Conflict of interest

Speaker: Corneel Coens

- Financial disclosure
  - Full-time employee of EORTC (European Organisation for Research and Treatment of Cancer)

- The opinions expressed in this presentation are my own and do not necessarily reflect those of EORTC or ISPOR.

How Will New Guidance Impact the Statistical Analyses and Interpretation for Patient-Reported Outcomes (PRO) in the Context of HA and HTA Submissions

EORTC perspective

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@EORTC

European Organisation for Research and Treatment of Cancer (EORTC)

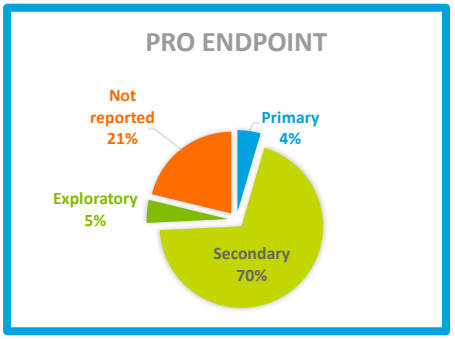
- Private non-profit organisation (charity), over 60 years old
- Over 3000 clinicians, researchers, etc. across the EU and beyond
- Main mission: promote and conduct research to improve cancer care and QoL
- Core activity: conduct cancer clinical trials
  - Mainly academic investigator-driven trials
  - International & multidisciplinary
  - Define new standards of care
  - QoL:
    - Collect patient-reported-outcomes in our trials
    - Develop tools to measure patient outcomes (EORTC QLQ library)

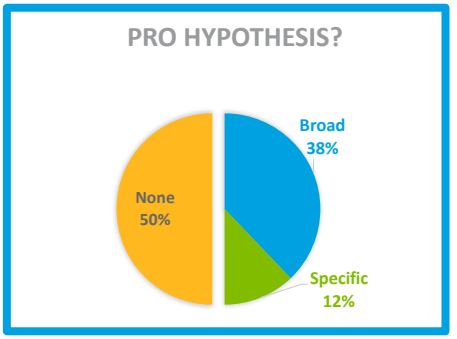
QoL in EORTC clinical trials

- One clinical trial = multiple stakeholders !
  - Scientific community, patients, pharma, regulators, …
  - direct or indirect (eg. HTA)
- QoL is encouraged in EORTC **when justified**.
  - If included: objective
  - If not included: rationale
- Rarely primary endpoint
  - QoL often underdeveloped & underreported
  - Not exclusive to EORTC !

QoL in clinical trials

Most trials do not report a specific PRO/QOL research hypothesis despite existing guidelines (eg. SPIRIT-PRO, CONSORT-PRO) → statistical analysis plan?





Ref: Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review, Pe et al. Lancet Oncol 2018.

Estimands and trial design

- QoL interest is in **treatment effect**.
- Before designing and analysing a clinical trial, it should clearly be defined which treatment effects are of interest.
  - Well understood for efficacy, less so for QoL.
- Estimands specify the objective criteria to be pre-specified:
  - Population
  - Endpoint to be obtained for each patient
  - Treatment
  - Intercurrent events (IE)
  - Population level summary

Estimand attributes are NOT independent of each other.
Decision on one estimand attribute → impact another estimand attribute

Value to EORTC

The good part:

- Estimands are not very different from how we currently work
- Estimands framework forces a focused approach to establishing objectives and assumptions upfront.

The bad part:

- Estimand framework as appendix to ICH E9
  → seen as statistical technicalities NOT as crucial fundamentals
- Terminology is not 'appealing' to clinical trial investigators not versed in regulatory guidelines.
- Details are 'fuzzy' → overreliance on examples
- For QoL in oncology: many of the examples not applicable
  - Eg. counting death as an ignorable intercurrent event.

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Example 1: Intercurrent Event

- QoL in oncology clinical trials: missing data
  - Due to patient non-completion.
  - Can have various causes.
  - More prevalent in academic studies (eg. no real-time monitoring)
- Common approaches to missing data:
  - Assume missingness = QoL failure
  - Impute data under various assumptions and check robustness.
  - Stratify according to missingness pattern (Pattern Mixture Model)
  - Integrate auxiliary data (cause of missingness, proxy data, time-varying model, …)

→ Few approaches readily transferable to estimand framework

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Example 2: Long term follow-up

- Long-term follow-up is often crucial for HTA (eg. QALYs)
- Difficult to achieve with PRO/QoL data
  - Declining patient motivation
  - Increasing difficulty to adhere to assessment schedule
  - No retrospective collection (cfr 'survival sweep') → cost
  - Content validity
- HTA interest <<
  - practical restrictions
  - interest to other stakeholders

Conclusion

- Standardized statistical techniques are only possible when **the research objectives are well-defined**.
  → HTA/HA requirements part of trial objectives.
- There is a need for more well-defined research objectives that can be **matched with appropriate statistical methods**.
  - **Estimand framework** is an organized approach to construct a well-defined objective BUT not well understood.
- SISAQOL initiative aims to establish consensus guidelines for statistical analysis of PRO/QoL data. *
  → HA/HTA submission is beyond the scope.
- Various stakeholders + lack of objectives = research waste
  - Crucial data/results are unpublished or not shared
  - Published results are difficult to synthesize
  - Design and publication guidelines exist → uptake?
  - Statistical guidelines will plug a gap but not solve overall issue.

** Ref: Coens C, Pe M, et al; Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol. 2020 Feb;21(2):e83-e96.*

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