



Guidelines to the design, analysis and interpretation of patient-reported outcomes in cancer clinical trials

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Patients reported outcomes (PRO)



- Important endpoints in the benefit/risk assessment of new cancer therapies
- PROs are becoming more important in research and clinical care
- There is increased collection of PRO data in cancer clinical trials
- However:
- Discrepancy in the analyses, interpretation and presentation of PRO results
- Clinicians find it difficult to interpret PRO results

- SISAQOL-IMI project
- Setting international standards in analysing PROs and QoL Endpoints



In 2021 SISAQOL-IMI started



- IMI (innovative medicines initiative) funded project
- Lead-by EORTC and Boehringer Ingelheim (BI)
- **Aim:** Establishing **international standards** in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials
- **By** seeking **consensus** internationally and across stakeholders (industry, academics, patients, trial organizations, regulators)

Stakeholders involved in SISAQOL-IMI



- Academia,
 - Industry,
 - Regulators
 - Health technology assessment bodies,
 - Clinicians,
 - Methodological and applied statisticians,
 - PRO experts,
 - Patient representatives
-
- And STRATOS

Recommendations: <https://www.sisaqol.org/>



- Final publication in Lancet Oncology 2025 – co authored by all 41 partners
- Interactive table
- Supporting tools
 - Guidebook
 - Patient checklist
 - Graphical templates for PRO endpoints
 - Glossary
 - Educational videos

SISAQOL-IMI recommendations according to PRO objective

	Confirmatory Objective Evaluate clinical benefit Superiority Equivalence/Non-inferiority		Descriptive Objective Describe patient perspective
Magnitude of PRO (change) score at time t	Recommendations ->	Recommendations ->	Recommendations ->
Responder with PRO improvement at time t	Recommendations ->	Recommendations ->	Recommendations ->
Responder with PRO worsening at time t	Recommendations ->	Recommendations ->	Recommendations ->
Time to PRO improvement	Recommendations ->	Recommendations ->	Recommendations ->
Time to PRO worsening	Recommendations ->	Recommendations ->	Recommendations ->
Overall mean or median PRO score over a specified time frame	Recommendations ->	Recommendations ->	Recommendations ->

Some key issues



- Recommendations for RCTs
- Recommendations for Single Arm Studies (SAT) ←
- Recommendations for PRO Score Interpretation Thresholds

PROs in single arm studies



- Single arm trials (SAT) play an increasingly important role in cancer research
 - Rare cancer types, late-stage cancer, targeted therapies
- Patient-reported outcomes (PROs) are highly relevant in cancer studies
 - Especially in SATs for late-stage cancer treatment
- Absence of randomized control group in SAT limits interpretation
 - Observed changes over time not always due to treatment
- PRO objectives in SATs often unclear or not mentioned at all

What might help?



- Apply the ICH E9 (R1) **estimand framework** to PROs in SATs
- Careful handling of **drop-out, intercurrent events** and **missing data**
- Valid methods for comparison of **data from different studies**

