Estimands in real world data

Estimands in clinical trials: Current practice and future directions

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Real-World-Data (RWD)

- Data collected during the routine delivery of health care
- Sources may include observational data, administrative data, research data, patient-generated data or professional-generated data. These data may be collected in administrative datasets, case notes, surveys, product and disease registries, social media, electronic health records, claims and billing datasets, or mobile health applications

Quelle: http://htaglossary.net/real-world-data

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Target-Trial-Emulation

Target trial emulation: applying principles of randomised trials to observational studies

The randomised trial is the preferred study design for evaluating the effectiveness and safety of interventions. Yet such trials can be prohibitively expensive, unethical, or take too long. When it is

Estimand framework

- Population
- Treatments
- Randomized
- Measures
- Coincide by design
- Population level summary

Target-Trial-Emulation framework

- Eligibility criteria
- Treatment strategies (including adherence)
- Assignment procedures
- Outcomes
- Start of follow-up
- Causal contrast of interest (ITT and PP)

Quelle: Matthews, A. A., Danaei, G., Islam, N., & Kurth, T. (2022). Target trial emulation: applying principles of randomised trials to observational studies. bmj, 378.

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Estimands in RWD empirical analysis

ORIGINAL ARTICLE

No inexplicable disagreements between real-world data–based nonrandomized controlled studies and randomized controlled trials were found

- In none of the studies a true “assignment of intervention” (ICH E9: treatment-policy) or “starting and adhering” (ICH E9: “principal [adherent patients] stratum”) estimand was calculated
- Estimand was usually unclear or undefinable

Possible path that a study participant could follow, including intercurrent events that could occur
Continues study exactly as per protocol and completes the end of study visit
Develops a side-effect, but still continues treatment and completes the end of final study visit, with complete assessment at all time-points
Starts alternative treatment while on the study and also continues with the study medication
Discontinues treatment due to lack of efficacy
Dies prior to completion of the study
Discontinues treatment due to side effects
Takes rescue medication and discontinues treatment for some period or for the entire period till study completion
Takes rescue medication, and continues in the study till its completion
Undergoes surgery unrelated to the study
Undergoes surgery related to the study

Quellen:

1. Mathes, T., Rombey, T., Kuss, O., & Pieper, D. (2021). No inexplicable disagreements between real-world data–based nonrandomized controlled studies and randomized controlled trials were found. Journal of Clinical Epidemiology, 133, 1-13.
2. Gogtay, N. J., Ranganathan, P., & Aggarwal, R. (2021). Understanding estimands. Perspectives in Clinical Research, 12(2), 106.

Intercurrent events and missing values

- In RWD it is often unclear if an intercurrent event has not occurred or if it is not reported/observed (e.g. treatment discontinuation)
- The same is true for outcomes (e.g. mortality)

→ How to calculate the estimand? Which values should be imputed?

→ Usually complete case analyses in patients with at least one redeemed prescription (modified ITT) or regularly refilled prescriptions (principle stratum)

