MISSING DATA

- *Not* missing data: QOL after death

- Censoring for all that follows:
  - residual death time and QOL-w-alive

- Intermittent missing data
- Missing data post intercurrent events
- Qol-missing prior to death (value depends on time to death)

To be or not to be MAR?

EXTERNAL CONTROL

- Two- dimensional outcome *(T, QOL(t) for t <T)*
- Control arm of external RCT
- Estimand at t: $\{S_a(t)\ ,\ \ QOL_a(t|\ T> t)\ \}$

- Intermittent missing data -> solved by Doranne (MAR)

- TTE idea: follow the RCT principle

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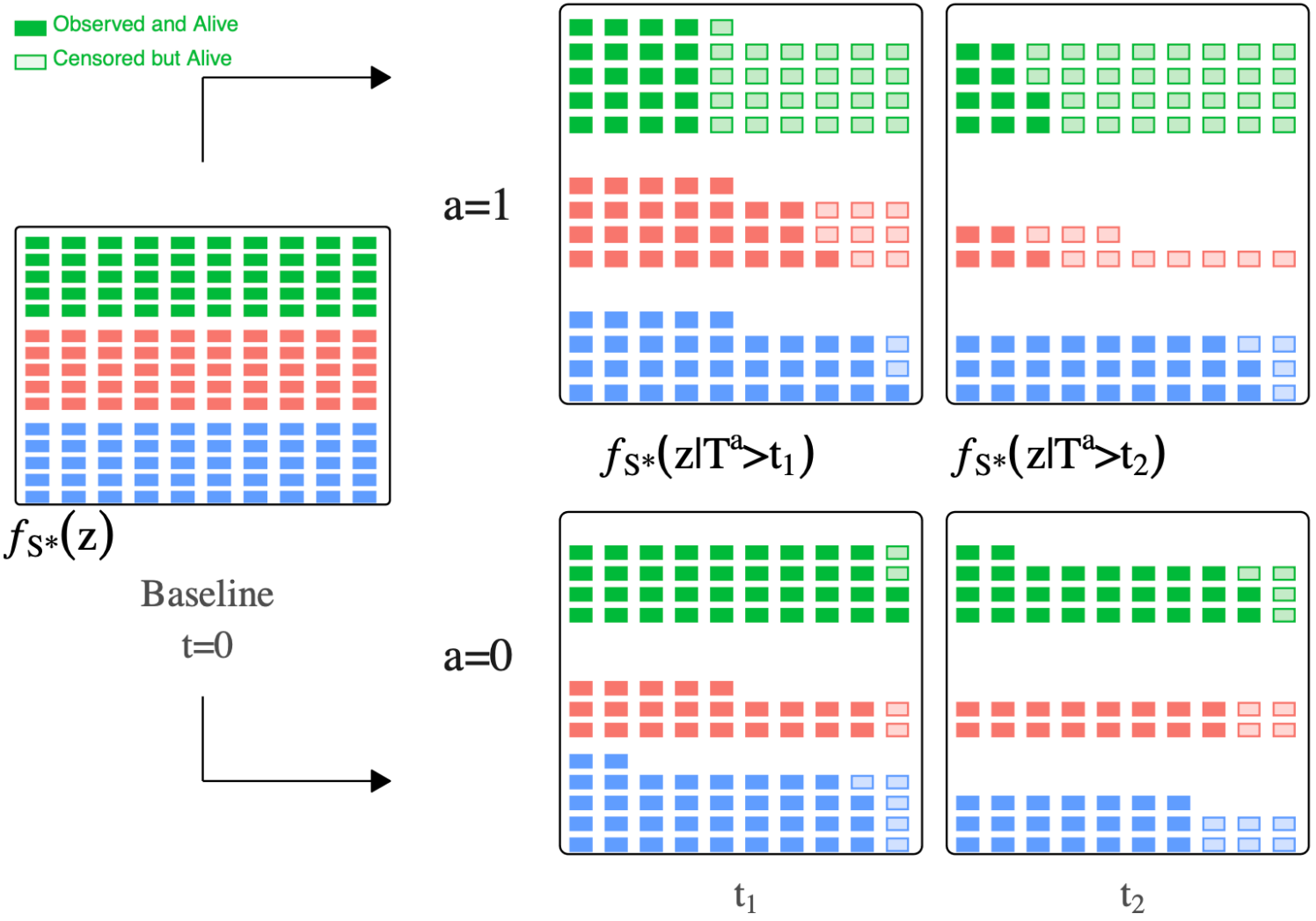
Work with IMI-SISAQOL

