STRATOS INITIATIVE

PRESENTED BY ELS GOETGHEBEUR – GHENT UNIVERSITY

ANALYZING PATIENT REPORTED OUTCOME MEASURES (PROMS) IN ONCOLOGY TRIALS

March 28, 2025

GHENT UNIVERSITY

TABLE OF CONTENTS

I. HOW IT STARTED

2021 LAUNCH OF SISAQOL-IMI

EU: IMI (innovative medicines initiative) funded project
A consortium of academia, industry, statisticians, clinicians, patients, regulators
Lead-by EORTC and Boehringer Ingelheim (BI)

https://www.imi.europa.eu/projects-results/project-factsheets/sisaqol-imi
https://event.eortc.org/sisaqol/

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)

STRATOS INITIATIVE ⇄ SISAQOL | IMI

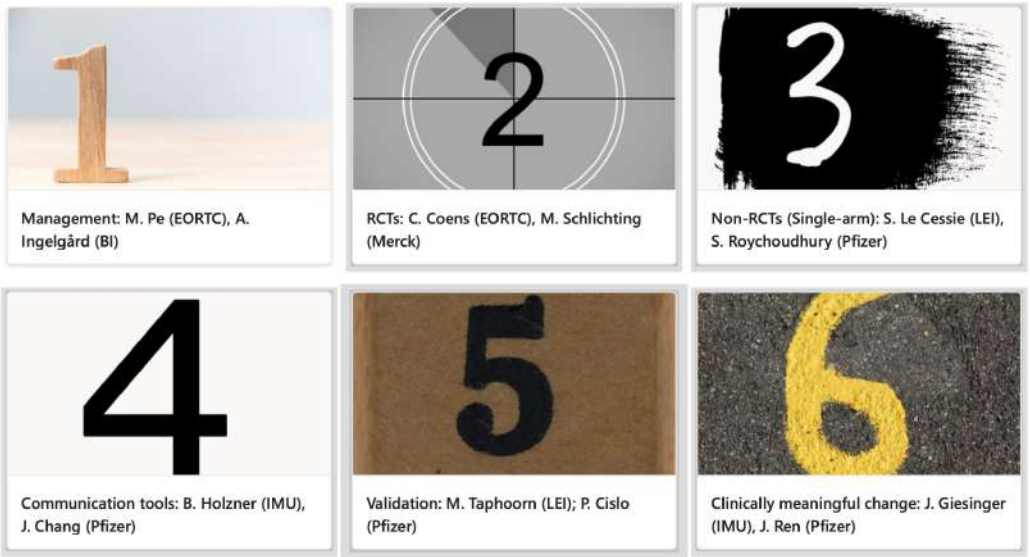
2021 STRATOS joined the EU SISAQOL*-IMI consortium for the development of guidance when estimating **treatment effects on PROMs** in oncology trials -> single arm trials focus in WP3

https://event.eortc.org/sisaqol/

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

ON HOW TO STANDARDIZE

… the use, analysis and interpretation of PRO data in cancer clinical trials



WP3 – CORE TEAM (STRATOS STATISTICIANS*)

Saskia le Cessie* (LUMC) and Satrajit Roychoudhury (Pfizer)

Cecilie Delphin Amdhal (Oslo, N)
Els Goetghebeur* (UGent, BE)
Jammbe Musoro (EORTC, BE)
*Dries Reynders** (UGent, BE)
Willi Sauerbrei* (Universitaetsklinikum Freiburg, DE)
*Doranne Thomassen** (LUMC, NL)

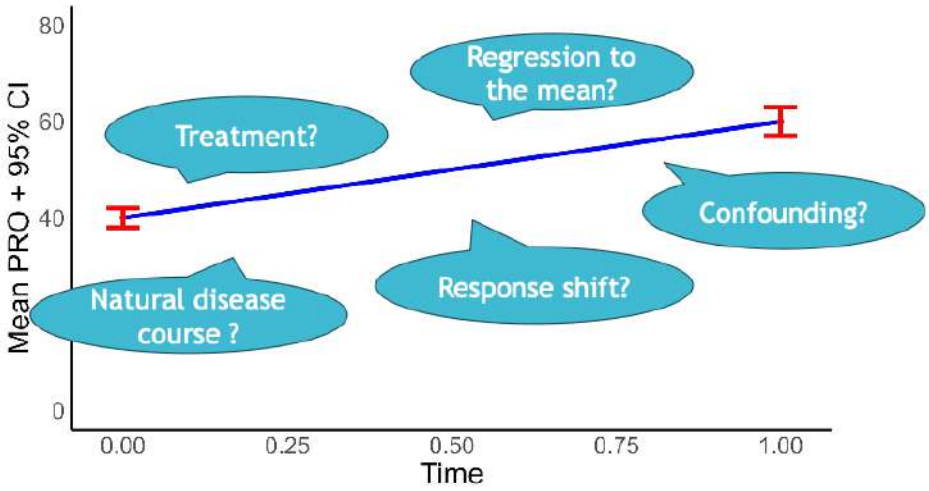
WHAT AND WHY SINGLE ARM?

