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Estimands, PICOs and Co – Are we losing or gaining in translation?

What about decision problems? And Target Trials? (!)

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Acknowledgements

- I was a member of NICE Technology Appraisal Committee B for 5 years, up to January 2023
- These are my own views – not NICE's!
- I'm thinking about this primarily from a UK perspective and this is how I see all the different aspects fitting together – I'm not saying I'm right!

PICOs, estimands, and decision problems

- PICOs are crucial for EUnetHTA, but NICE doesn't refer to them
  - "PICOs" are not referred to at all in the NICE health technology evaluations manual
- EUnetHTA refers to "estimands", but NICE doesn't
  - The word "estimand" is not used at all in the NICE manual
- Instead, NICE talk about "decision problems". EUnetHTA doesn't (I don't think)
  - The phrase "decision problem" is used 17 times in the NICE manual

- So how do estimands and PICOs fit in with decision problems? Are we talking about the same things?
- …and how do Target Trials fit in with this?

NICE decision problems

- In the NICE setting, the definition of a decision problem is (from the glossary of terms on the NICE website):

"The decision problem describes the proposed approach to be taken in a sponsor's submission of evidence to answer the question in a scope. This includes the population, intervention, comparator(s), outcomes, cost analysis, subgroup analysis and any special considerations." [1]

So, the decision problem includes 3 key components:

1. **The question we're trying to answer**
2. **The PICO relevant for the question we're trying to answer**
3. **The analyses required to answer the question**

It's already clear that the PICO is a crucial component of the HTA decision problem. What about estimands? Let's think about these 3 components

[1] https://www.nice.org.uk/Glossary

Three components of the NICE decision problem

1. **The question**

   What is the effectiveness and cost-effectiveness of inserting the new treatment into the treatment pathway at the specified line of therapy, compared to retaining the current standard treatment pathway?

2. **The PICO**

   Populations – based on the marketing authorisation, can include subgroups
   Intervention – the new treatment, based on it's license
   Comparators – treatments currently given in the NHS as routine care
   Outcomes – outcomes that are important to patients

3. **The analyses required to answer the question**

   Given the PICO, what analyses will we do to answer the question in (1)?
   There are a lot of elements to this: how to estimate effects, costs, QALYs, extrapolation

To see how estimands fit in, let's think about how the NICE decision problem is usually addressed

How is the NICE decision problem usually addressed?

- Usually evidence on treatment effectiveness, treatment duration (and therefore costs), survival, adverse events, etc. is taken from randomised controlled trials (RCTs)
- There are lots of issues with this, which relate back to the PICO…

  Populations – is the trial population representative of the population the decision is for?
  Intervention – is the intervention in the trial the relevant one for our decision?
  Comparators – are the comparators in the trial the relevant ones for our decision?
  Outcomes – are the outcomes in the trial the relevant ones for our decision?

This is why it's very important to think about PICOs when designing trials

- Will the trial allow us to answer the questions posed by HTA?

We will come back to this, but first imagine that our RCT has an appropriate PICO

How should we analyse the RCT to address the question posed by the decision problem?

How is the NICE decision problem usually addressed?

Remember the question

> What is the effectiveness and cost-effectiveness of inserting the new treatment into the treatment pathway at the specified line of therapy, compared to retaining the current standard treatment pathway?

- Most RCTs are analysed using an intention-to-treat (ITT) analysis
- ITT analysis compare groups as randomised, and has lots of benefits
- But, it means that post-baseline events such as treatment switching are ignored

Treatment policy estimand

- **What if patients in the trial receive subsequent treatments that deviate from those available in the NHS?** (this is quite common, especially in cancer trials – patients randomised to the control group switch onto the experimental treatment after disease progression)
- **Does an ITT analysis still allow us to address the decision problem?**

Poll: What do you think?

Poll: I work for NICE and want to estimate the cost-effectiveness of introducing a new drug as a first-line therapy. The drug is not available at any other line of therapy in clinical practice. Some patients in the control group switched onto the new drug after disease progression. Should I use an intention-to-treat analysis to estimate the effect of the new drug?