Compare with control

RCT like

Population Causal Effect



TWO ESTIMATION APPROACHES

Assuming: non-differential censoring & no unmeasured confounders } conditional on baseline Z

1) **Double weighting** of observed data QOL(t)
   - IPTW (towards target population S*)
   - IPWC (towards alive population S*(t))

$$\frac{f_{S*}(z)}{f_{S_a}(z)}$$

$$1/P(C > t|Z, A = a)$$

e.g. Fit Cox model for censoring distribution

Fit GEE model (with dummies or ow.) independence correlation

Kurland et al, 2005

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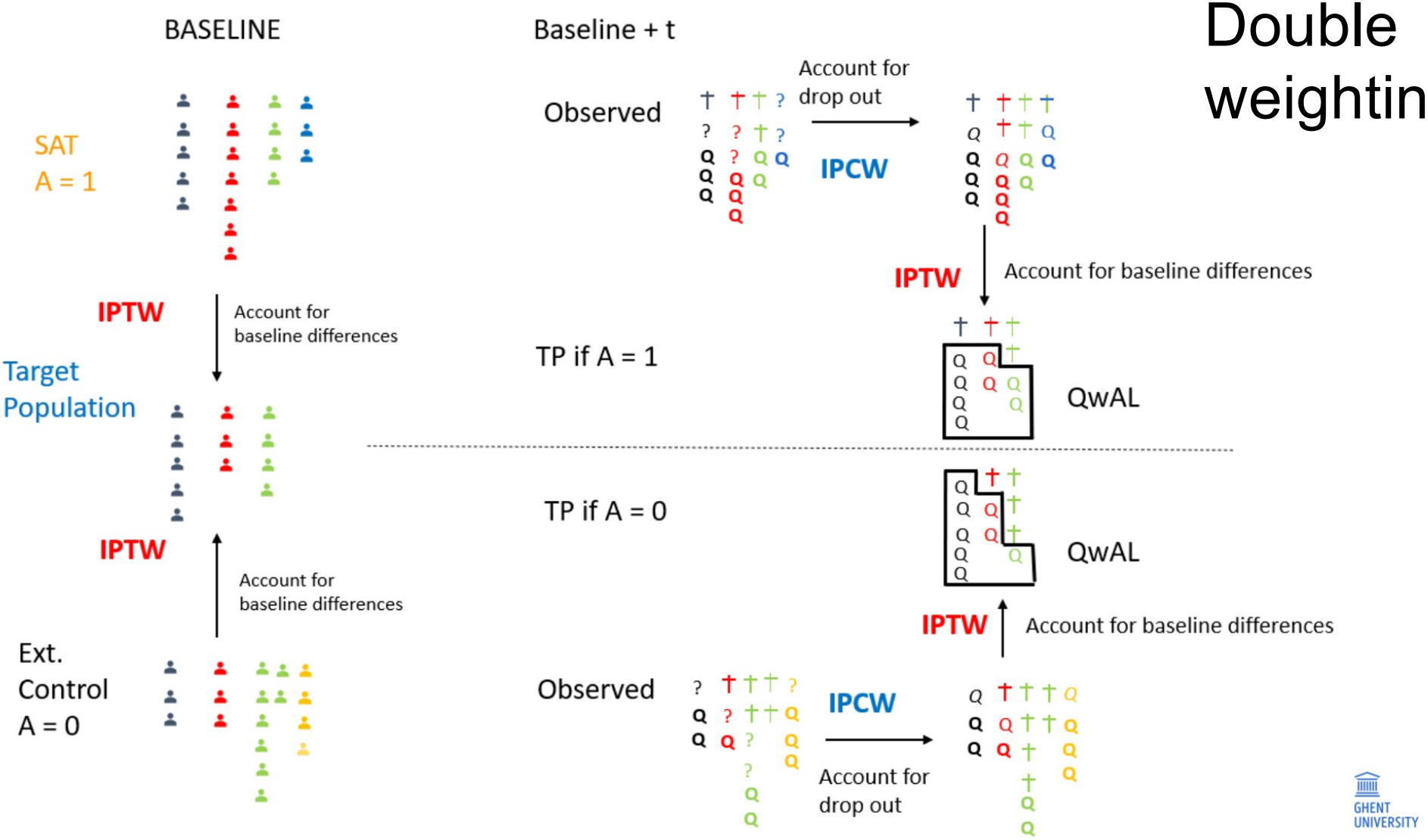
Double weighting



