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:

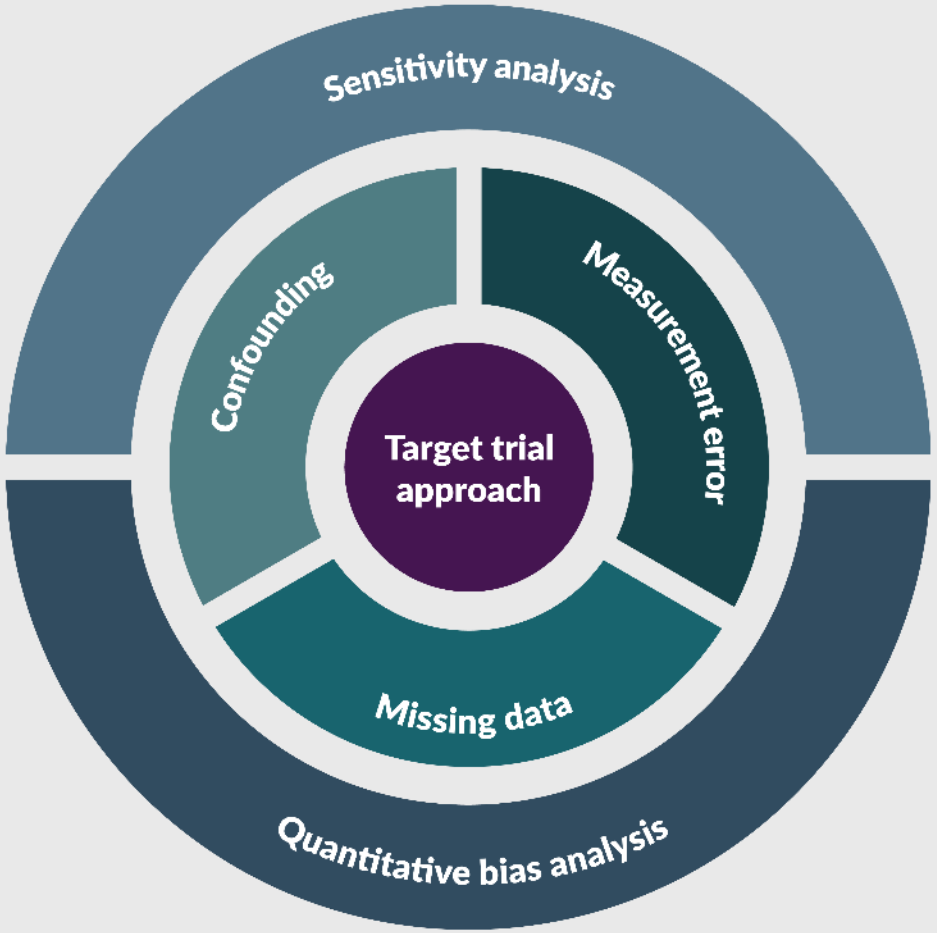
- Increase use of RWE to fill evidence gaps and improve recommendations
- Improve quality and transparency of RWE studies that inform guidance
- Inform critical appraisal of RWE studies
- Increase trust in high-quality RWE studies

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"

Generalisability assessments	Incorporates Estimand framework	Selection & time-related bias
Confounding bias	Outcomes & Detection bias	Extensions for other scenarios
Applies across study designs common in HTA	Unmeasured confounding and negative controls	Sensitivity analysis