A. Yes

B. No

- → Usually in HTA we want to adjust effectiveness estimates, moving beyond the ITT analysis, if patients in the control group switch onto the experimental treatment, in order to address our decision problem
- → May also want to adjust if patients in either randomised group switch onto other treatments not available in routine care (in whatever jurisdiction the decision is being made for)
- → These involve moving away from a **treatment policy estimand**, towards a **hypothetical estimand**

Use of hypothetical estimands by NICE

Hypothetical estimands have been used in NICE appraisals for a long time (without ever referring to “estimands”!)

TA179 (2009), sunitinib for GIST [84% of control switched]

- ITT analysis: OS HR = 0.88, ICER = £77k
- RPSFTM: OS HR = 0.51, ICER = £32k

→ **RPSFTM considered acceptable** by Committee
→ Sunitinib was recommended

ERG: Evidence Review Group
GIST: Gastro-intestinal stromal tumours
HR: Hazard Ratio
ICER: Incremental cost-effectiveness ratio
IPCW: Inverse probability of censoring weights
ITT: Intention-to-treat
OS: Overall Survival
PBAC: Pharmaceutical Benefits Advisory Committee
RPSFTM: Rank preserving structural failure time model
TA: Technology Appraisal
TSE: Two-stage estimation

TA904 (2023), pembrolizumab with lenvatinib for endometrial cancer [x% switched onto PD1/PD-L1s not available in UK]

- ITT analysis: OS HR 0.65, ICER = ?
- RPSFTM: OS HR ?, ICER = ?
- TSE: OS HR ?, ICER = ?
- IPCW: OS HR ?, ICER = ?

→ ERG and AC expressed some concern but believed **adjusted estimates preferable to unadjusted**
→ Treatment was recommended, noted adjustment reduced ICER

Use of hypothetical estimands by NICE

- Sometimes analyses of hypothetical estimands are accepted, and sometimes they're not

TA263 (2012), bevacizumab for metastatic breast cancer [52% of control switched]

- "Unadjusted": ICER = £182k
- RPSFTM: ICER = £82k

→ **RPSFTM considered unreliable** by Committee, bevacizumab not recommended

- When analyses are not accepted, this is usually due to:
  i. Concerns about the assumptions the adjustment methods rely on
  ii. When methods have been used to adjust for the wrong thing (e.g. adjust for switches to non-standard treatments in the control group, but not in the experimental group)

→ This second issue essentially means that adjustment analyses are rejected when they don't address the correct estimand

→ So, again, estimands are being used by NICE without ever referring to estimands!

What does this mean?

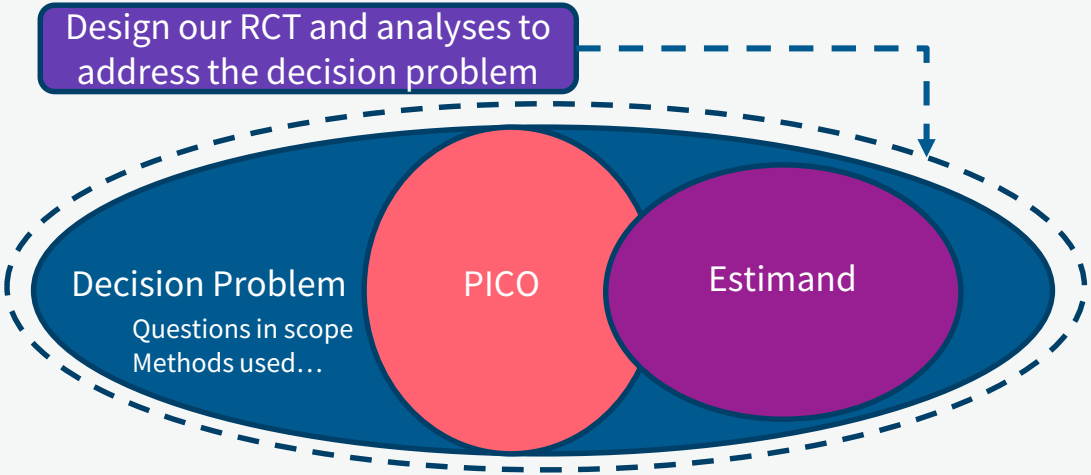
The third component of the NICE decision problem involved specifying the analyses required to answer the question posed by the technology appraisal

→ **So we have to think about what the required estimand is**

→ **So the PICO framework *and* the estimand framework sit within the decision problem framework**

Also note that HTA agencies that focus on PICOs and estimands (like EUnetHTA) also implicitly address decision problems

- But this does not necessarily mean HTA agencies all do the same thing
- May choose different questions, PICOs, estimands, methods…



Note overlap between PICO and estimand: both involve populations, interventions, comparators and outcomes, but the PICO is more about the setting and the estimand is more about what we need to estimate

What about Target Trials?

