The value of TTE for Health Technology Assessment

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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
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

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

*Clear applications for cohort/ECA studies
The goal of observational research is to emulate the ideal target trial
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%)


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

Transparency

- 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

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)

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?

- ...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)**

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
- ITT can be misleading, or conservative for non-inferiority trials or safety outcomes
- Existing approaches inadequate e.g. naïve per-protocol

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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.

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