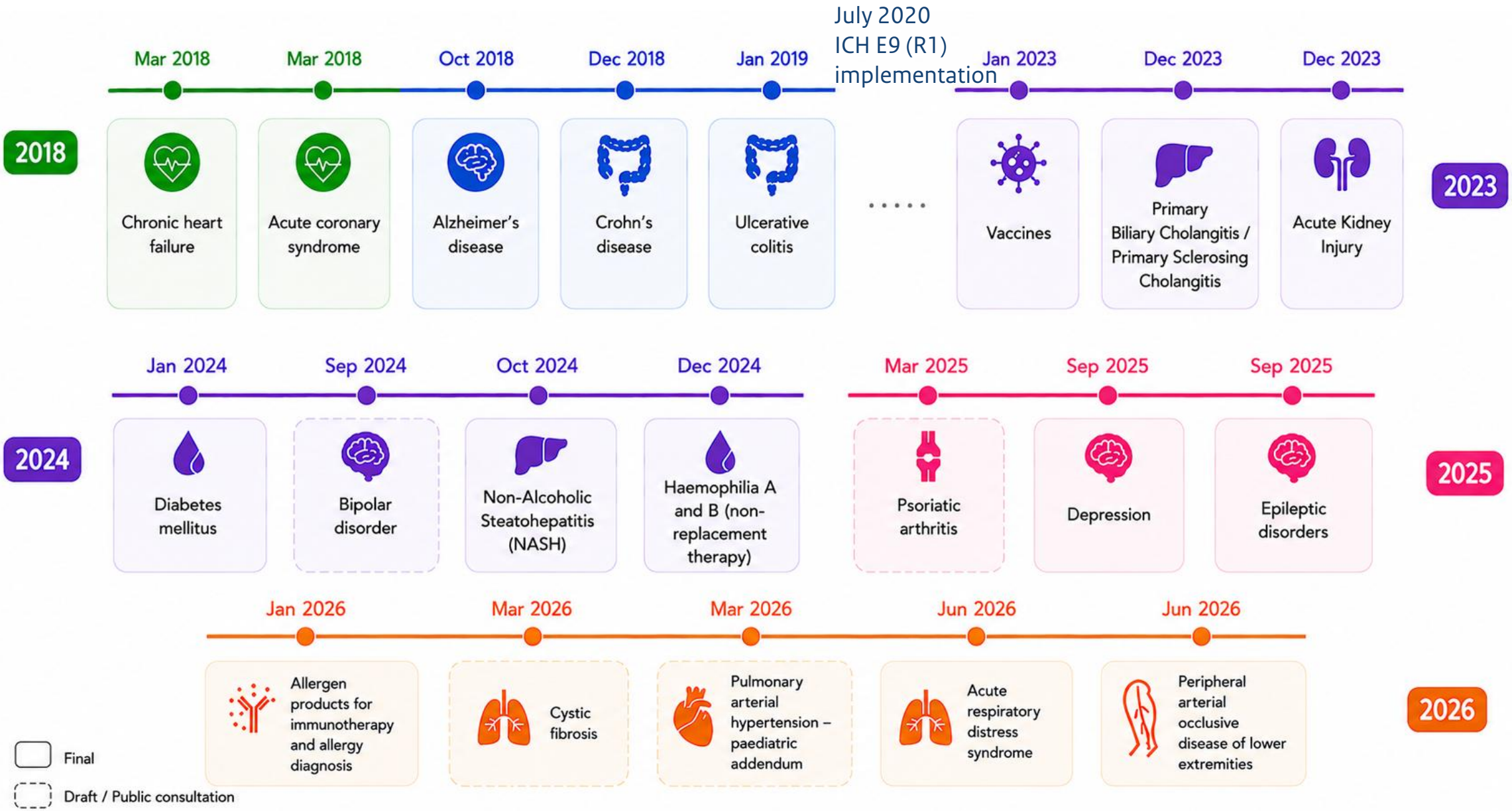
Disclaimer

The views expressed in this presentation are the presenter‘s personal views and not necessarily the views of the Medicines Evaluation Board (MEB) or the European Medicines Agency (EMA).