Studies without a randomized control group
Increasingly popular for (provisional) drug approval
… in rare or end-stage diseases and innovative drugs

- may be `unavoidable' for ethical or practical reasons,
- may be cheaper/faster
- may be more real world setting

BIGGEST PROBLEM TREATMENT EVALUATION:

no concurrent control (+ `soft' outcome)



II. What has been done

OUR DEVELOPMENT ON THE SINGLE ARM

1. **Literature review**
2. High level paper on **estimands** in this setting (target)
   -> with longitudinal outcomes and mortality
   -> accounting for intercurrent events
3. Standard **estimation** approaches in the single arm ->
   -> under common missing data patterns (MAR)
   - ✓ a) the best possible under basic assumptions
   - ✓ b) *in the making* (MNAR) TG1-TG7

4. SINGLE ARM AND EXTERNAL CONTROL

1. Target trial emulation: a common **starting point**
2. A complex **outcome**, issues also in RCT…
   1. Differential **death** under two treatments is
      a first difference in outcome, not `selection bias'
   2. The two-dimensional outcome adds **QoL while alive**
      mean comparisons over time

LITERATURE REVIEW ON SINGLE ARM TRIALS (LIMIN LIU ET AL, LANCET ONCOLOGY 2023)

- 60 single arm cancer studies with PRO measurements
- 13 studies had PRO as (co)primary endpoint

- **Predefined research hypotheses** regarding PROs were rare.
- Handling of **intercurrent events** (death, treatment) not discussed
- PRO data almost never **collected after stopping treatment**.
- Often no **method for missing data**, or no justification for method
- Majority of studies: **PROs supported treatment conclusion**. Only one study advised against treatment based on PRO data.

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4 Highlighted recommendations…

RESEARCH OBJECTIVES AND ESTIMANDS

Single-arm trials should have **pre-specified PRO objectives** that should be translated into **key clinical questions** using the **estimand framework**.

PRO OBJECTIVES WITHOUT RCT

- PRO objectives can be **descriptive or confirmatory**
- The analysis strategy should be aligned with the research question using the estimand framework to address the question of interest.
- Comparisons can be made using **change from baseline or a suitable external control**
- Appropriate steps should be taken in the **design and conduct** to **reduce bias** and avoid misleading interpretations
- **Absence of randomisation** and blinding should be **addressed**

HANDLING DEATH IN SINGLE-ARM TRIALS

∃ **different strategies to handle death** in single-arm trials.

- The **chosen strategy** should be **defined prior to analysis** *in line with* the pre-defined PRO objective. Eg. the while-alive strategy is generally preferred for QOL over time
- The population-level summary for this approach i**ncludes** the **PRO score of participants alive** and **descriptive statistics about death** such as the proportion of patients still alive at the time point of assessment.

INTERCURRENT EVENTS & MISSING VALUES

Specify strategies used **for the intercurrent events in the estimand…** and how missing values are handled.

State plausibility of **assumptions underlying** the analysis method relies and whether the result is still in line with the intended estimand should be examined.