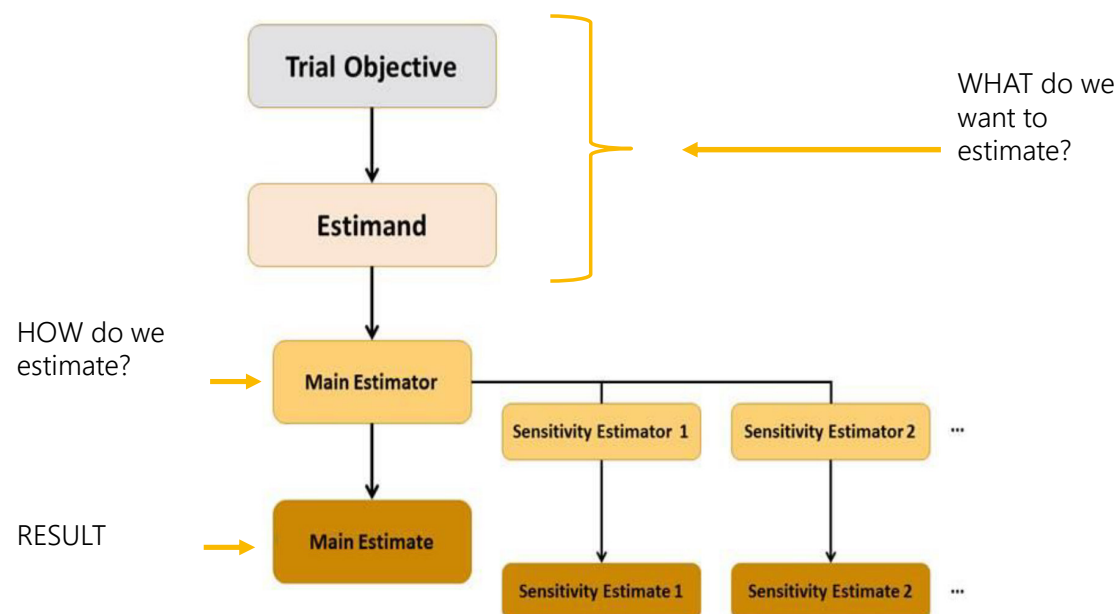
The Estimand framework

1 30 August 2017
2 EMA/CHMP/ICH/436221/2017
3 Committee for Human Medicinal Products

4 ICH E9 (R1) addendum on estimands and sensitivity
5 analysis in clinical trials to the guideline on statistical
6 principles for clinical trials
7 Step 2b

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018

Comments should be provided using this [template](#). The completed comments form should be sent to ich@ema.europa.eu



The ICH E9 (R1) estimand framework

ID	Recommendation
EstFrame6_SAT	Specify the PRO objective through five attributes:

01

**Target
population**

02

**Treatment
condition(s) of
interest**

03

**Variable /
endpoint**

04

**Population-level
summary**

05

**Strategy to deal
with
intercurrent
events (ICEs)**

Align the analysis methods with the estimand.



Choice of PRO variable of interest

Overall mean or median PRO scores over a specified time frame

- Absolute outcome value

Magnitude of PRO (change) score

- Change in outcome from baseline
 - Ceiling and floor effects

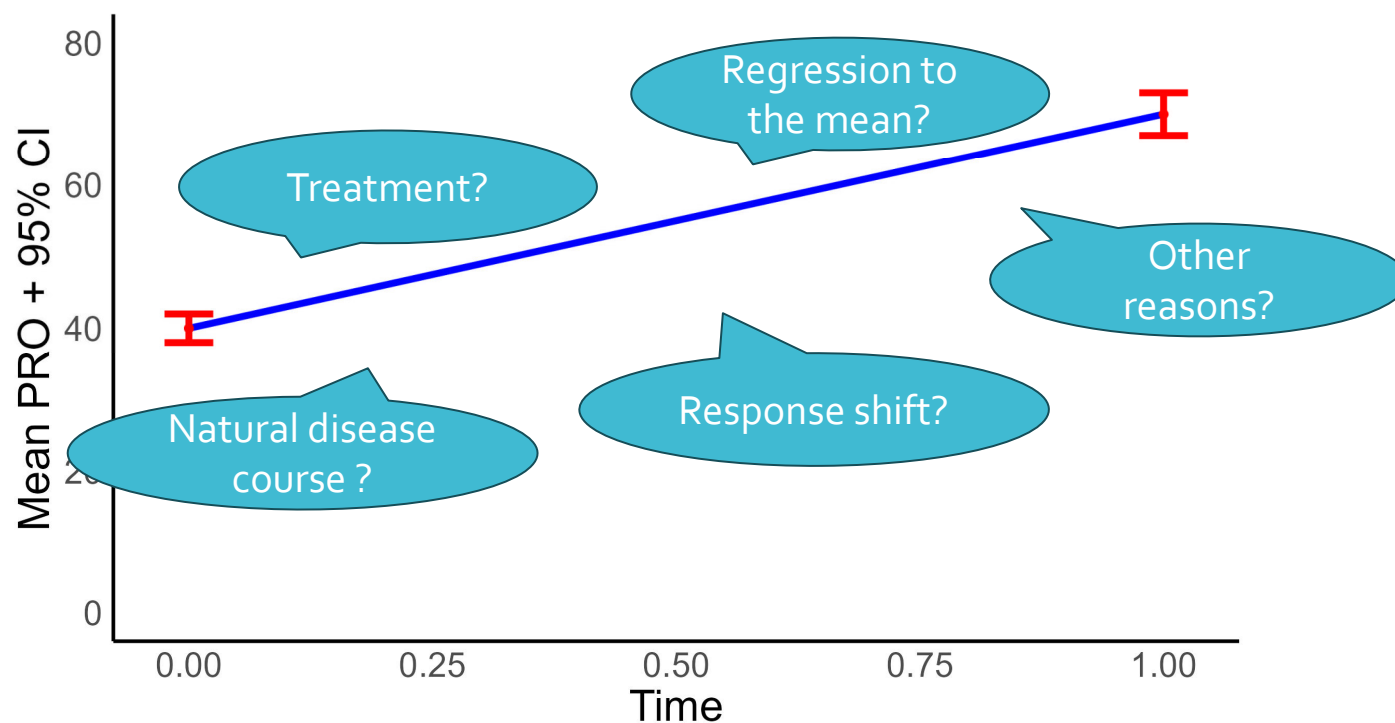
Responder with PRO improvement/Worsening