Where are we seeing progress?

The estimand framework is working its way into clinical guidelines



Scientific advice and marketing applications

- There is an increased focus on the estimand in questions asked during scientific advice as well as in protocols and SAPs

- But the discussions on the estimand largely remain “transactional” they still lack justification – the WHY?

- The lag in uptake used to be related to the timing of when trials started (i.e. pre-addendum). Now it feels like the gap is becoming more related to the experience and expertise of the Sponsors

We’re talking the talk, but are we also walking the walk?

Example in oncology: Progression free survival

- PFS
  - Time from randomisation to progressive disease or death

- Intercurrent events
  - Treatment discontinuation
  - **Use of new anticancer therapy** before progression or death

Example in oncology: Use of new anticancer therapy as an intercurrent event in PFS

	Question of interest	Estimand strategy	Analysis
Primary estimand	Does receiving the investigational therapy increase the time to progression or death compared to SOC **without any influence of subsequent therapy**? (Isolation of treatment effect)	Hypothetical	Censor at last assessment prior to use of new anticancer therapy
EMA preferred	Does receiving the investigational therapy increase the time to progression or death compared to SOC **allowing for subsequent therapy when needed**? (allocation = start of a treatment sequence)	Treatment policy	Continue to follow up patients regardless of use of new anticancer therapy

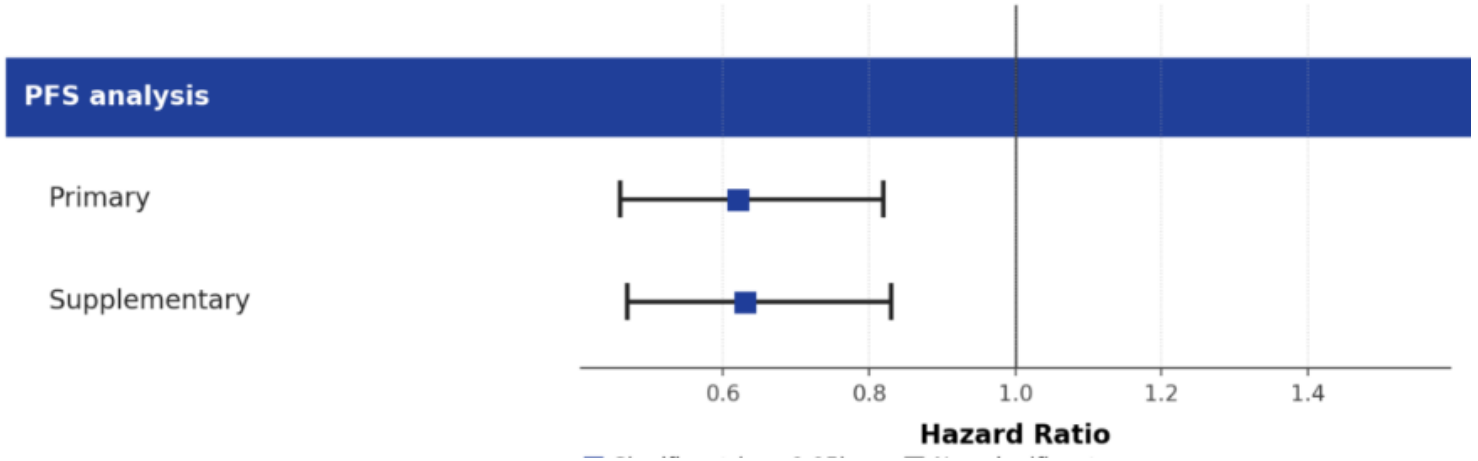
SOC = standard of care

Fictional example (representing multiple real examples)

Primary analysis: with censoring for new anticancer therapy

Supplementary analysis planned in the SAP: Not censoring at start of anti-cancer therapies (*Treatment policy* estimand)

Point estimates very similar, no (or only a few) additional events, slightly higher median PFS times in both arms



Percentage of patients who were censored for use of new anticancer therapy:

Treatment arm: 10%
Control: 8%

What is really going on here?