ESTIMANDS AND INTER CURRENT EVENT STRATEGIES (THOMASSEN ET AL., BMC MRM, 2024)

Treatment policy –> keep our eye on original QOL

Composite outcome -> include ICE in `QOL outcome'

Hypothetical -> *What if* no ICE -> potential outcome

While *no ICE* (while alive, while on-treatment, …)

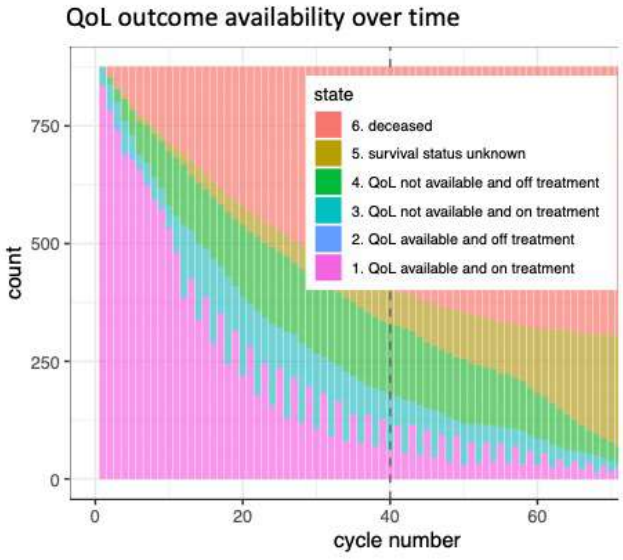
Trial design

SISAQOL | IMI

Clinical trial in advanced lung cancer, single arm

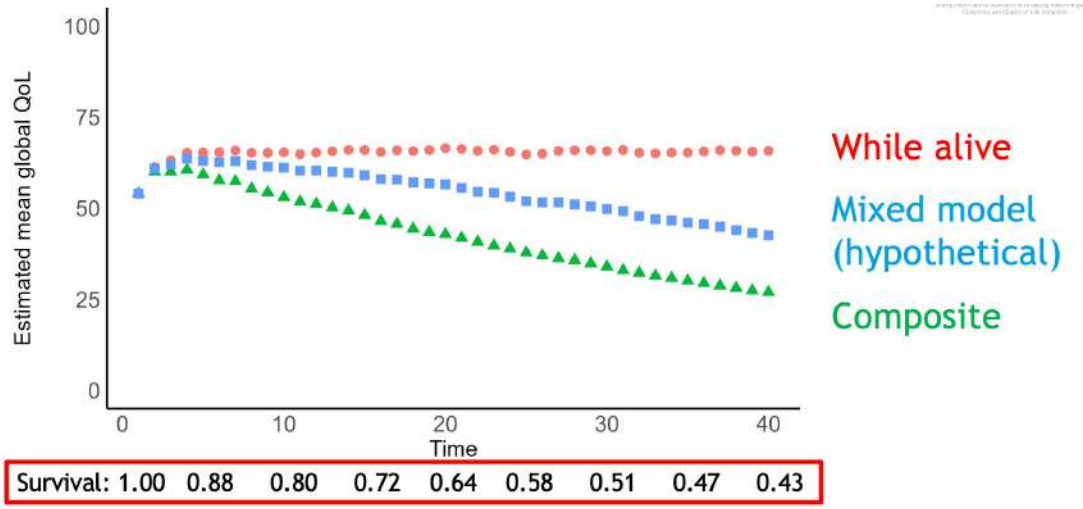
Repeated PRO measurements scheduled in 3 week cycles
Global quality of life (**QoL, 0-100**)

Intercurrent events
Progression of disease (**PD**)
Treatment discontinuation (**TD**)
Death



INTERCURRENT EVENT STRATEGIES				ANALYSIS	
While no IE	Composite	Hypothetical	Treatment policy	QoL data included in the analysis (assuming missing data is handled separately)	Estimation of mean QoL at each cycle (cycle number categorical in all analyses)
Death			PD, TD	All outcomes until death, including after TD/PD.	Generalized estimating equations (**GEE**) + independence correlation structure Linear mixed model (**LMM**), average predictions only over those alive, bootstrap SEs
	Death		PD, TD	All outcomes until death, including after TD/PD. After death, QoL set to 0.	GEE with independence correlation structure LMM also possible
		Death	PD, TD	All outcomes until death, including after TD/PD.	Marginal means from LMM
Death		TD	PD	All outcomes before TD or death, including after PD.	LMM, average individual predictions only over those alive, bootstrap SEs

