Adelphi

ADELPHI VALUES

Patient-Centered Outcomes

Estimands in Oncology Working Group PRO TaskForce

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PRO Task Force – Members/Contributors

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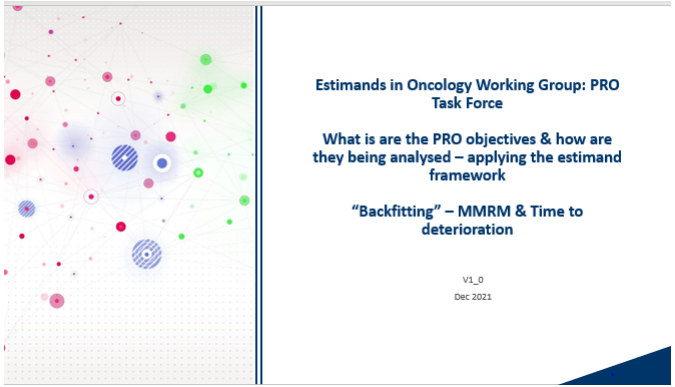
2021 – Backfitting Work

- Took 2 common statistical analysis approaches for PRO data in oncology:
  - MMRM
  - Time to deterioration
- Tried to “backfit” using estimand framework
- Produced a slide-deck for all on the Estimands in Oncology website:



- https://oncoestimand.github.io/oncowg_webpage/docs/talks/PRO%20TF%20(2021)%20Backfitting%20MMRM.pdf

What did we learn?

Key Challenges

- Not standard use, nor exact definitions of, QoL endpoints across healthcare industry, even when measuring the same concept
- There is generally a lack of clarity of the precise scientific question targeted for PRO analysis
- The variety of endpoints limits comparisons between trials
- Differences in protocols lead to different data points collected e.g. PRO data collected at clinical visits until disease progression, or whilst on-treatment?
- Examples:
  - "Change from baseline in QoL"
    - Does that mean At Week X, by Week X, over-time (until when?), on-treatment??
  - "Time to deterioration in QoL"
    - Deterioration in QoL score or progression or death?
    - Thresholds for deterioration – should it be confirmed? Limitations of the questionnaire
    - Exact censoring rules (missing timepoints) – rules really depend on the research question

“Backfitting” - MMRM

MMRM CAN

- MMRM, in its most commonly applied form, applies a **hypothetical** strategy for any ICE after which data are unobserved, e.g. *“Change from baseline in QoL as if patient is still taking randomized treatment”*
- If post-ICE data are collected, and an on- and off-ICE indicator is included, then **treatment policy** (for that ICE) is possible

MMRM CANNOT

- Answer questions like – “*Change from baseline in QoL…*”
  - **While on (randomized) treatment**
  - **Before progression**
  - **While alive**
  - **In survivors**
  - **In patients that would tolerate txt**
  - **Where death is a “bad” outcome**
- When such questions are of interest, analysts should seek analytical solutions beyond the standard MMRM framework

While-on-treatment

Principal stratum

Composite

“Backfitting” – Time to deterioration

Considerations

- What is the definition of an event – is it decline in PRO score alone or a composite of PRO score decline and death? Is the decline in PRO score used appropriate?
  - What about composite include disease progression, treatment discontinuation, cross-over also?
- Censoring – censor at an event (like treatment discontinuation, or disease progression) or last PRO score? - are assumptions about censoring equally valid in the case of death or no data for other reasons?
- Ensure that the definition of an event is completely transparent – it may vary between studies/between treatments and makes comparing results across studies challenging
- Does a change in score have to be confirmed at a later timepoint – if so what about if no further PRO data available – due to death or due to other reasons?
- Is a deterioration expected in disease setting? Is it clinically meaningful to interpret? Are there enough timepoints for a comparative analysis?
- For certain PRO domains/scores there may be low QoL at baseline or a symptom score not impacted by treatment – therefore it is possible that not all patients will experience a decline in all PRO domains/scores – is a survival analysis the most appropriate approach for these PRO domains/scores?

Conclusions

- Not standard use, nor exact definitions of, QoL endpoints across healthcare industry
- Lack of clarity of the precise scientific question targeted for PRO analysis
- It is very difficult to “backfit” to an estimand statement for “typical” PRO analysis – generally much more detail is required
- Among the task force members basic “assumptions” differ – generally due to lack of clarity of the scientific question of interest – which makes “backfitting” challenging if not enough is known.
- MMRM – this is a hypothetical strategy for all ICEs – death or treatment discontinuation
- Time to deterioration – may be composite for death (if death or deterioration in score is an event) – otherwise other ICE usually lead to censoring (and therefore potentially informative censoring)
- How to handle death? – isn’t handled in any special way in MMRM; review definition use for time to deterioration
- Recommendation: be completely transparent in all aspects of analysis methods used to enable clarity of the exact question that is being addressed – don’t assume can compare to other studies easily

Next steps

- Biggest question….. How to handle death
  - QoL after death not a concept
  - How do we make sure our estimation approaches align?

- Also looking into building on others work and creating template text for protocols/SAPs for PRO endpoints

Thank you – any questions?