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

Methodological pitfalls are common

- Time-related bias (57%)
- Non-user comparator (55%)
- Prevalent user design (51%)
- Depletion of outcome-susceptibles (44%)
- Inapp. adjustment for postbaseline variables (41%)
- 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 (7%)
- Depletion of susceptibles (2%)
- Non-contemporaneous comparator (14%)
- Active comparator (0%), New user (5%) design
- Bias due to overadjustment (34%)
- 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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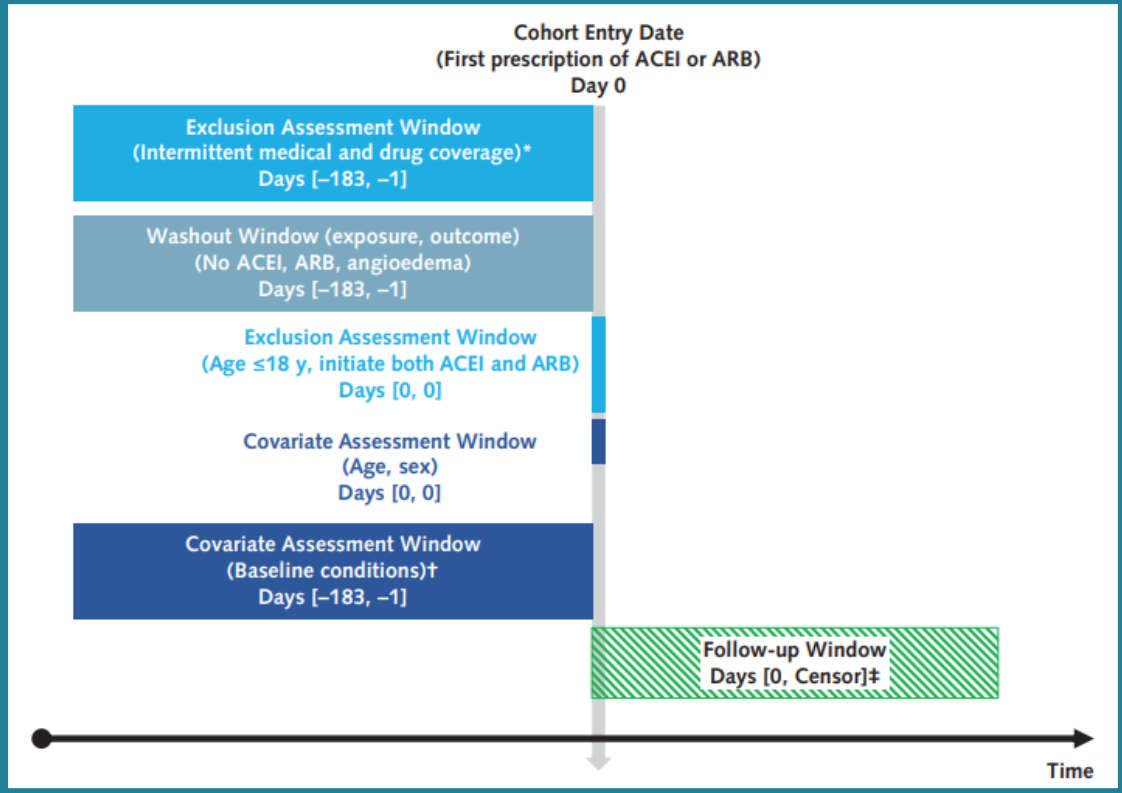
Transparency

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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Estimands

- Fits well within the target trial emulation framework – RWE framework places considerations of intercurrent events within “analysis plan”
- Not yet widespread adoption:
  - 54% of trials treatment effect could not be determined[1]
  - CONSORT guidelines published before ICH E9[1]

Why is the adoption of the Estimand framework important for payers?

What was the mean difference in glycated haemoglobin for a once-weekly insulin regimen compared to a once daily regimen?

-0.18 percentage points (95% CI -0.38 to 0.02, p=0.08)

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1. Cro S, Kahan BC, Rehal S, Ster AC, Carpenter JR, White IR, Cornelius VR. Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands. bmj. 2022 Aug 23;378.

