Federal Institute
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Regulator's view on estimands for time-to-event data

Andreas Brandt

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Introduction

- Estimand concept has been started to be included in indication-specific EMA guidelines
- Focus on continuous and binary endpoints
- Time-to-event endpoints (and count data/recurrent events) require other considerations

Current status

- Advice in some GLs implies specific estimands for time to event endpoints
  - PFS: “follow principles of ITT as far as possible”
  - Stroke prevention in non-valvular atrial fibrillation patients
    - Superiority: “include all primary endpoint events occurring through end of study”
    - NI: “on-treatment analysis”
- But: what was the original intent?
  - PFS: giving advice on research question of primary interest, or avoid informative censoring?

Topics requiring discussion

- Aligning estimand and statistical analysis: role of censoring
- Population level summary measure
- Competing events

Censoring: a universal tool?

- Censoring is used as universal tool
  - Handling of patients who are known to be event-free at data cut-off
  - Missing data (pre-mature drop-outs)
  - Intercurrent events
  - Sensitivity analysis

Censoring intercurrent events

- “while intercurrent event did not occur”
    - Censoring intercurrent event appropriate
- Hypothetical
    - Censoring ie appropriate when ie is non-informative
- Treatment policy
    - Censoring ie inappropriate (uncontroversial)
    - But: censoring intercurrent events is coming back through the “missing data” back door

Censoring drop-outs

- Censoring study drop-outs: often censoring (after) intercurrent event
- Most important: reduce missing data as far as possible
- Alternative ways for handling missing data are needed to align estimand and analysis
    - Inverse probability of censoring weighting
    - (Multiple) Imputation
    - …
- But: limited experience, assumptions, robustness?
- Sensitivity analyses beyond changing censoring rules are needed
    - Changing censoring rules = changing estimand

Population-level summary measure

- Cox HR still most popular summary measure
- But: ph assumption is often not plausible for treatment policy strategy
    - Proportion of patients on active treatment decreases with time
- Cox HR is not a causal treatment effect
- Alternative summary measures?
    - Difference of medians, survival difference at fixed time point, restricted mean survival, average HR,…
    - Not all are causal, all are time-dependent
- Are there implications for testing?
    - Null hypothesis of log-rank test still the relevant one?

Strategy for competing event?

- Treatment policy: not possible
- Composite: competing events occur often because composite shall be avoided (cause-specific mortality instead all-cause mortality)
- Hypothetical: questionable relevance, strong assumptions for estimation
- While no competing event occurred: cannot be interpreted in isolation
- Principal stratum: only for a restricted time horizon
- Competing risk: new strategy?
    - > 1 outcome needs to be analysed
    - more complex than composite

Conclusion

- Implementation of estimand concept for time to event endpoints requires rethinking about the role of fundamental survival analysis concepts
  - Censoring
  - Proportional hazards assumption
  - Competing events

Thank you very much for your attention!

Contact

Federal Institute for Drugs and Medical Devices
Division Research, Unit Biostatistics and Special Pharmacokinetics
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Contact person
Dr. Andreas Brandt
andreas.brandt@bfarm.de
www.bfarm.de
Tel. +49 (0)228 99 307-3797