Model Uncertainty in HTA
A UK perspective

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Agenda

- Uncertainty in context of NICE decision making
- Key sources of uncertainty
- Handling uncertainty
- Case Study - Dinutuximab beta for neuroblastoma
- Conclusion

Uncertainty in context of NICE decision making
ICER estimates

The current NICE Guide to Methods of Technology Appraisal (2013) refers to uncertainty (section 6.3.3) states that:

- "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take into account [inter alia]… the degree of certainty around the ICER."
- "In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented."

https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making

Uncertainty in context of NICE decision making
Sensitivity analysis

The current NICE Guide to Methods of Technology Appraisal (2013) refers to uncertainty (section 5.8) states that:

- "The impact of structural uncertainty on estimates of cost effectiveness should be explored by separate analyses of a representative range of plausible scenarios."
- "Uncertainty about the appropriateness of the methods used in the reference case can also be dealt with using sensitivity analysis, but these analyses must be presented separately"
- "…implications of different estimates of key parameters must be reflected in sensitivity analyses (for example, through the inclusion of alternative data sets). Inputs must be fully justified and uncertainty explored by sensitivity analysis using alternative input values."
- "Probabilistic sensitivity analysis is preferred. This enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model."

https://www.nice.org.uk/process/pmg9/chapter/the-reference-case

Sources of uncertainty

MODEL STRUCTURE

PICOT

Model structure

Sensitivity to ICER changes

- Parameter variations an indicator of how much uncertainty there may be (ICER stable/unstable);
- PSA/CE plane also give good indication of CE

ICER>Cost/QALY threshold significantly

- For JP more precision required if used in price setting

Models inherently uncertain but nevertheless a useful tool to help decision-making

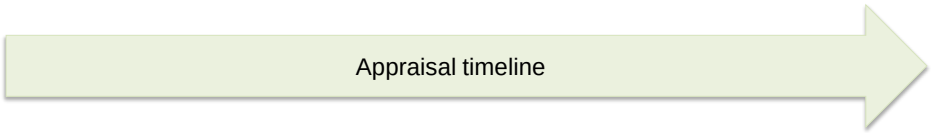
MODEL INPUTS/PARAMETERS

Generally most uncertainty around clinical benefit/effect, still unresolved?

- Variation amongst different therapeutic area e.g. oncology vs chronic vs. acute
- Selection of clinical data used
- Timeframe under consideration i.e. proxy outcomes (PFS vs OS etc.)
- Duration of effects/stopping rules etc.
- Selection of data/trials is key in avoiding bias and reducing uncertainty

Common criticism is use of over optimistic assumptions

Handling uncertainty



Pre-appraisal

- Scoping meeting
- Draft/final scope
- PICOT statement

During appraisal

- ACD
- Extrapolation algorithm (NICE DSU)

Post-appraisal

- Conditional Reimbursement (Cancer Drugs Fund)
- Patient Access Scheme
- Managed Entry Agreement (MEA)

Case study - Dinutuximab beta for neuroblastoma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Long-term benefit of Qarziba uncertain, says NICE

4th May 2018

Dinutuximab beta (Qarziba, EUSA)

Treatment of high-risk neuroblastoma

Immunotherapy – a monoclonal, chimeric antibody that targets GD2, a glycolipid in neuroblastoma cells

Intravenous infusion administration

Acquisition cost: £7,610 per vial; average cost of a course of treatment: £152,200

https://www.nice.org.uk/guidance/ta538

Case study - Qarziba (dinutuximab) Timeline

August 2016:
- Final scope issued by NICE

May 2018:
- Appraisal consultation document published
  - "Dinutuximab beta is not recommended within its marketing authorization"
  - "…indirect comparison … suggests dinutuximab beta increases overall survival and the length of time before the disease progresses … But there is substantial uncertainty about its long-term benefits, which has a large impact on the cost-effectiveness estimates."
  - "…most plausible estimate (£62,300 to £79,900 per QALY gained) considered much higher than what NICE normally considers a cost-effective use of NHS resources"

July 2018:
- Final Appraisal Document
  - " recommended as an option for treating high-risk neuroblastoma only if
    - they have not already had anti-GD2 immunotherapy and
    - the company provides dinutuximab beta according to the commercial arrangement "
  - "…does not meet NICE's criteria for a life-extending treatment at the end of life. Also, the range of cost-effectiveness estimates presented (>£40,000) is higher than what NICE usually considers a cost-effective use of NHS resources"
  - "Data collection in the Cancer Drugs Fund would not resolve uncertainty about dinutuximab beta's long-term benefit"

https://www.nice.org.uk/guidance/ta538

Political will

Political will can be a key factor in determining how robust NICE criticism might be

- Political persuasion has also been used by patient groups & manufacturers to overturn NICE decisions
- Unmet need – how willing is the HTA committee willing to accept uncertainty – more for greater areas of unmet need?

"Uncertainty is sometimes ignored when [committee members] are happy about the way the decision is going and might figure more highly in the discussions when more members of the Committee are unhappy about the way the decision is going"

"The committee is prepared to be flexible in its decision-making given the rarity and severity of the disease" Qarziba FAD (Aug, 2018)

Calnan et al. Still Elegantly Muddling Through? NICE and Uncertainty in Decision Making About the Rationing of Expensive Medicines in England; International Journal of Health Services 2017, Vol. 47(3)

Conclusion

- Uncertainty is an unavoidable part of all decision-making, and in particular, of the way that choices are made in HTA
- Handling (reducing) uncertainty can be a critical factor in achieving HTA success
- Political will can be a key factor in determining how robust NICE criticism might be
- Despite many issues & challenges, UK continues to list and reimburse medical technologies and enable patient access

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