The value of TTE for Health Technology Assessment

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NICE National Institute for Health and Care Excellence

About NICE

Who are we?

We are the experts in evidence-based best practice and value for money in the UK health and care system.

What do we do?

We balance the best care with value for money, delivering both for individuals and society

We drive innovation into the hands of health and care professionals to enable best practice

We are fiercely independent: our decisions are rigorous, transparent and based on evidence

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NICE Vision for RWE

1. RWD access
2. Use of RWE
3. Capability building
4. Signposting
5. Partnership and research

NICE's RWE Framework

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Aims to:

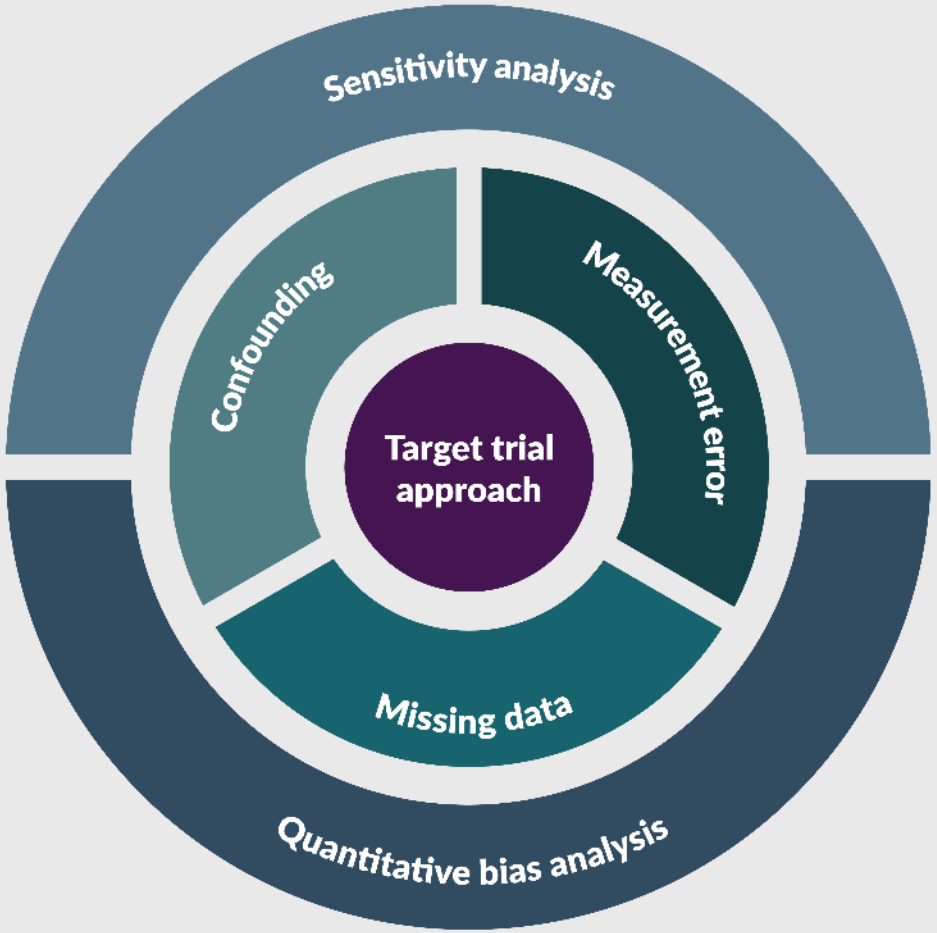
- Increase use of RWE to fill evidence gaps and improve recommendations
- Improve quality and transparency of RWE studies that inform guidance
- Inform critical appraisal of RWE studies
- Increase trust in high-quality RWE studies

Describes

- Where and how RWE can be used to improve recommendations
- Best-practices for planning, conducting, and reporting RWE studies

Best practice for comparative effects

*Clear applications for cohort/ECA studies



Target trial approach

- **Intuitive**: Design studies to emulate the preferred randomised controlled trial
- **Avoid selection bias** e.g. time-related biases due to differences in point of patient eligibility, treatment assignment, and start of follow-up
- **Reduce risk of other biases -** confounding bias e.g. consideration of active comparators
- **Improve transparency** of design choices and the causal effect under study

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Intuitive

"The goal of observational research is to emulate the ideal target trial"