Doranne @ eurocim 2024



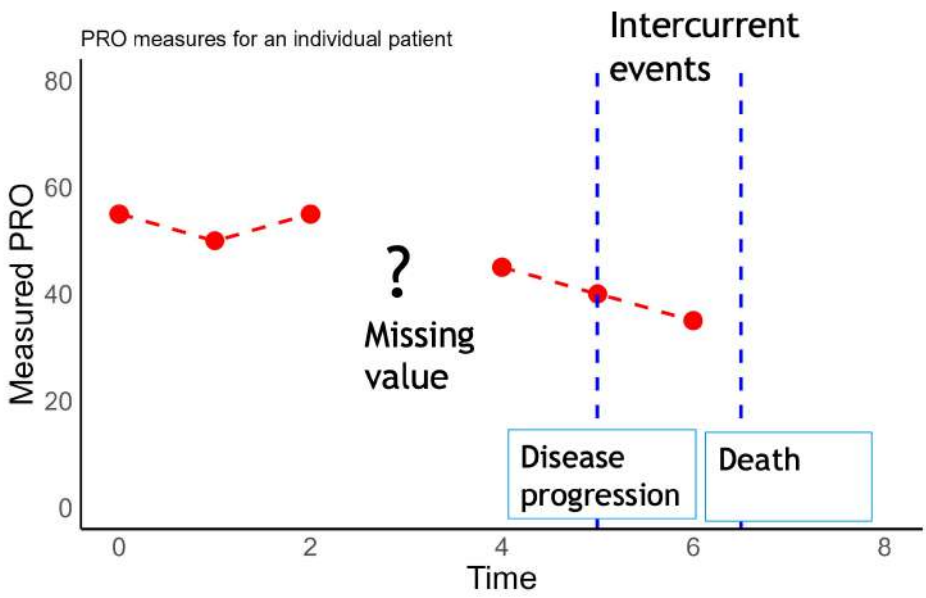
Thomassen et al. BMC Med Res Meth 2024

MISSING & INTERCURRENT EVENTS
(THOMASSEN ET AL., BMC MRM, 2025)

- *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?

MISSING & INTERCURRENT EVENTS



EXTERNAL CONTROL
REYNDERS ET AL, UNDER REVIEW

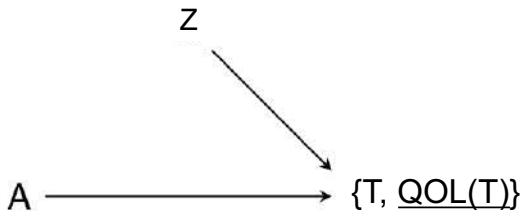
- Two- dimensional outcome *(T, QOL(t) for t <T)*
- Control arm of external RCT
- Estimand at t: {$S_a(t)$, $QOL_a(t| T> t)$ }

- Intermittent missing data -> solved before (MAR)

- TTE idea: follow the RCT principle

RESISTING 2-DIMENSIONAL OUTCOME ?

1. `Selection bias'

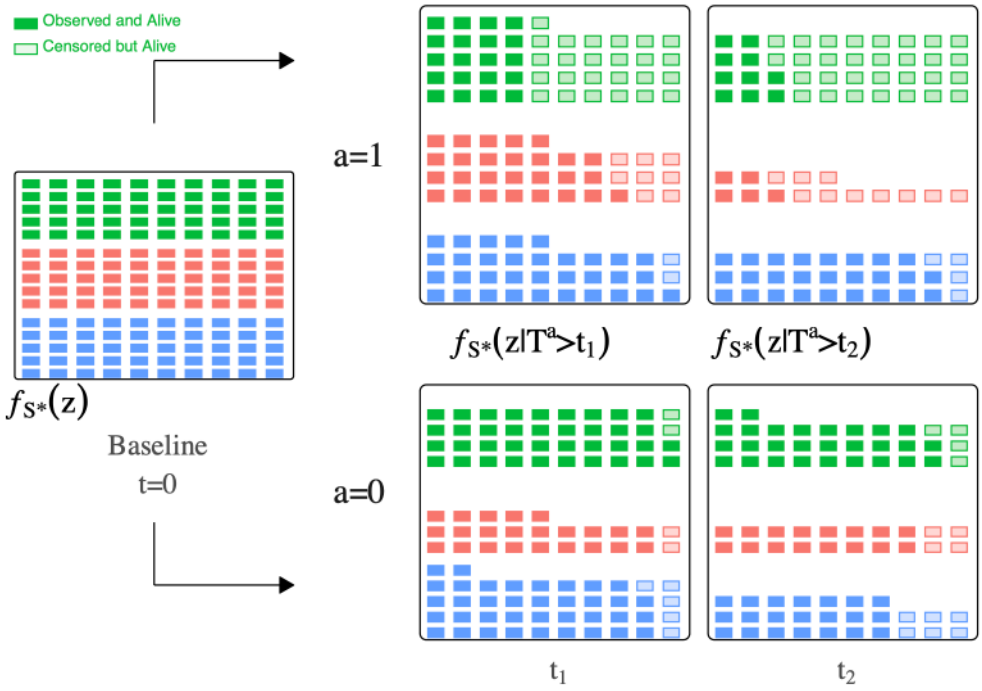


2. Impute QOL after death (LMM)
3. SACE: $E(QOL_1(t) - QOL_0(t) | T_1>t$ *and* $T_0 >t)$
   - Never observed (assumption driven)
   - Actionable target population for intervention?
   - What for those outside the target?

