Regulator’s view on estimands for time-to-event data

Andreas Brandt
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The views expressed in this presentation are the presenter’s personal views and not necessarily the views of BfArM or EMA.
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