TWO ESTIMATION APPROACHES

Assuming: non-differential censoring & no unmeasured confounders } conditional on baseline Z

2) Outcome regression E(QOL(t) | Z, A=a, min (C,T) > t)
   - Standardize over Z | alive in S* when A=a

$$E(QOL_a(t) \mid Z=z) \times P_{S^*}(Z=z) \times P(T_a>t \mid Z=z)$$

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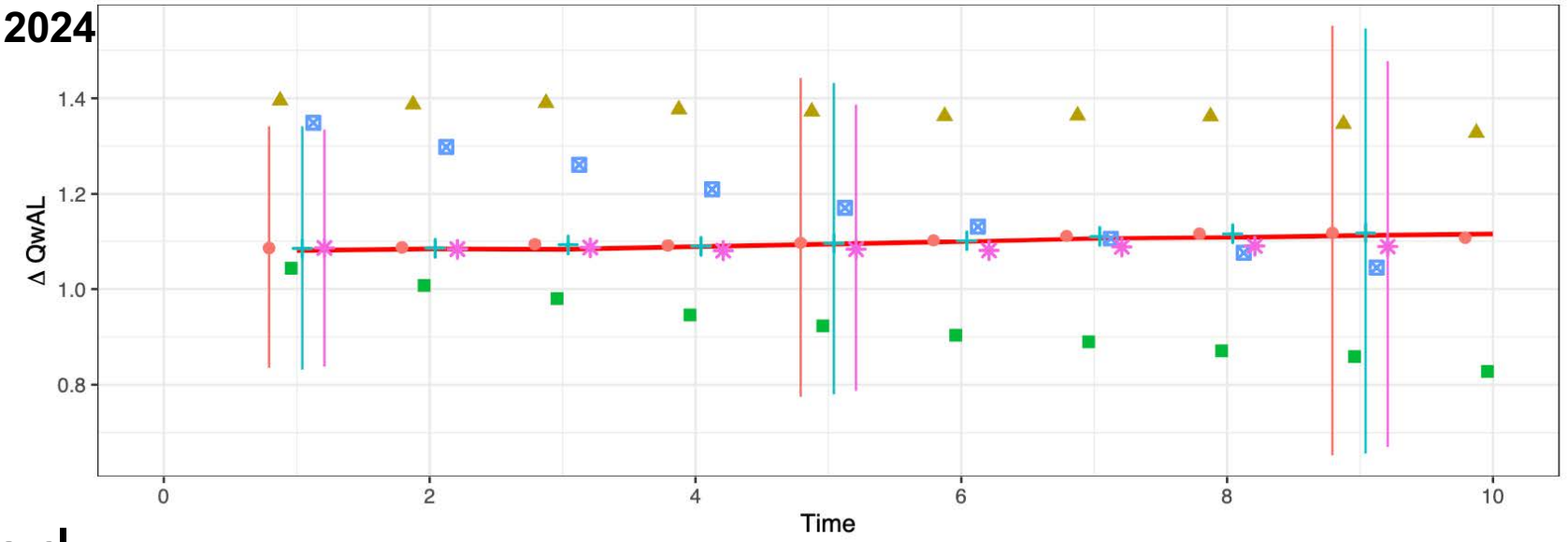
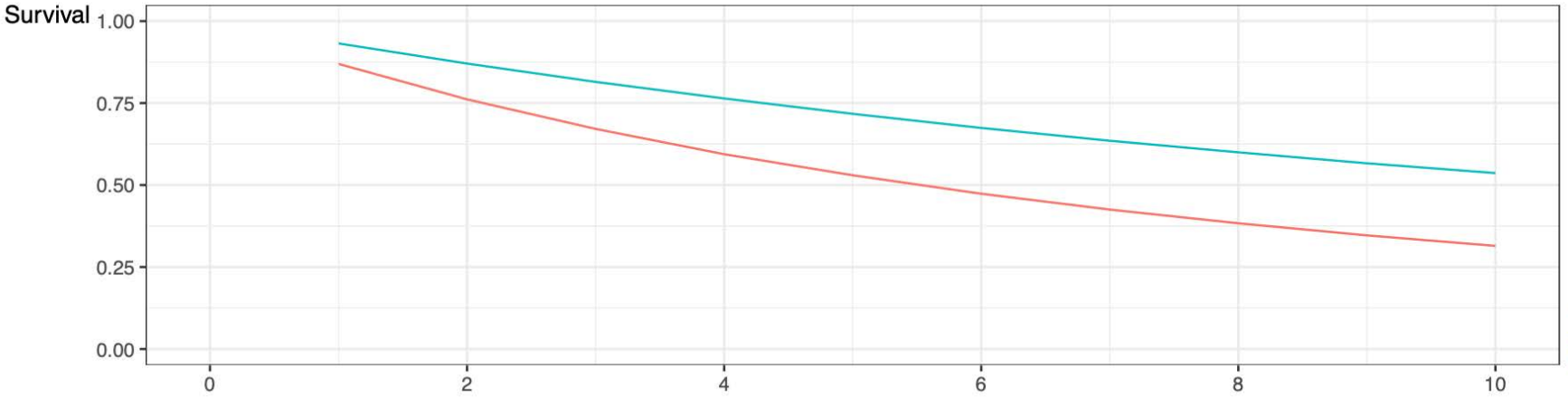


