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When Can an Unanchored Analysis be More Credible Than an Anchored One?

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Introduction

Methodological guidance for ITCs of RCTs typically recommend anchored analysis over unanchored analyses, since the latter relies on the assumption of all prognostic variables being balanced or adjusted[1]. We sought to explore scenarios where unanchored analyses may be more credible than anchored counterparts.

Objective

Discuss scenarios where unanchored analyses may lead to more credible conclusions than anchored ones.

Results

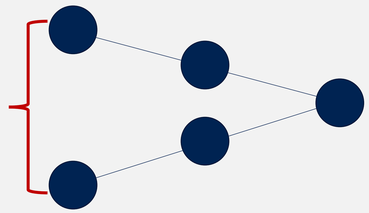
Unanchored comparisons (either adjusted or unadjusted) may be more credible than anchored alternatives in three broad scenarios:

1. Chains of evidence are long or travel through heterogeneous studies.
2. Comparator events are rare.
3. Highly effective comparators have biological/empirical rationale to be stable across patient populations while placebo/control is highly variable.

Long Chains of Evidence

Chains of evidence are long or travel through studies with variable populations, designs, or outcome definitions.

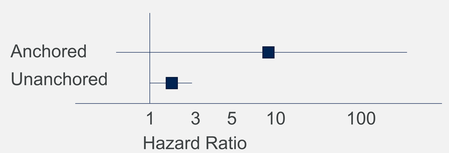
Validity of focal comparison relies on balance of effect modifiers (patient, design, and outcome characteristics) across the **entire** chain[2]



Rare Comparator Events

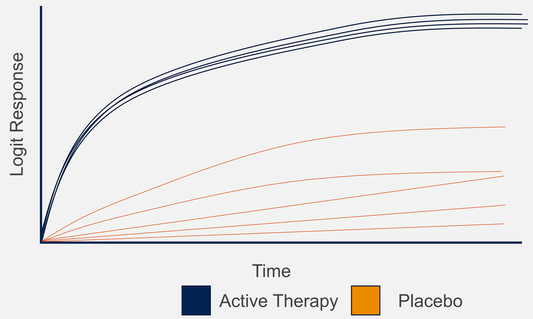
Events in the shared comparator are rare leading to unstable effect estimates and inappropriately inflated uncertainty intervals. This can lead to confidence/credible intervals that suggest compatibility with clinically implausible effects, increase the risk that statistically significant differences are inflated relative to the truth, and offers little theoretical benefit over unanchored comparisons in terms of bias.

Confidence intervals and point estimates often lack credibility in anchored comparisons with rare events since the variance of an anchored comparison includes the variance in control arms



Stable Actives – Variable Controls

When active therapies are highly efficacious across patient subgroups, control anchors like placebo or usual care can be highly variable on the scale of the linear predictor. Unanchored comparisons with average treatment effect on the treated weights therefore rely on a small number of prognostic variables that have modest effects while anchored comparisons add many additional effect modifiers with potentially large magnitude.



Conclusions

Recommendations to prefer anchored comparisons are based on theoretical considerations that may not apply in practice. Unanchored comparisons may make fewer or weaker assumptions in special cases. Making methodological decisions based on a generic hierarchy of approaches will likely lead to delayed or inappropriate decision-making.

References

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