Exposure misclassification	Time-related bias	Selection bias	Informative censoring
Outcomes & Detection bias	Confounding bias	Generalisability assessments	Estimands
Defining the Index date	Grace periods	External control arms	Sensitivity analysis & unmeasured confounding

TTE can help avoid selection bias and other common forms of bias

Methodological pitfalls are common

- Time-related bias (57%)
- Depletion of outcome-susceptibles (44%)
- Inapp. adjustment for postbaseline variables (41%)
- Potential for reverse causation (39%)
- Non-user comparator (55%)
- Surveillance bias (21%)

Bykov K, Patorno E, D'Andrea E, He M, Lee H, Graff JS, Franklin JM. Prevalence of Avoidable and Bias-Inflicting Methodological Pitfalls in Real-World Studies of Medication Safety and Effectiveness. Clinical Pharmacology & Therapeutics. 2022 Jan;111(1):209-17.

Critical appraisal tools may not pick them up!

- Time-related bias (3%)
- Depletion of susceptibles (2%)
- Bias due to overadjustment (34%)
- Reverse causation (18%)
- Active comparator (0%), New user (2%) design
- Surveillance bias (9%)
- ROBINS-I a more complete tool

D'Andrea E, Vinals L, Patorno E, Franklin JM, Bennett D, Largent JA, Moga DC, Yuan H, Wen X, Zullo AR, Debray TP. How well can we assess the validity of non-randomised studies of medications? A systematic review of assessment tools. BMJ open. 2021 Mar 1;11(3):e043961.

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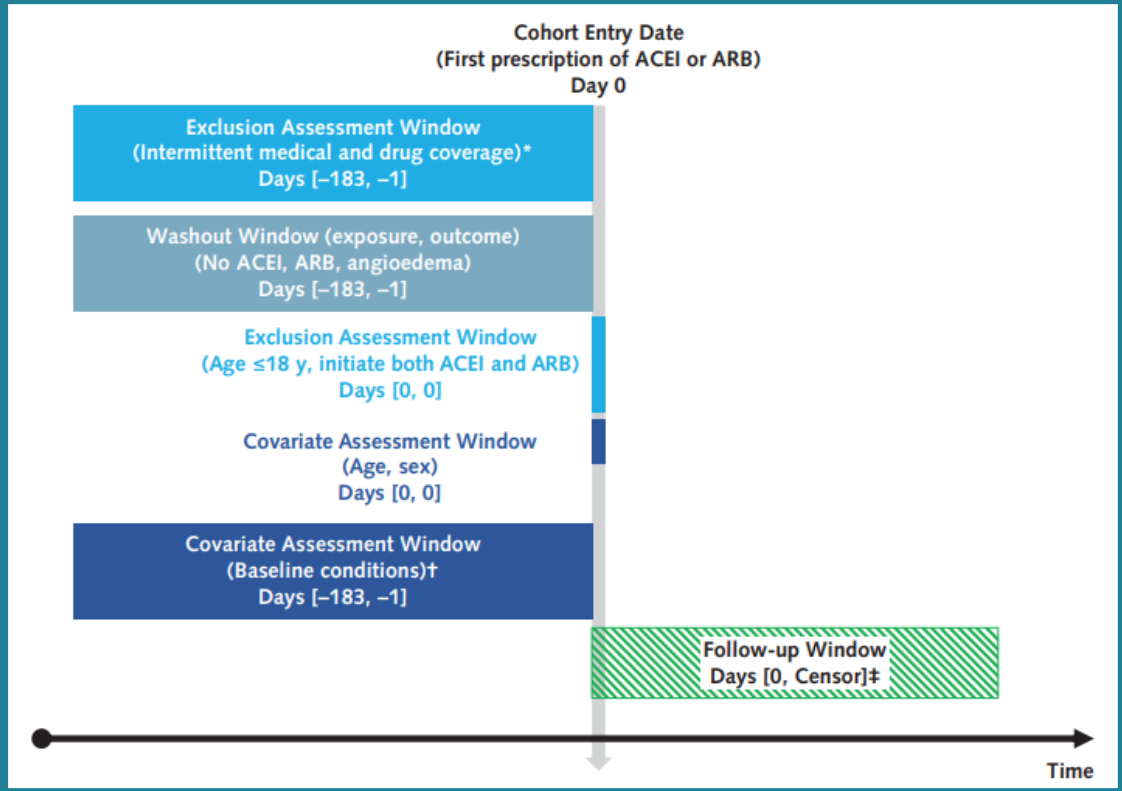
Transparency