Along comes a regulatory Sherlock Holmes to dig into the individual patient data listings…

Patient ID	PFS analysis	Time (months)	Censoring reason
1	Primary	16.3	Use of new anticancer treatment
	Supplementary (treatment policy)	**16.3**	**In follow-up for progression, last available assessment**
2	Primary	9.5	Use of new anticancer treatment
	Supplementary (treatment policy)	**9.5**	**In follow-up for progression, last available assessment**
3	Primary	10.2	Use of new anticancer treatment
	Supplementary (treatment policy)	**11**	**Withdrawal of consent for all follow up**

1 Hypothetical strategy

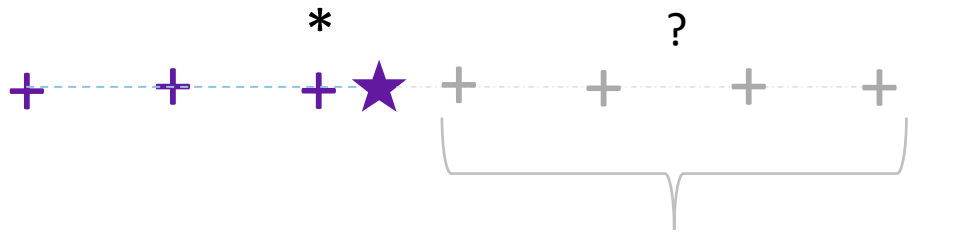
Censored for the reason:
Use of new anticancer therapy

2 Treatment policy strategy

Outcome assessed regardless
of initiation of new anticancer therapy

3 What actually happened

Censored for the reason:
In follow up for progression,
last available assessment



+	Tumour assessment	*	Censoring (at last assessment before NAT)	★	Initiation of new anticancer therapy (NAT)