Compare with control

RCT like

Population Causal Effect



TWO ESTIMATION APPROACHES

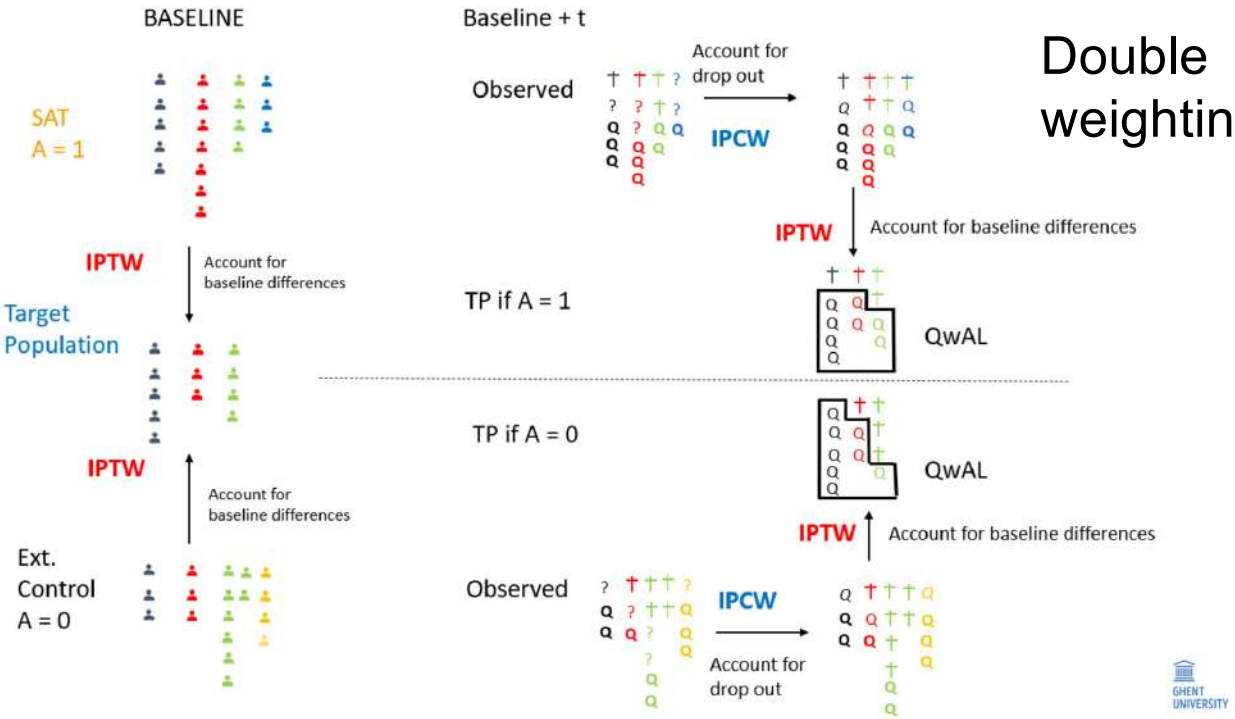
Assuming: non-differential censoring & no unmeasured confounders } conditional on baseline Z