Simulated



GHENT UNIVERSITY

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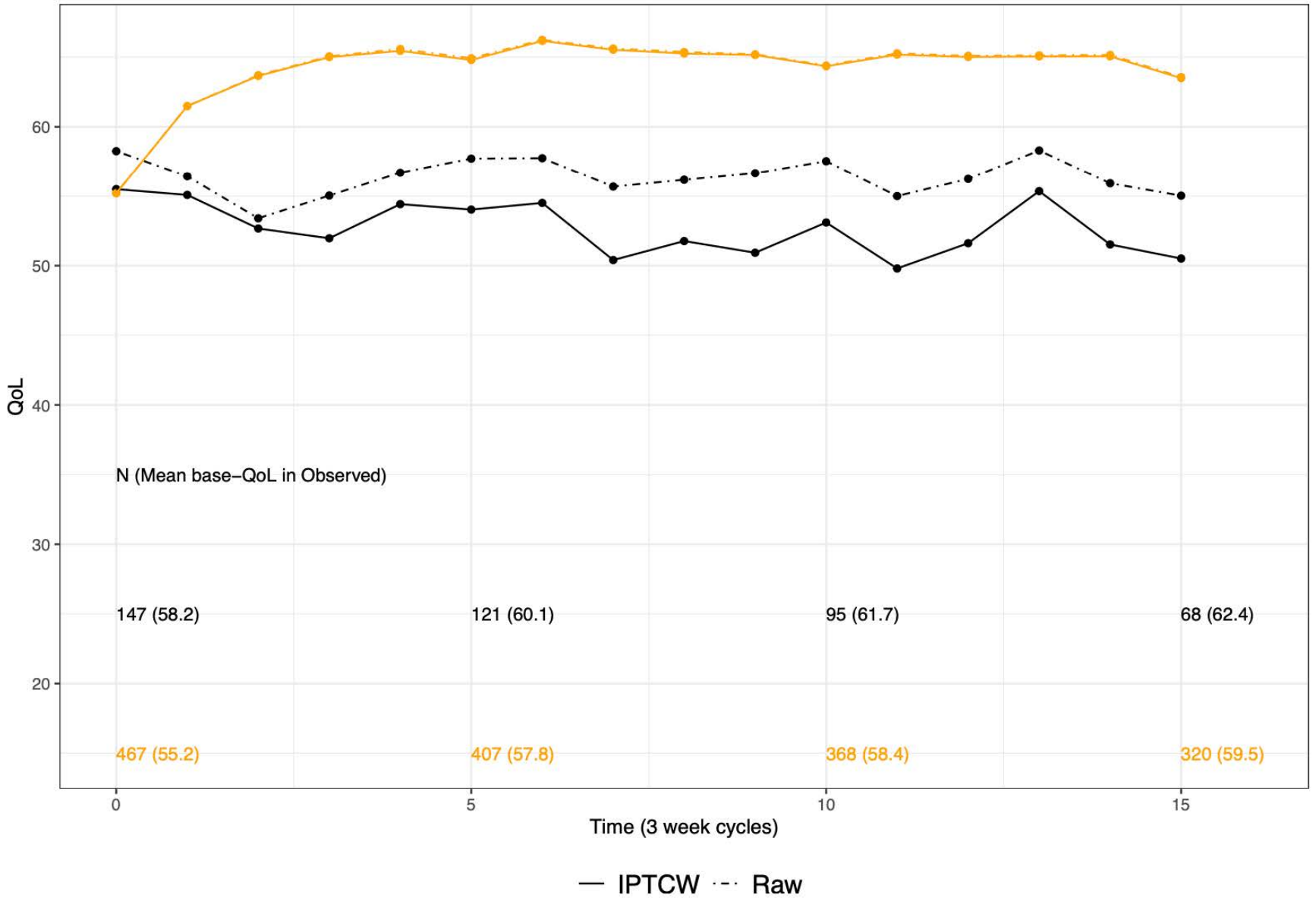
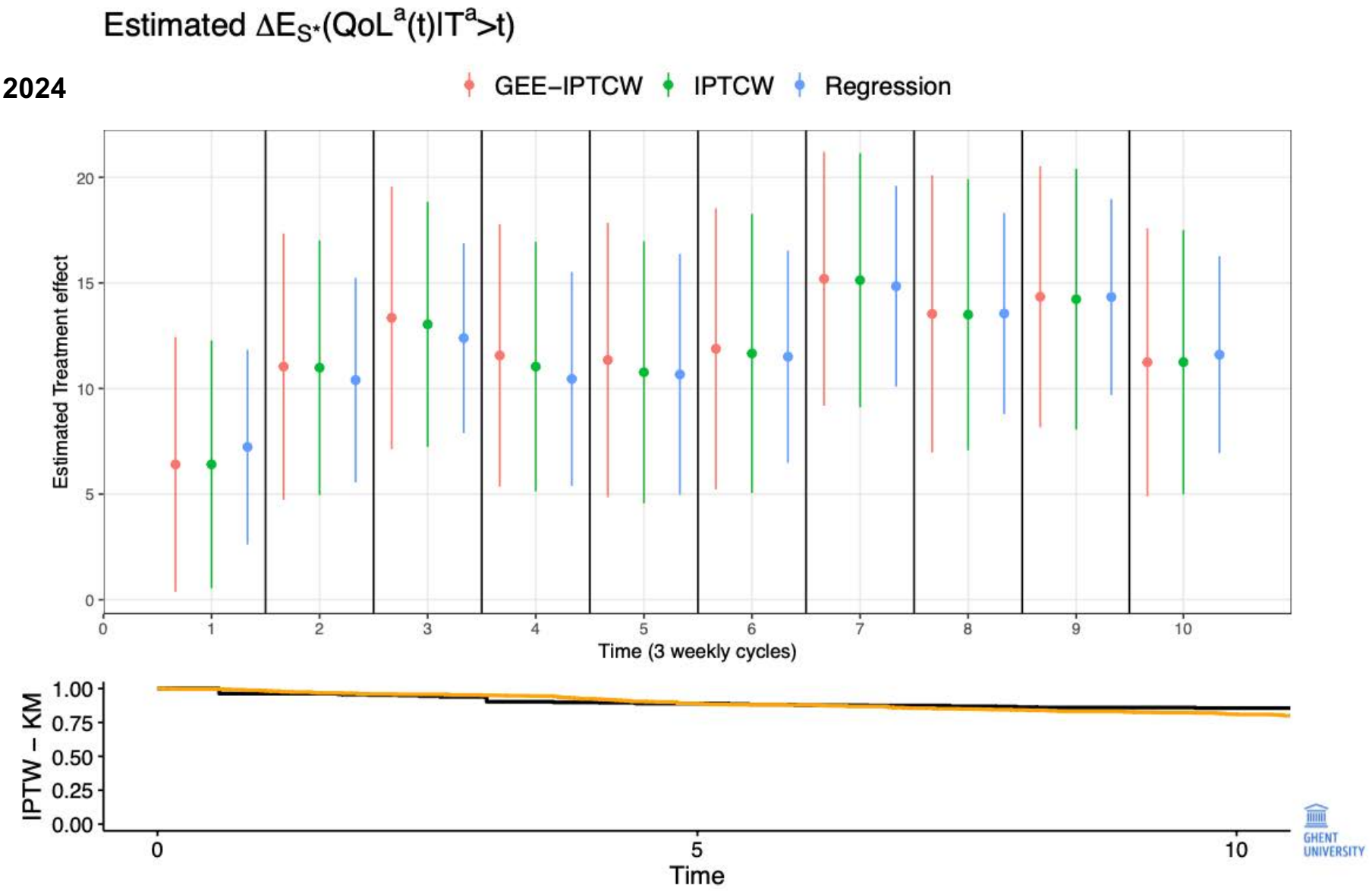
The data!