- ☐ Response/nonresponse

Potentially artificial dichotomy

Interpretation difficult when 'response' is temporary (esp. in time to event analysis)

Challenges in interpreting mean PRO changes in SAT due to lack of randomization



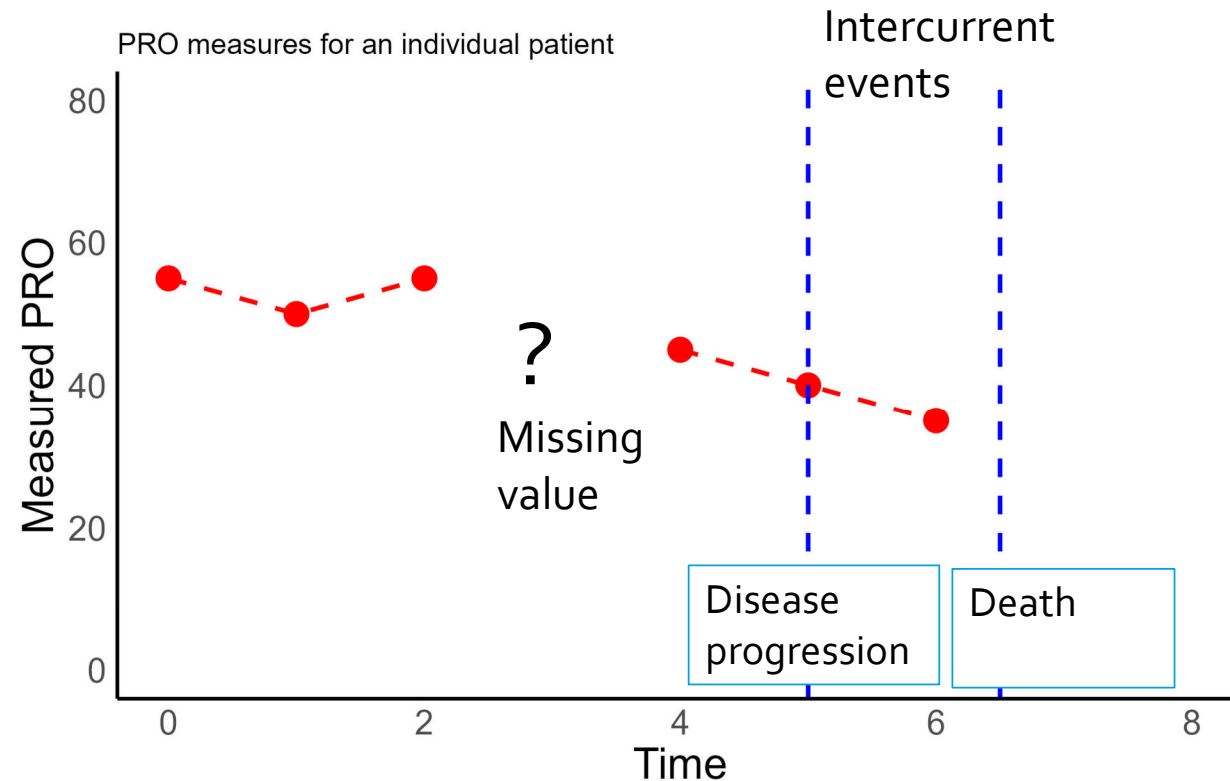


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Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints

Missing values versus intercurrent events

- Patients may not fill out some questionnaires -> missing PRO data
- Intercurrent events may change data collection or interpretation of outcomes