1) **Double weighting** of observed data QOL(t)
   - IPTW (towards target population S*) $\frac{f_{S*}(z)}{f_{S_a}(z)}$
   - IPWC (towards alive population S*(t)) $1/P(C > t|Z, A = a)$

e.g. Fit Cox model for censoring distribution

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

Kurland et al, 2005



Double weighting

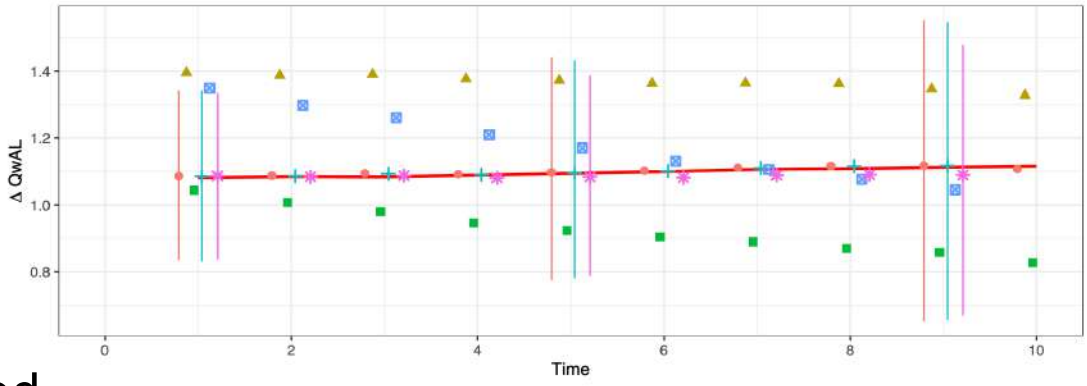
© Dries

TWO ESTIMATION APPROACHES

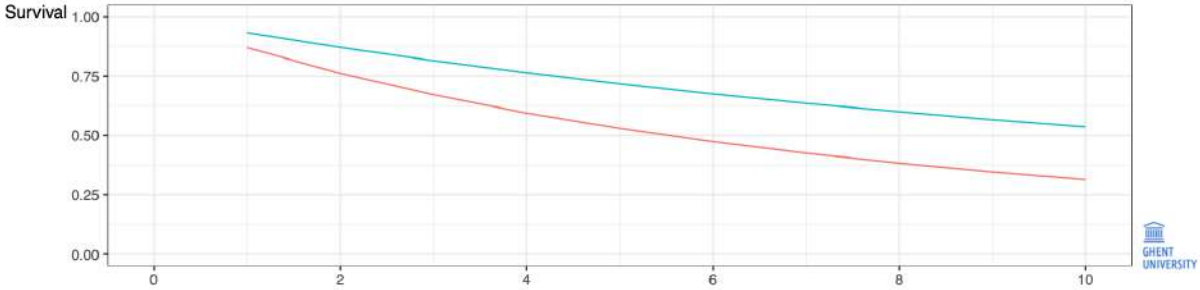
Assuming: non-differential censoring & no unmeasured confounders } conditional on baseline Z