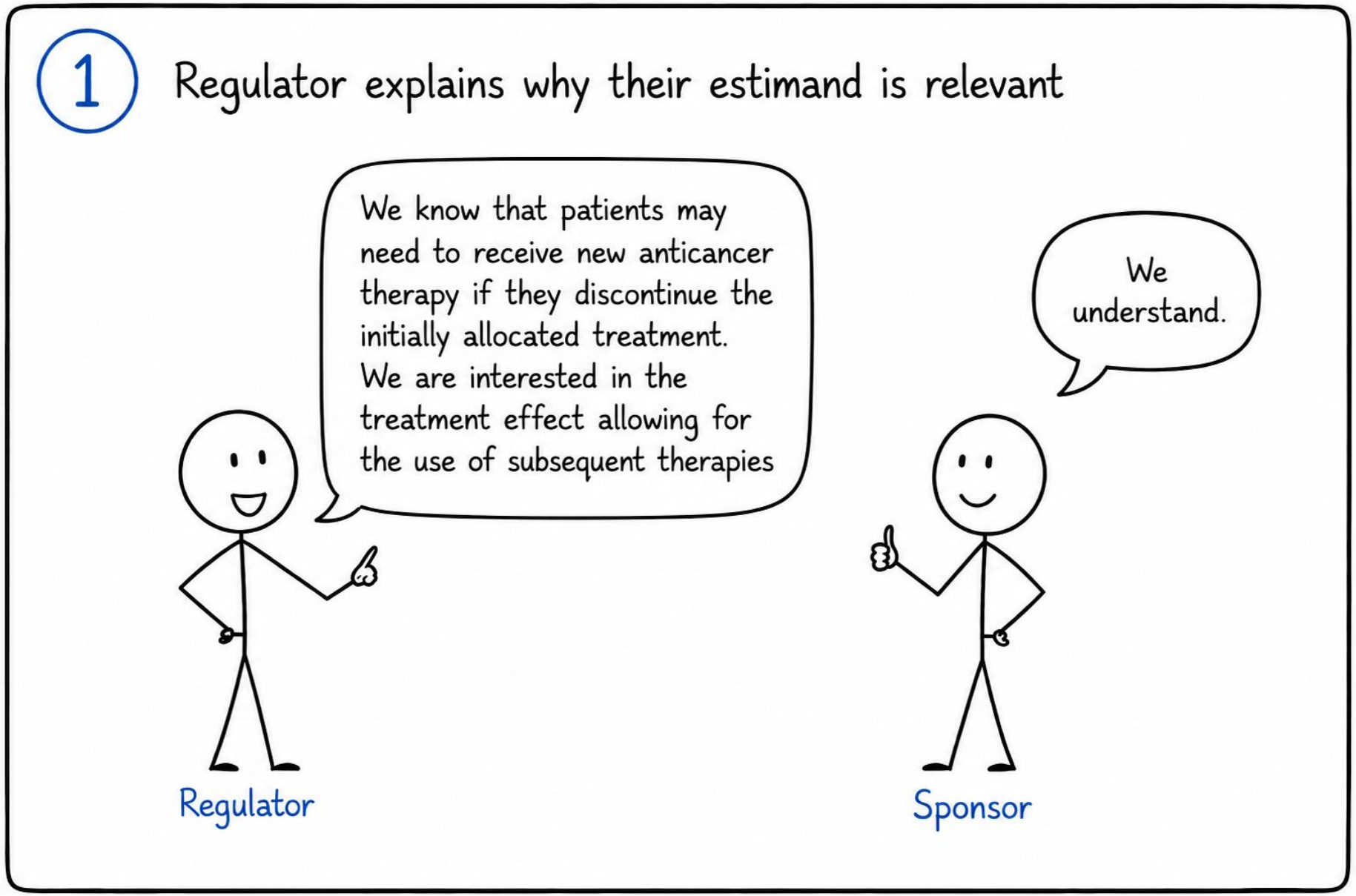
The results were presented in the CSR as if they were targeting the estimand of interest – this is NOT the case. The analysis only shifted patients into different censoring categories and ignored the issue of incomplete follow up.

There was no information provided in the CSR to support an assessment of whether the estimand could be reliably estimated.