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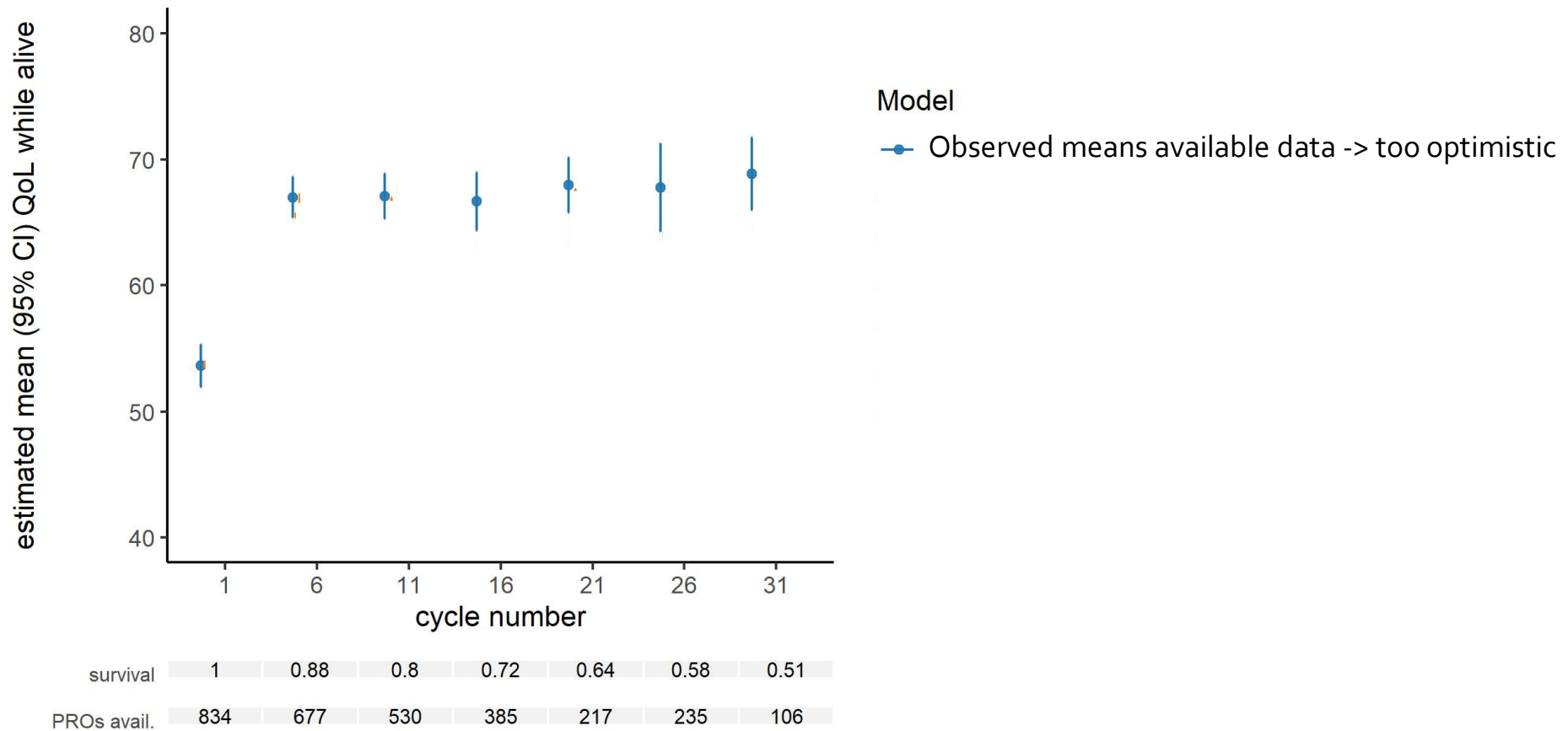
Setting International Standards in Analyzing Patient-Reported
Outcomes and Quality of Life Endpoints

How to deal with missing PRO values?

- Two approaches
 - Reweighting based on probability of missingness
 - Imputation
- Distinguish between missing/imputation model and analysis model
- In imputation model, use information on intercurrent events, timing of intercurrent events, time of death and all other information
 - Assume Missing at Random given the all intercurrent information