SAT
versus
RCT
control



Dries @ eurocim 2024

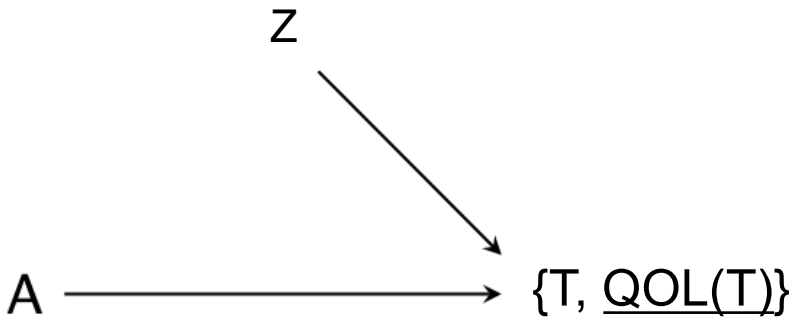


DISCUSSION

- Much more to think through about missing data
- Double/Triple robust – AIPW ?
- Time-varying covariates: IPCW(t)
- Positivity issues?

RESISTING 2-DIMENSIONAL OUTCOME ?

1. `Selection bias'



2. Impute QOL after death (LMM)
3. SACE: $E(QOL_1(t) - QOL_0(t) \mid T_1>t \text{ and } T_0>t)$
   - Never observed (assumption driven)
   - Actionable target population for intervention?
   - What for those outside the target?

III. NEXT

WHAT GUIDANCE NEXT?

- Time-varying exposure
  - Continuous endpoint
  - Survival outcome (TG8)

- MNAR: missing QOL depends on more than is seen (TG1)

- Imputation of {T, QOL(T)} past censoring?

- Non-positivity issues?

LOOKING FORWARD TO THE LORENTZ WS!

REFERENCES

Goetghebeur, Els, Saskia le Cessie, Bianca De Stavola, Erica EM Moodie, Ingeborg Waernbaum, and "on behalf of" the topic group Causal Inference (TG7) of the STRATOS Initiative. 2020. "Formulating Causal Questions and Principled Statistical Answers." *Statistics in Medicine* 39 (30): 4922–48. https://doi.org/10.1002/sim.8741.

Hilal, Talal, Miguel Gonzalez-Velez, and Vinay Prasad. 2020. "Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration." *JAMA internal medicine* 180 (8): 1108–15. https://doi.org/10.1001/jamainternmed.2020.2250.

Kurland, Brenda F., and Patrick J. Heagerty. 2005. "Directly Parameterized Regression Conditioning on Being Alive: Analysis of Longitudinal Data Truncated by Deaths." *Biostatistics* 6 (2): 241–58. https://doi.org/10.1093/biostatistics/kxi006.

Liu, Limin, Jungyeon Choi, Jammbe Z Musoro, Willi Sauerbrei, Cecilie Delphin Amdal, Ahu Alanya, Yolanda Barbachano, et al. 2023. "Single-Arm Studies Involving Patient-Reported Outcome Data in Oncology: A Literature Review on Current Practice." *The Lancet Oncology* 24 (5): e197–206. https://doi.org/10.1016/S1470-2045(23)00110-9.

Thomassen, Doranne, Satrajit Roychoudhury, Cecilie Delphin Amdal, Dries Reynders, Jammbe Z Musoro, Willi Sauerbrei, Els Goetghebeur, and Saskia le Cessie. n.d. "The Role of the Estimand Framework in the Analysis of Patient-Reported Outcomes in Single-Arm Trials." *Submitted*.