The EMA was never going to get the answer to their question

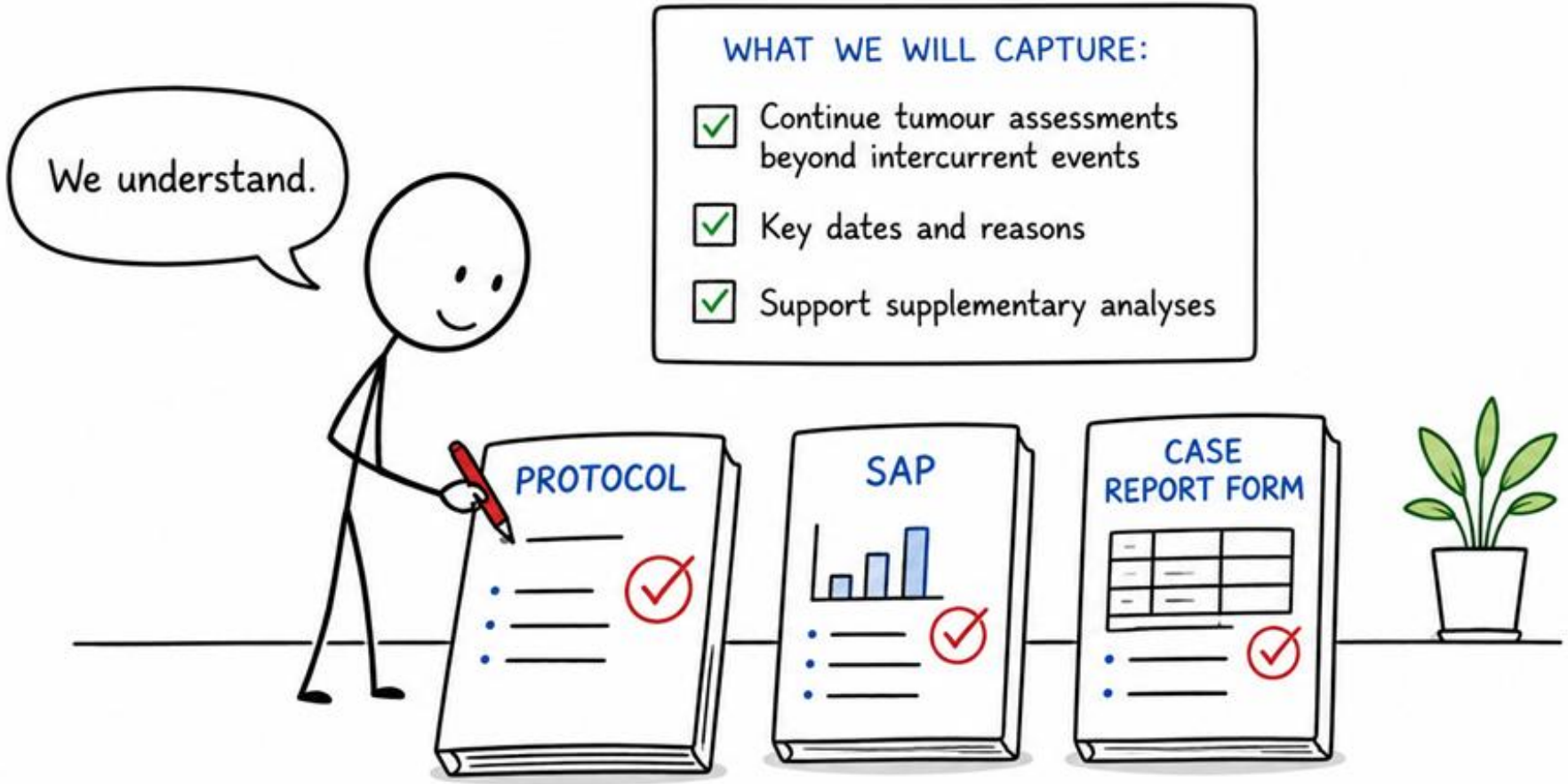
"Patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have tumor assessments until disease progression or **initiation of other anti-cancer treatments.**"

What is needed to get this right?