The story so far…

- The PICO framework is explicitly part of the NICE decision problem
- The decision problem also encompasses estimands
- It might not be explicit, but PICOs and estimands are both part of the NICE decision problem
  (and for HTA agencies that focus on PICOs and estimands, these make up part of the decision problem)

- I've explained this in the context of using an RCT to address the decision problem

  → Sometimes a treatment policy analysis of an RCT might not address our decision problem, so we might need to conduct an analysis for a hypothetical estimand

What if the RCT is not in the right population?

What if the RCT has the wrong comparator?

What if an RCT doesn't exist?

What about Target Trials?

- We might need to:
  - Adjust/weight a population
  - Do an indirect comparison
  - Generate a synthetic control arm
  - Analyse observational data

→ All of these can involve complex methods that make strong assumptions and can be prone to bias

→ This talk is not about methods

→ **But whatever we do, whatever data we analyse, we need to consider the PICO and the estimand to make sure we address our decision problem!**

→ **The Target Trial framework operationalises this in an observational data setting**

What about Target Trials?

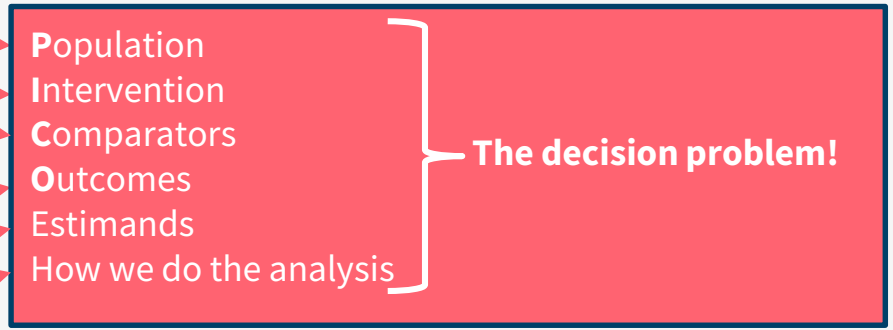
Target Trial framework [2]

Rationale: Analyses of observational data should follow the same rigorous design principles of RCTs to reduce the chance of bias

Concept: Specify a protocol for a hypothetical RCT (the "target trial") that would answer the question of interest, but using an observational data source

7 Key components of the protocol:

- Eligibility criteria
- Treatment strategies
- Assignment procedures
- Follow-up period (and time zero)
- Outcomes
- Estimands
- Analysis plan