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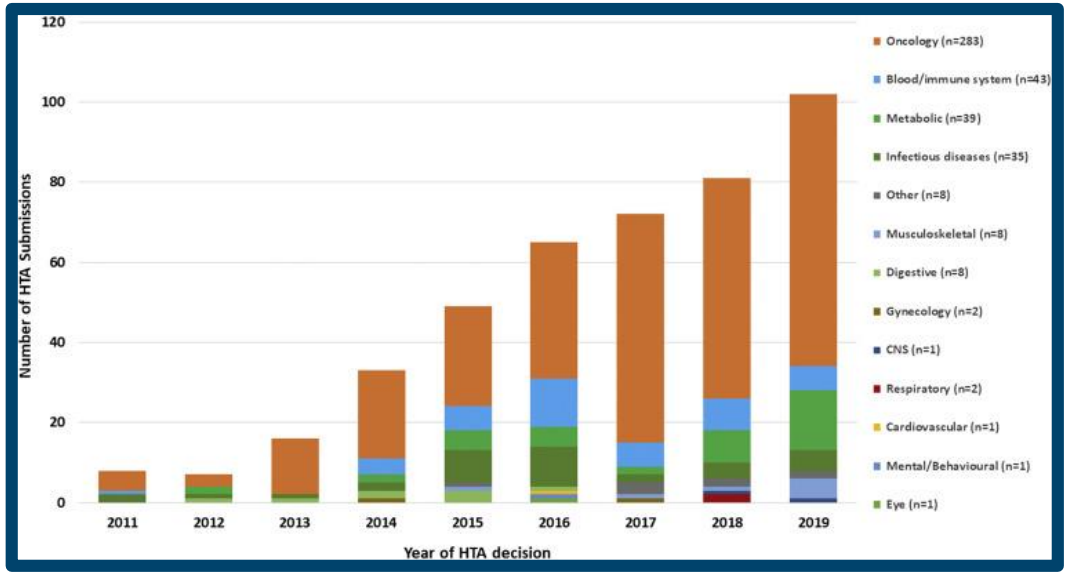
- ….if all participants had hypothetically adhered to the treatment regimens and not received ancillary treatment? **-0.18 percentage points (95% CI -0.38 to 0.02, p=0.08)**
- …regardless of the amount of randomised treatment or ancillary treatment received? **-0.09 percentage points (95% CI -0.29 to 0.20, p=0.35)**

1. Cro S, Kahan BC, Rehal S, Ster AC, Carpenter JR, White IR, Cornelius VR. Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands. bmj. 2022 Aug 23;378.

ECAs and hypothetical estimand in the UK context

- ^ 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 outcomes
- Existing approaches inadequate e.g. naïve per-protocol

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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T-BASEL (on-going study)

Target trial Bias ASsEssment in Lung cancer (T-BASEL)

- For 3 completed randomized clinical studies in aNSCLC, in combination with observational data from Flatiron Health, the objectives are to assess the feasibility and utility of TTE methods to estimate the relevant hypothetical estimand in the external control arm setting by:
  1. Assessing a decision-relevant hypothetical estimand derived using external control arm in conjunction with TTE methods for longitudinal data
  2. Applying quantitative bias analysis methods to address missing data and unmeasured/mismeasured confounding

- **Considerations:**

1. Will data permit us to take into account: a) permitted subsequent therapies (UK-context?) b) reasons for discontinuation c) time-varying confounding?
2. How is the emulation of RCTs affected by varying sample sizes, treatment regimens, line of therapy and precision of effect estimates

TTE: target trial emulation; PP: per protocol; RCTs: randomized clinical trials

Preliminary results from OAK emulation

- Hypothetical estimand of interest = Overall survival in the hypothetical scenario where participants initiated study drugs at the dosage prescribed by the study and only switched to permitted treatments.
  - Crossover or initiation of non-permitted subsequent therapies were censored.
- Estimates were adjusted for age, gender, race, cancer stage at diagnosis, smoking status and ECOG scores at baseline.
- Results: hypothetical estimand was lower than the ITT estimate from RCT, and similar between trial and SCA.

Estimand	Comparison	Adjustment	HR estimates (95% CI)
Intent-to-treat (ITT)	Randomized trial	N/A	0.78 (0.68-0.89)
Hypothetical estimand	Trial active arm (n=609) vs Trial control arm (n=580)	Crude	0.58 (0.49-0.69)
		Adjusted	0.53 (0.43-0.65)
	Trial active arm (n=609) vs ECA (n=142)	Crude	0.48 (0.37-0.62)
		Adjusted	0.53 (0.37-0.75)

Summary

- **Better study design, transparency, and critical appraisal** of evidence is supported by target trial emulation and the estimand framework
- **Design trumps analysis** – TTE is central to the methods recommendations in NICE's RWE framework, including for ECA studies, consideration of estimands is also recommended
- **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