All pictures created by L. Rodwell and Chat “Picasso” GPT

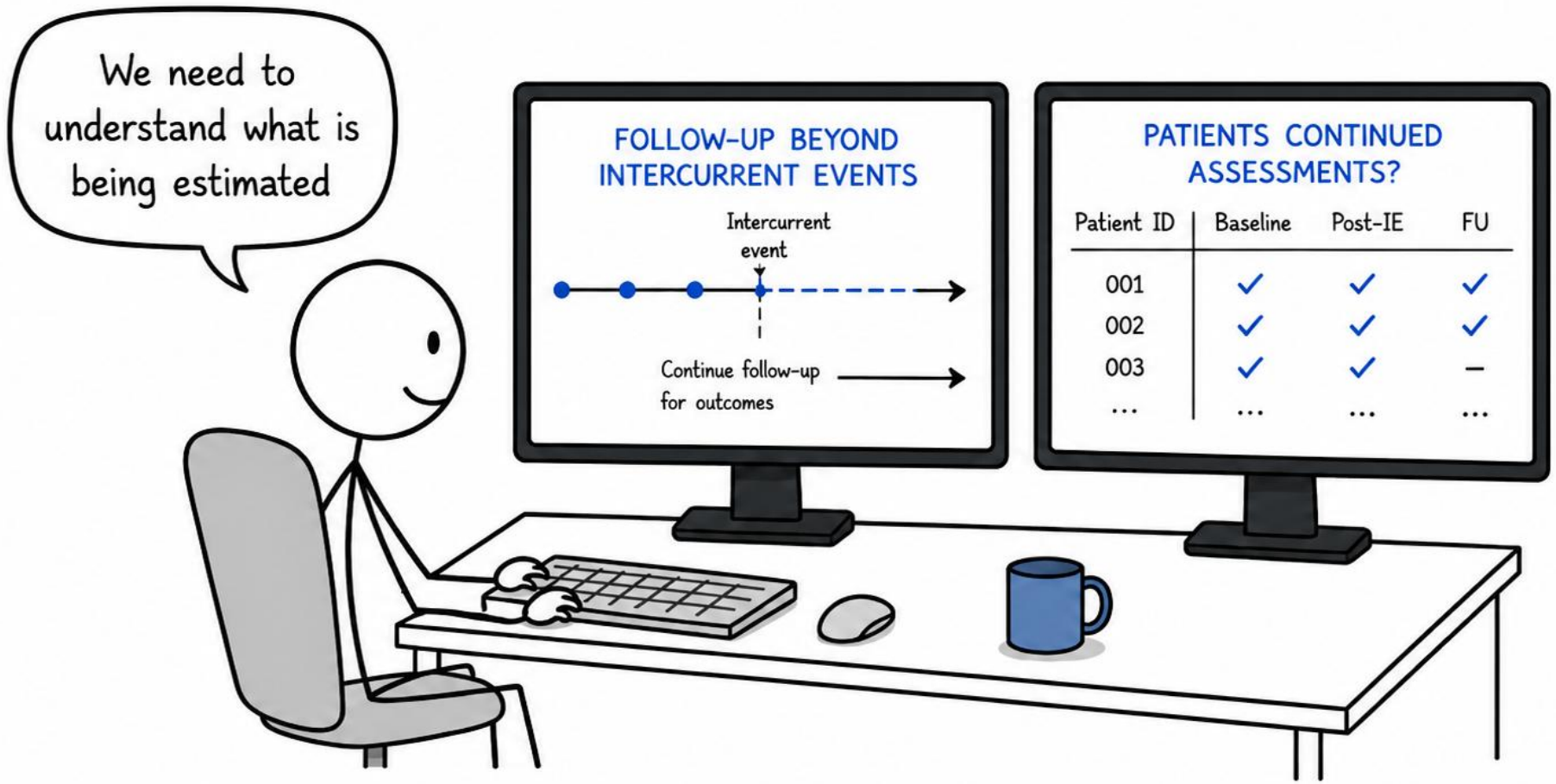
2 Sponsor recognises the importance of the estimand and updates the protocol, SAP, case report form