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

$$E(QOL^a(t) \mid Z=z) \times P_{S^*}(Z=z) \times P(T^a>t \mid Z=z)$$

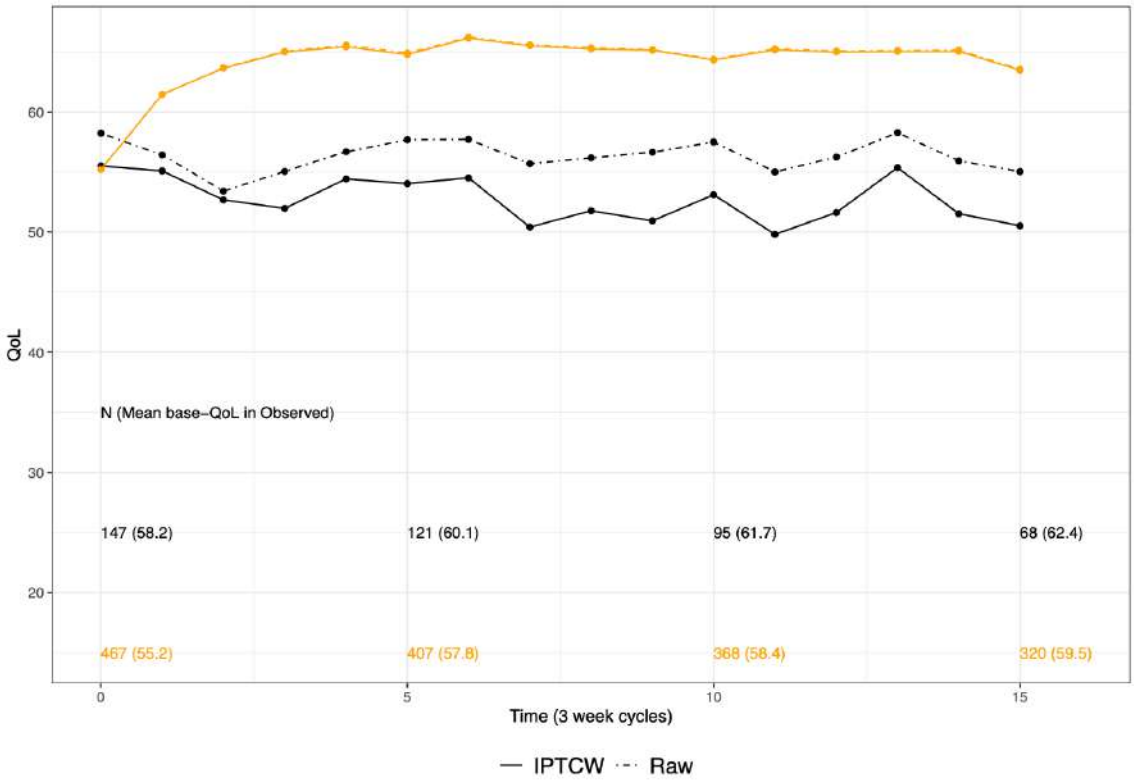


Simulated



The data!

SAT versus RCT control



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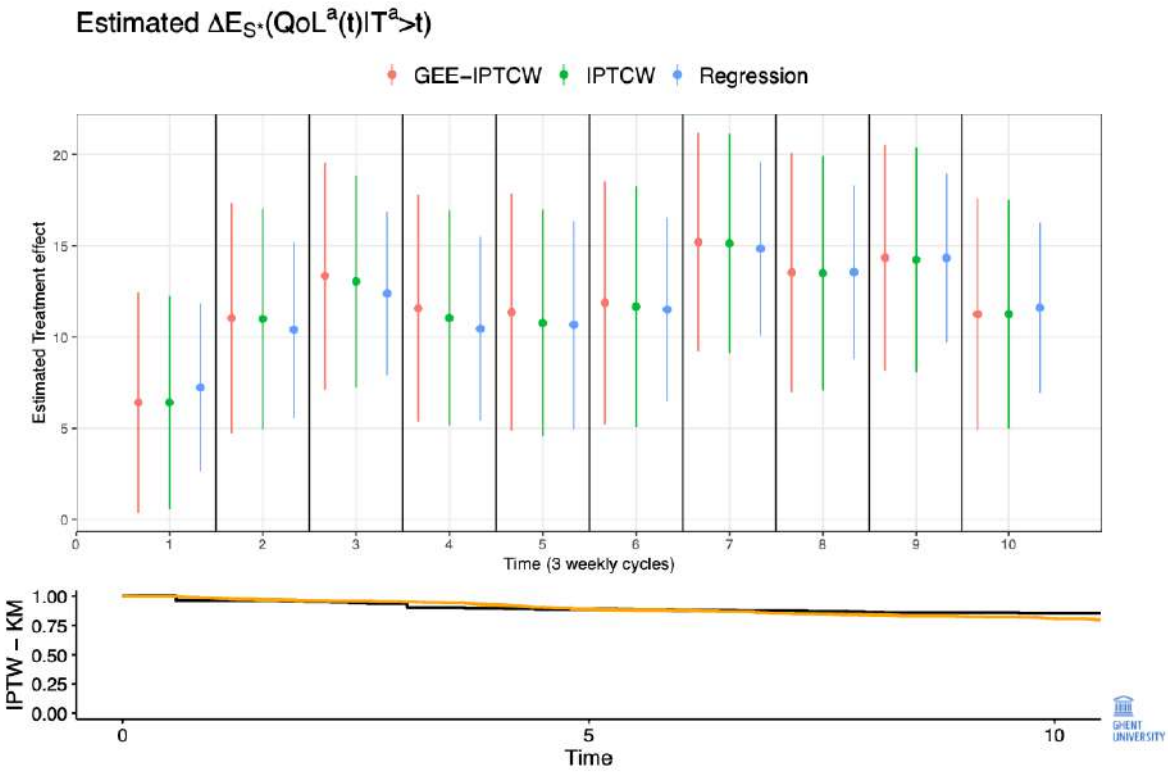

III. NEXT

WHAT GUIDANCE NEXT?

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

- MNAR: missing QOL depends on more than is seen (TG1)
  ``Reported reasons for missingness" helpful?
- Non-positivity issues?

BERLIN PALAST SUMMARY

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