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Characterizing the Effect of Treatment Using Hierarchical Composite Endpoints Risks and Benefits of Win Statistics and Beyond in the HTA context

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Setting/Context

- Composite endpoints are commonly used in therapeutic areas such as cardiovascular and oncology to capture different aspects of the treatment effect.
- Traditional analyses of individual components may not fully capture the treatment's overall clinical benefit.
- The Win Ratio method[1,2] analyzes composite endpoints by hierarchically prioritizing more important outcomes.
  → Increasingly relevant for regulatory and Health Technology Assessment (HTA) submissions, where nuanced interpretation of benefit-risk is critical[1,2]
  → New IQWiG Methods Guidance v8.0 (draft) recognizes win ratio approach as an option for analyzing composite endpoints in the context of HTA[3]

Win Statistics: A Brief Overview

- Patients from treatment and control arms are paired, and for each pair, outcomes are compared hierarchically, by when they occur, e.g., first (Death), second (DDM) and third (LDM) endpoint (Figure 1).
- The pair is classified as a "win" for treatment (i.e., has a better outcome), "win" for control, or a tie. (Figure 2).
- The Win Ratio = (# wins in treatment arm) / (# wins in control arm).
- A Win Ratio > 1 indicates treatment benefit.
- Other alternatives like Win Odds[4] take into account unresolved ties.

Implications for HTA Decision-Making: Benefits and

Pros/Benefits	Cons/Risks
Respects clinical priority of endpoints	Requires careful endpoint hierarchy definition (much heterogeneity between sponsors)
Handles competing risks and censoring well	Limited regulatory precedents, evolving acceptance
Nuanced benefit assessment and intuitive to interpret	Different variants of the approach and other generalized pairwise comparison methods available that can get complex
Flexible for multiple types of endpoints (time-to-event, binary, etc.)	Software tools less widespread than traditional methods

Figure 1

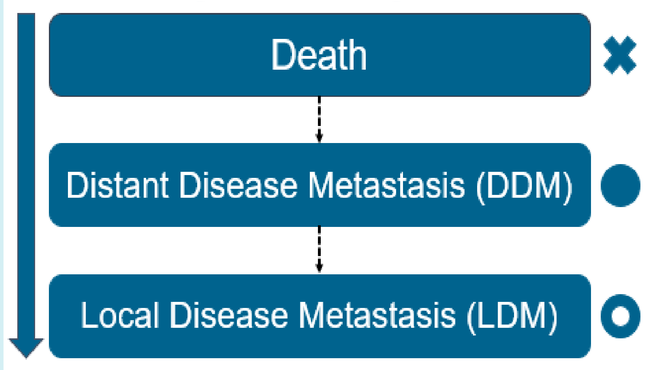
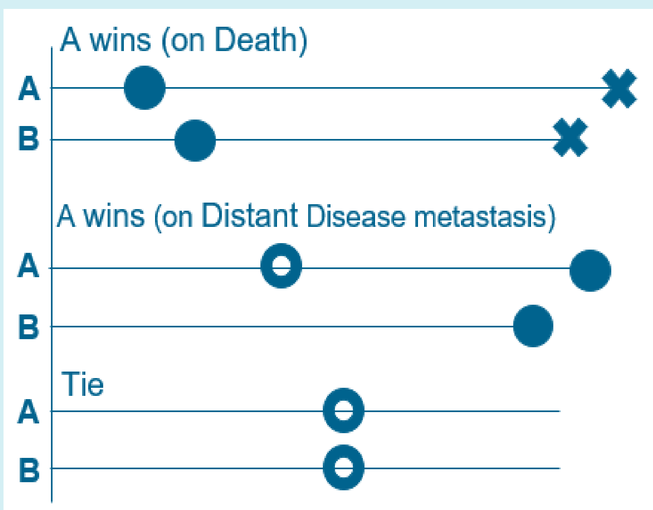


Figure 2



Key Takeaways

- Prioritizing clinical relevance of composite endpoint components, the Win Ratio offers a useful way of contextualizing & communicating treatment effects
- Proper planning of endpoint hierarchy, statistical methods, and interpretation is essential for successful support to regulatory and HTA submissions.
- Engagement with stakeholders ensures relevance and acceptance

[1] Pocock SJ et al., Eur Heart J, 2012, [2] Wang R & Pocock SJ, Stat Med, 2016, [3] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), https://www.iqwig.de/ueber-uns/methoden/methodenpapier, 2025, [4] Song J et al., J Biopharm Stat, 2022.

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