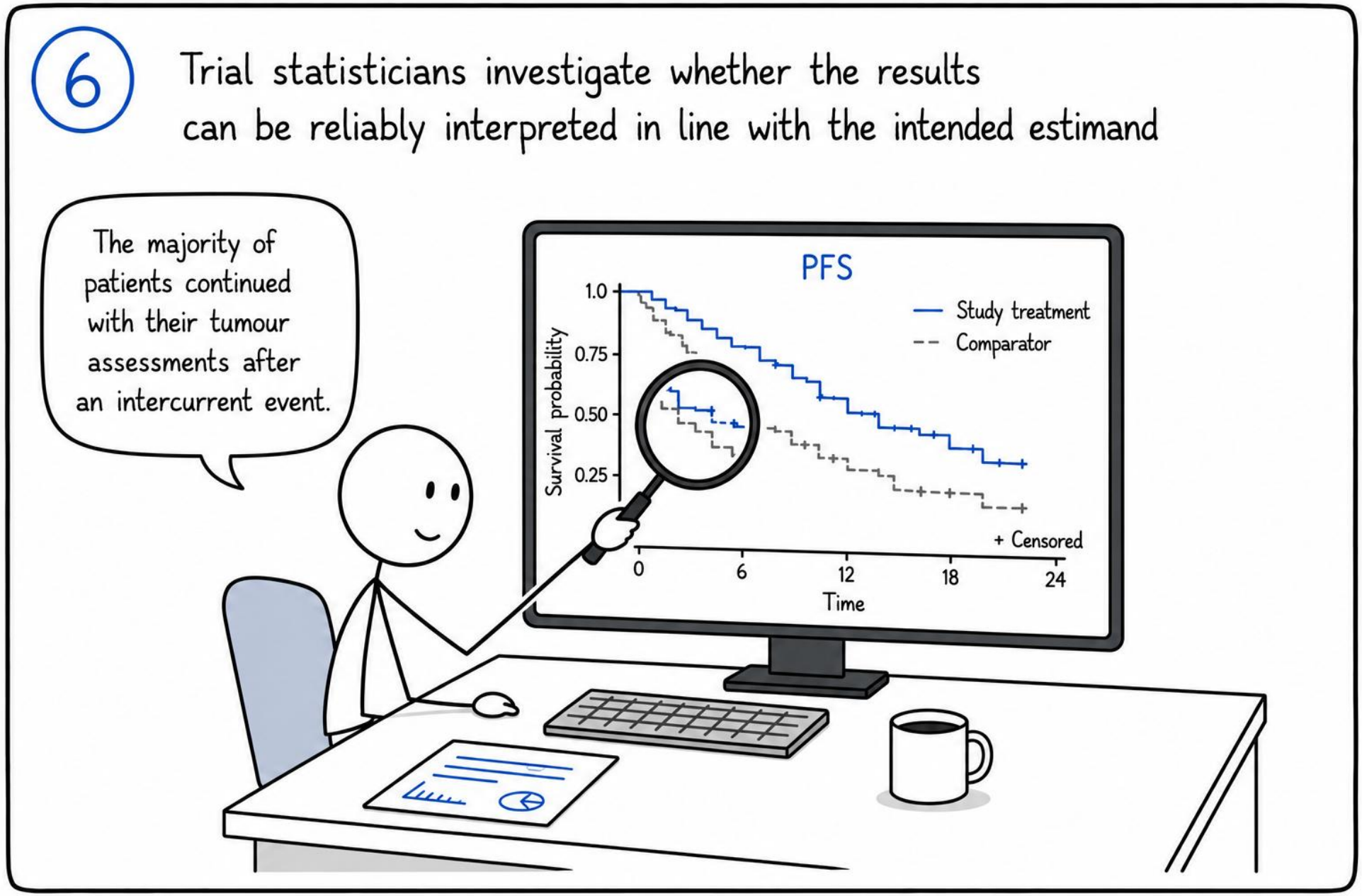


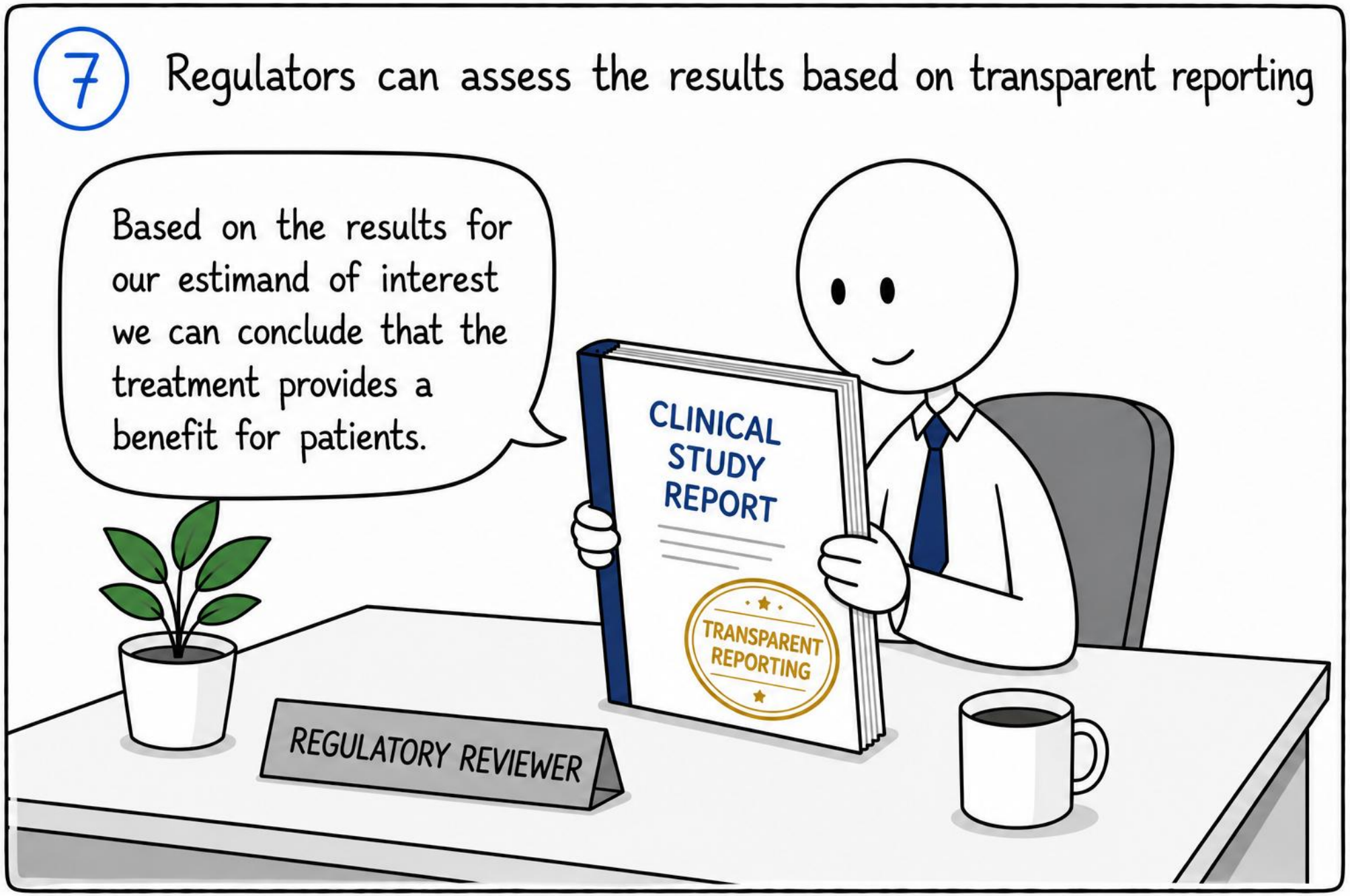
3 Investigator materials are updated to share the importance of continuing tumour assessments regardless of new anticancer therapy

4 Investigators and patients discuss the need to continue tumour assessments as part of the clinical trial

5 Statistical programmers understand the goals of the analyses and what data are needed to support them




6
Trial statisticians investigate whether the results can be reliably interpreted in line with the intended estimand
The majority of patients continued with their tumour assessments after an intercurrent event.
PFS
Survival probability
1.0
0.75
0.50
0.25
Study treatment
Comparator
+ Censored
0
6
12
18
24
Time


7
Regulators can assess the results based on transparent reporting
Based on the results for our estimand of interest we can conclude that the treatment provides a benefit for patients.
CLINICAL STUDY REPORT
TRANSPARENT REPORTING
REGULATORY REVIEWER

What does the ideal future look like for estimands implementation?

When will there no longer be a need for estimands implementation groups?

- All clincal guidelines include discussions on the clinical questions of interest and estimands
- All protocols describe the estimand including clinical reasoning (the WHY), design and analyses are clearly aligned
- There is full transparency when reporting results

  e.g., Number of intercurrent events per treatment arm, completeness of follow up, required assumptions and an evaluation of their plausibility...
- Clinical conferences have sessions dedicated to estimand-related topics, and clinical journals publish lively discussions...