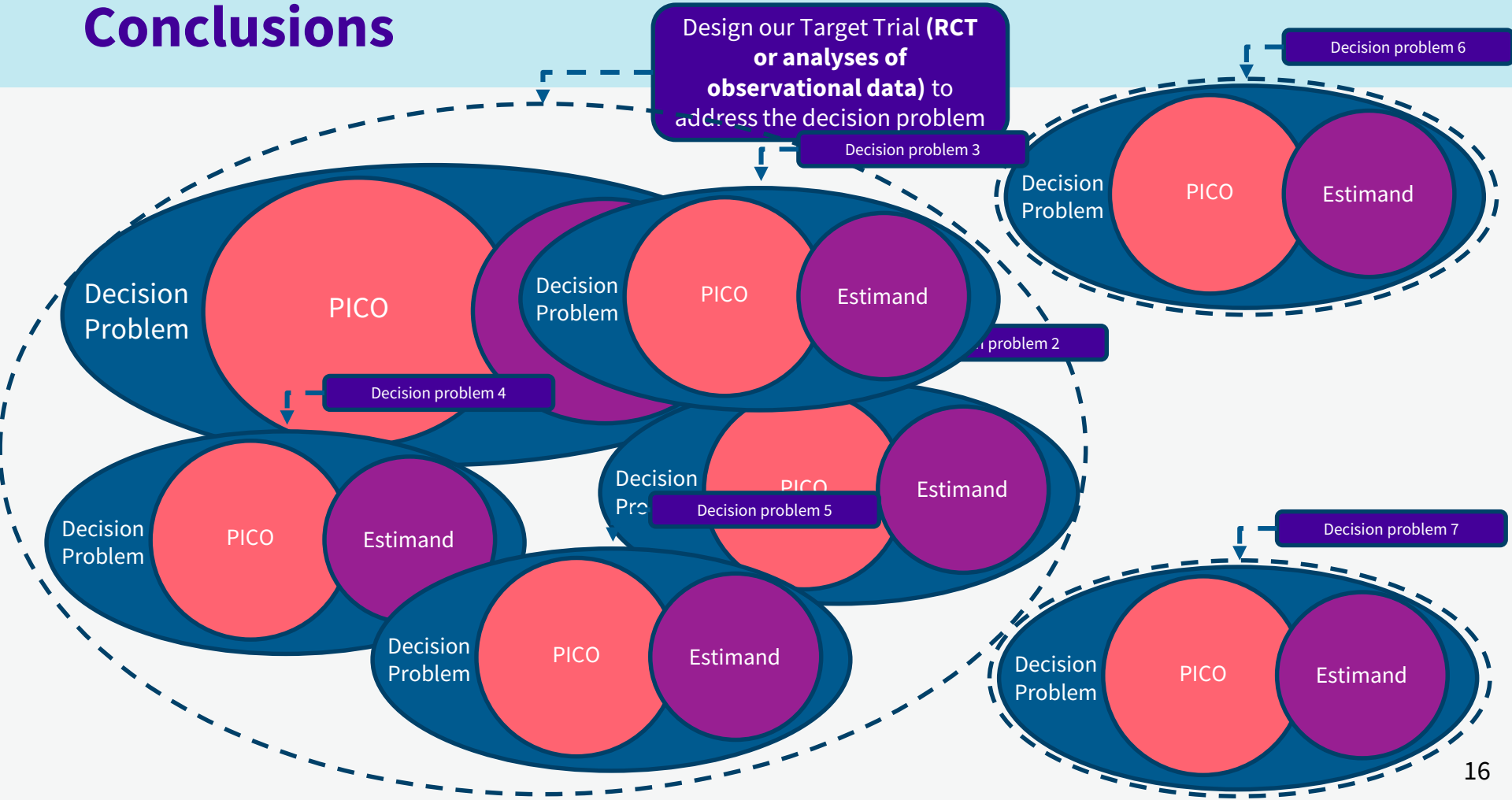


[2] Hernan and Robins, Am J Epidemiol. 2016;183(8):758-64 [12]

What about Target Trials?

- **The components of the target trial are standard things we should already be doing when we plan RCTs**
  → We should design studies that address our decision problem
- **Perhaps we are not thinking broadly enough at this planning stage**
  → Different stakeholders have different decision problems
  - HTA vs Regulatory
  - Different HTA agencies (and different regulators?)
- **We need to try to design studies that address all the relevant decision problems (this may be very hard)**
- **We should do exactly the same things when analysing observational data**
  → Design studies that will address the relevant decision problems

Conclusions



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- **Often we can use the same studies to address different decision problems**
  - But we may need different analyses (and sometimes we may need different studies)
  - Thinking early about each stakeholder from a PICO, estimand, decision problem perspective should be helpful and should avoid delays / disappointment later

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  - Thinking early about each stakeholder from a PICO, estimand, decision problem perspective should be helpful and should avoid delays / disappointment later
- **We should think about the decision problem, PICOs and estimands whether we are planning / analysing RCTs, or observational data**

An aside: We still need to be careful! Methods are important

- Methods for estimating hypothetical estimands are complex. As are methods for analysing observational data. They need careful interpretation

Excerpt from NICE TA904 Guidance document [3]

unadjusted values. The committee also noted that the TSE method uses a new baseline at progression, assuming all those who progressed have the same prognostic factors. However, the committee agreed that it is unlikely that all will have the same prognostic factors at the new baseline. It also noted that switching does not necessarily happen

[3] NICE, Technology Appraisal Guidance: Pembrolizumab with Lenvatinib for previously treated advanced or recurrent endometrial cancer. 21 June 2023,
Available from www.nice.org.uk/guidance/ta904

- We have to be concerned when results are interpreted incorrectly due to lack of understanding – this is a risk when introducing new methods, which is inevitable when we move beyond ITT analyses

Thanks for listening!