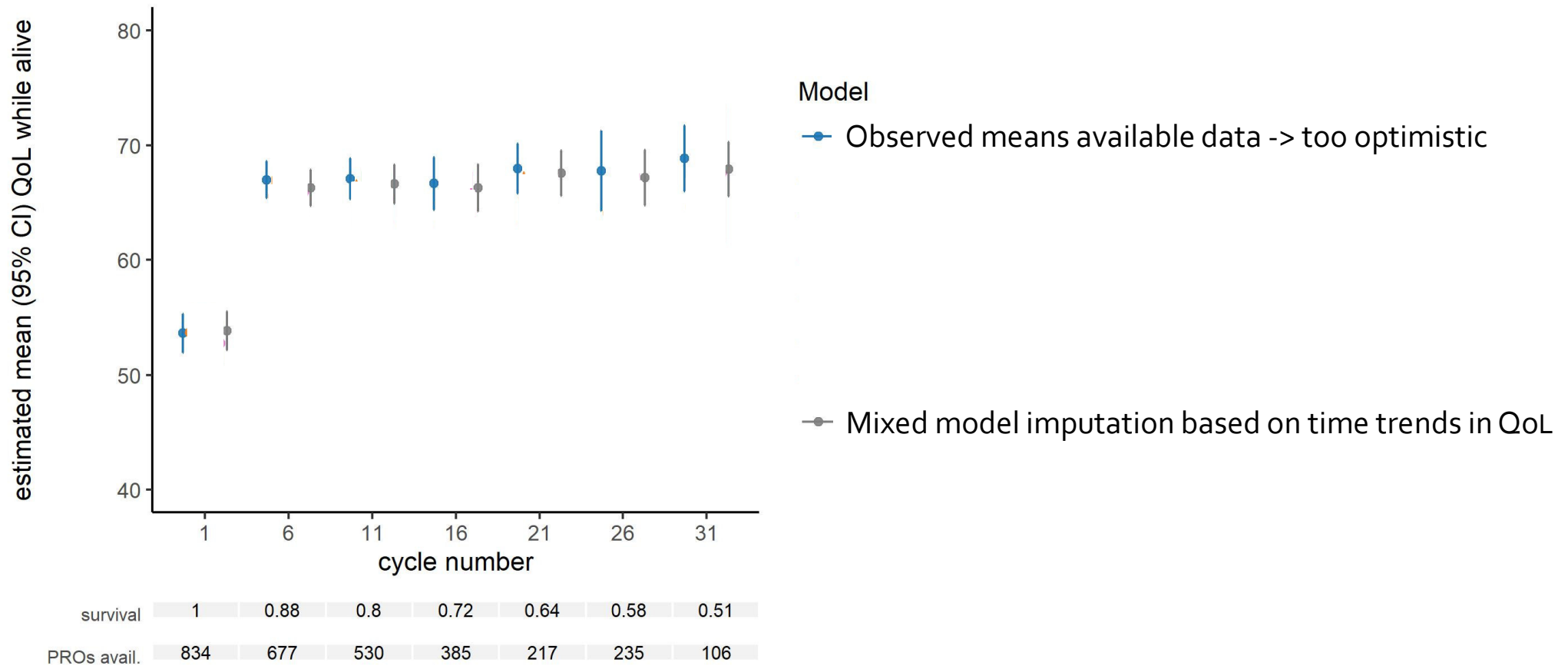
Imputation of missing QoL in case study

Thomassen et al., SISAQOL WP₃ (2025) BMC Med Res Methodol