Target trial	Emulation with RWD
Eligibility	Eligibility
Treatment	Treatment
Assignment	Assignment
Follow up	Follow up

- Not only emulation but characterisation
- Study elements tabulated: eligibility criteria, treatment strategies, assignment procedure, follow up period, outcome, causal effect of interest, analysis plan
- Trade-offs explicit
- Uncertainties highlighted



Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, Dal Pan G, Goettsch W, Murk W, Wang SV. Graphical depiction of longitudinal study designs in health care databases. Annals of internal medicine. 2019 Mar 19;170(6):398-406.

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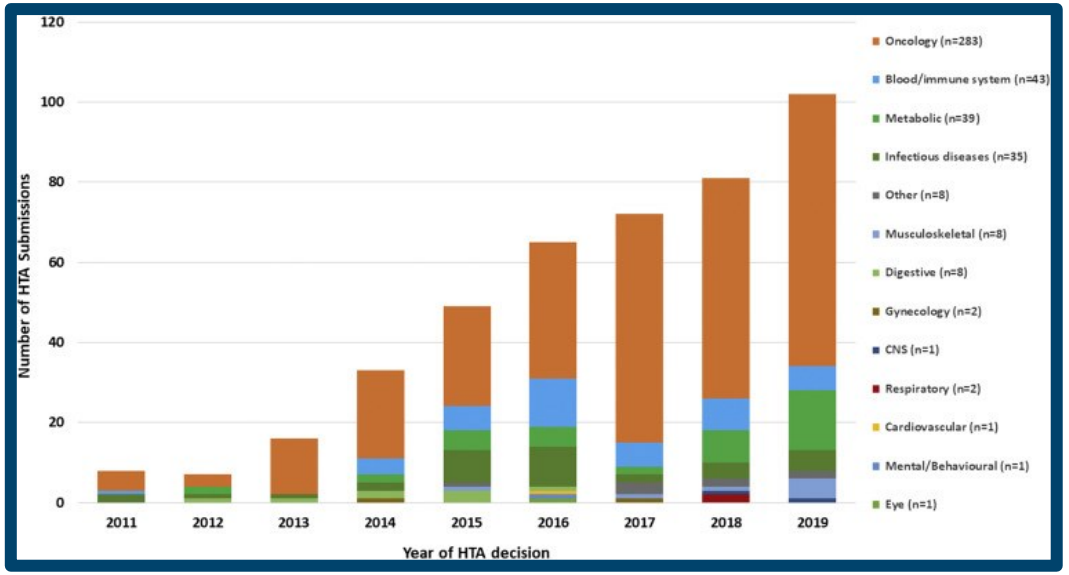
Importance of TTE for ECAs and per-protocol analysis

- ^ subsetting of patients & complexity in tx pathways
- Additional differences post-tx initiation
- SATs and RWD controls increasing as a proportion of submissions to NICE & HTA bodies
    - 13-fold increase in SAT submissions (2011 – 2019)
    - RWD ECs increased 22% as a proportion per year[1]
- ITT can be misleading, or conservative for non-inferiority trials or safety
- Existing approaches inadequate e.g. hypothetical estimand

Single arm trial submissions to HTA bodies



Combines data from NICE (England), CADTH (Canada), G-BA (Germany), HAS (France), and PBAC (Australia), 2011-2019 [1]

1. Patel D, Grimson F, Mihaylova E, Wagner P, Warren J, van Engen A, Kim J. Use of external comparators for health technology assessment submissions based on single-arm trials. Value in Health. 2021 Aug 1;24(8):1118-25.

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Summary

- **Better study design, transparency, and critical appraisal** of evidence is supported by target trial emulation
- **Design trumps analysis** – TTE is central to the methods recommendations in NICE's RWE framework, including for ECA studies
- **Increasing infiltration** into NICE HTA processes from advice given to developers to appraisal of current evidence submissions across teams in NICE (NSA, MA, EVA, CHTE, MTEP, CfG)
- **Increasing international adoption** across HTA bodies: EMA/EnCEPP, anticipated FDA and CADTH

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Thank you