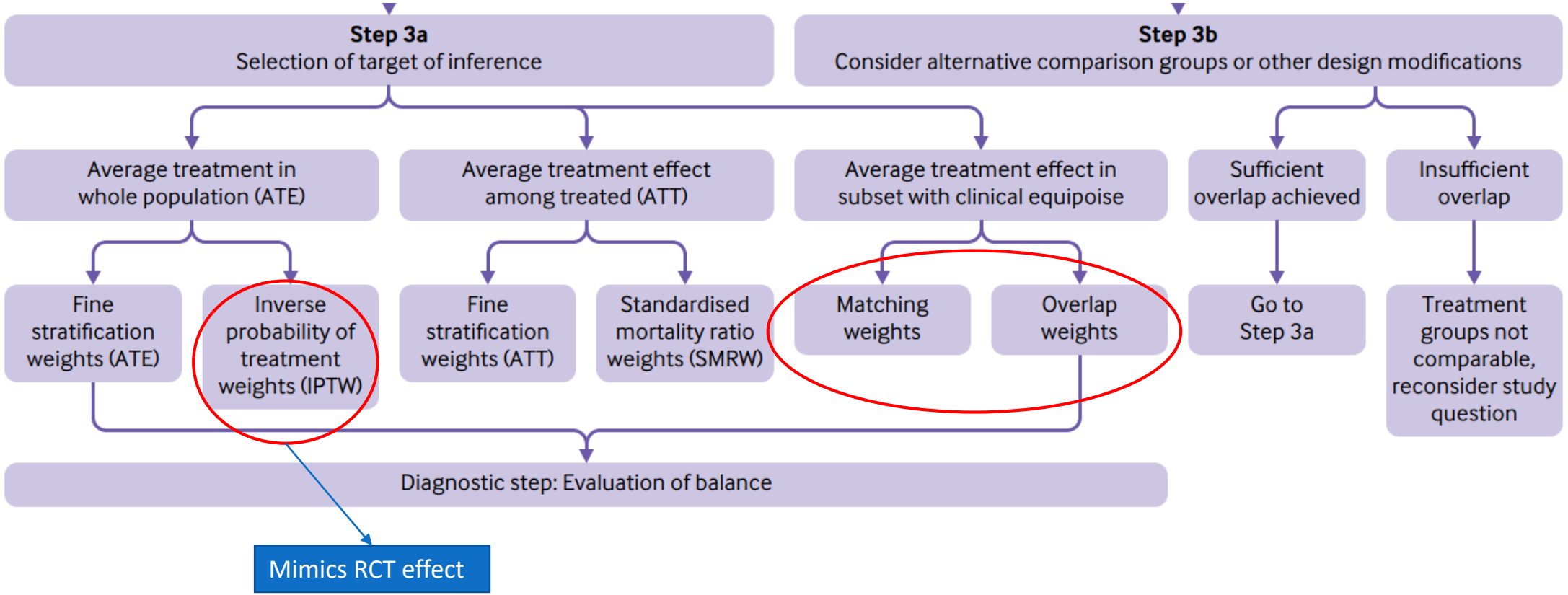
→ Best-case worst-case sensitivity analyses?

Example study

Statistical Analysis
Within this retrospective cohort, cancer risk was compared among those who first started using metformin and those who started using other OHAs, and then participants were followed up without regard to any subsequent changes in pharmacotherapy (i.e., akin to an ITT

Confounding adjustment and “estimand”

Patients targeted by the scientific question



Quelle: Desai, et al. (2019). Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. bmj, 367.

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Conclusion

- In RWD it is often unclear if an intercurrent event has not occurred or if it is not reported/observed

→Often not possible to emulate a clear strategy

- More detailed guidance on estimands in RWD-based non-randomized studies appears necessary
- For regulatory or HTA decisions it appears useful to adapt the ICH E9 estimand-frame-work and harmonize terminology

Thank you for your attention!

References

1. Desai, R. J., & Franklin, J. M. (2019). Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. bmj, 367.
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3. Mathes, T., Rombey, T., Kuss, O., & Pieper, D. (2021). No inexplicable disagreements between real-world data–based nonrandomized controlled studies and randomized controlled trials were found. Journal of Clinical Epidemiology, 133, 1-13.
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5. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., ... & Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. bmj, 355.

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Results of first attempts to systematically emulate RCTs

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Understanding variation in the results of real-world evidence studies that seem to address the same question

Shirley V. Wang • Sushama Kattinakere Sreedhara • Lily G. Bessette • Sebastian Schneeweiss

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Results

Most variation remained unexplained (60–88%). Of the explained variation, two-thirds were related to data and population differences, and one-third were related to the use of alternative study design and analysis parameters. Among these, the most prominent were differences in outcome algorithms and criteria used to define follow-up.

Conclusion

When making policy decisions based on database study findings, it is important to evaluate the validity, consistency, and robustness of results to alternative design and analysis decisions.