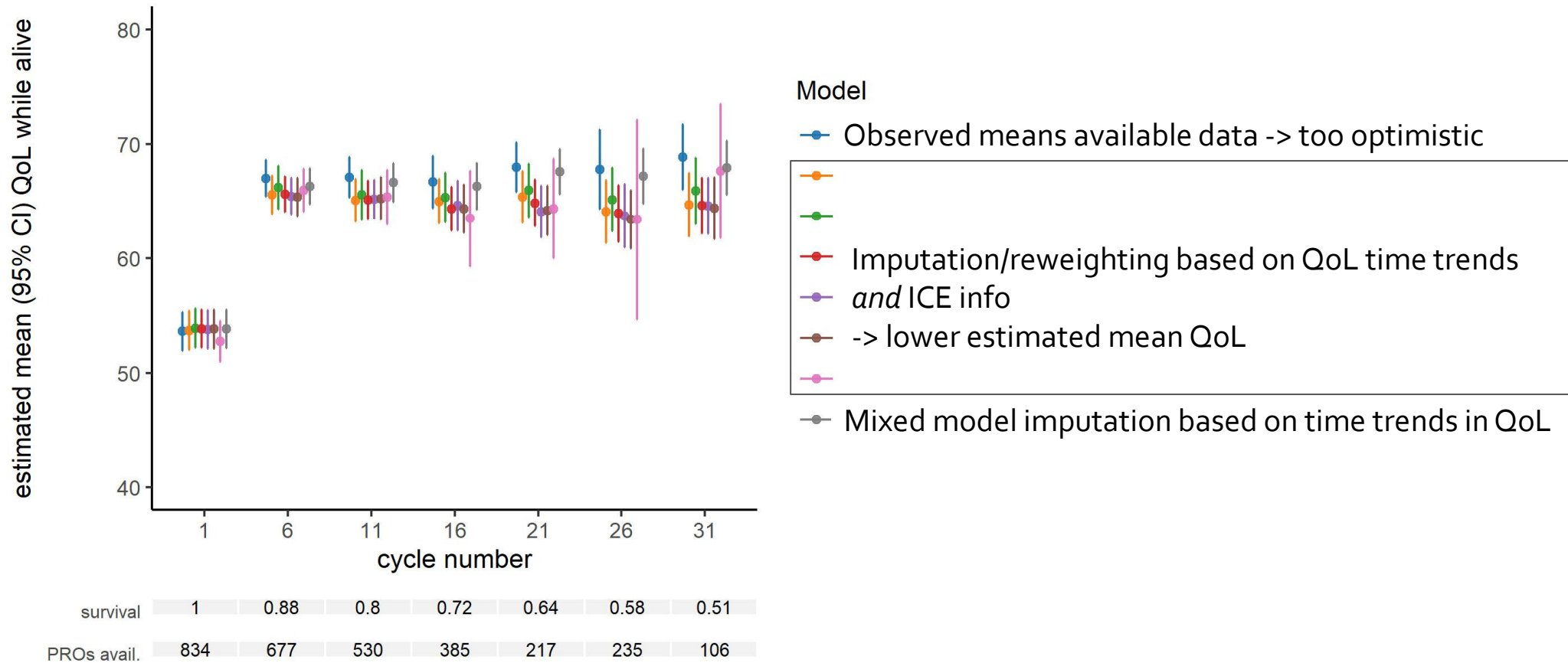
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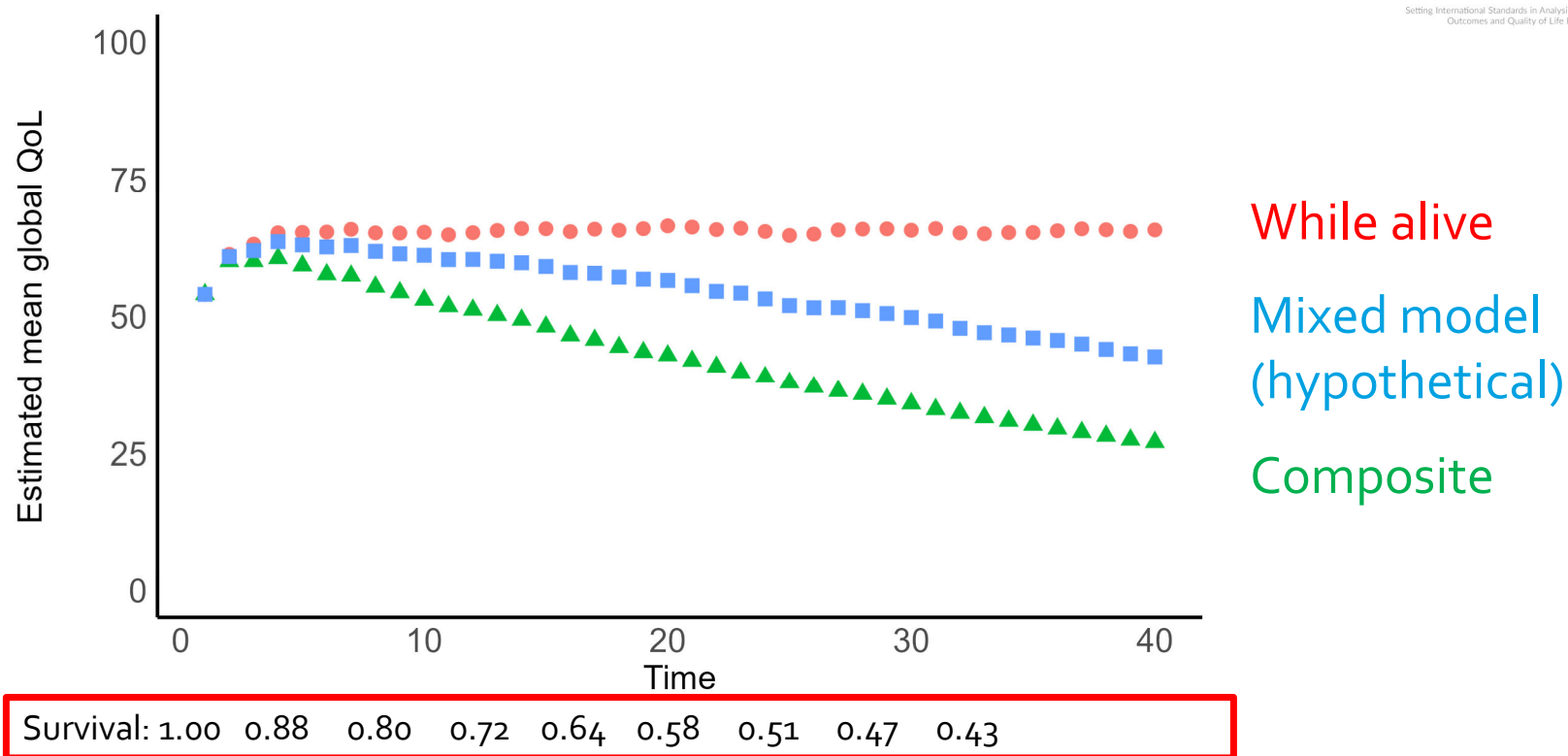


Strategies to deal with death

- While alive
- Hypothetical: what if patients would not die during follow-up?
 - Note: marginal means from **mixed models** imply hypothetical estimand!
- Composite: include death in outcome
 - Assign a QoL value to the state of death (e.g. value 0, cf. EQ-5D)

With all strategies: important to present estimated survival probabilities with results

Handling death: different estimands in single arm study



Use of external control data

In SATs: lack of control group limits interpretation
Observed changes in PRO not solely due to treatment



Compare to external data?

The criteria for selection of patients in the SAT and in the external comparison group must be accurately described (ExComp1_SAT).

Selecting an external control group

Comparability issues:

Characteristics of the study population, both for the single arm study and control setting

PROMs being used

The timing and frequency of PROMs

Variability in PROs, both within and between patients

Duration of the follow-up

How ICEs were defined and how data were collected after ICEs

Differences in patients' perceptions of PROs, such as cultural variations in pain evaluation

Whether the external control setting is blinded or un-blinded

The time period during which PROs were collected.

To summarize



- Quality of design, analyses and reporting of PROs in trials can be improved
- Sisaqol-IMI provides recommendations to do so

SISAQOL-IMI WP3 references



- Amdal C, Falk R, Alanya A et al. [SISAQOL-IMI consensus-based guidelines to design, analyse, interpret, and present patient-reported outcomes in cancer clinical trials](#), *The Lancet Oncology*, 26, e683-e693
- Liu L, Choi J, Musoro JZ, Sauerbrei W, Amdal CD, Alanya A, ..., Thomassen D, Roychoudhury S, Goetghebeur E, le Cessie S. [Single-arm studies involving patient-reported outcome data in oncology: a literature review on current practice](#). *The Lancet Oncology*. 2023;24(5):e197-e206.
- Thomassen D, Roychoudhury S, Amdal CD, Reynnders D, Musoro JZ, Sauerbrei W, Goetghebeur E, le Cessie S; on behalf of SISAQOL-IMI Work Package 3. [The role of the estimand framework in the analysis of patient-reported outcomes in single-arm trials: a case study in oncology](#). *BMC Medical Research Methodology*. 2024;24(1):290.
- Thomassen D, Roychoudhury S, Amdal CD, Reynnders D, Musoro JZ, Sauerbrei W, Goetghebeur E, le Cessie S; on behalf of SISAQOL-IMI Work Package 3. [Handling missing values in patient-reported outcome data in the presence of intercurrent events](#). *BMC Medical Research Methodology*. 2025;25(1):56.
- Reynnders D, Thomassen D, Roychoudhury S, Amdal CD, Musoro JZ, Sauerbrei W, le Cessie S, Goetghebeur E; on behalf of SISAQOL-IMI Work Package 3. [Evaluating treatment effects on longitudinal outcomes with attrition due to death: Methods for While-Alive estimands with a case study in Quality of Life](#). 2025. *Submitted*.