NICE National Institute for Health and Care Excellence

Endpoints in expedited regulatory approval processes

An HTA Perspective

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HTA seeks to establish the relative effectiveness of technologies

Efficacy

Incremental benefit of using a technology for a specific indication in ***ideal conditions*** of use, for example, in a strict protocol of a randomized controlled trial

(Comparative) Effectiveness

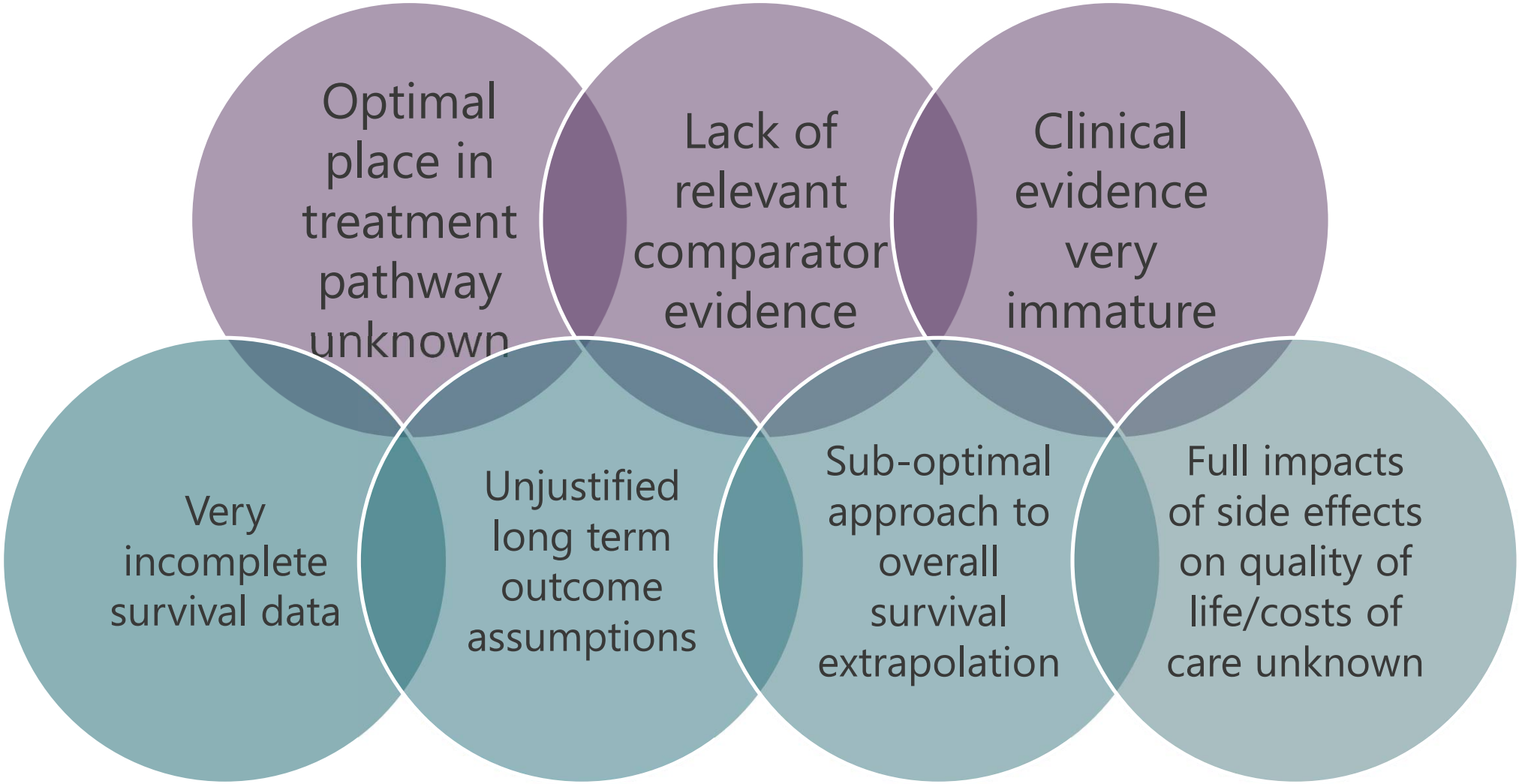
Comparative Incremental benefit of using a technology for a specific indication in ***general or routine conditions*** of use

Health technology assessment uses data submitted to the regulators on efficacy comparisons for relative effectiveness comparisons

Challenges for HTA in expedited approval processes

Problem with clinical trial designs	• Not designed to inform clinical practice • Adaptive designs/other master protocols difficult to interpret • ***Surrogate endpoints have unclear relationship with OS and HRQL***
Fewer comparative randomised clinical trials	• Increasing number of single arm trials • Historical comparisons are not robust
Increasing frequency of conditional approvals	• Survival outcome measurement not complete • Ongoing data collection not 'tuned' to HTA requirements • Increased uncertainty

General issues in generation of clinical evidence generation for HTA



TA517: Avelumab for Merkel cell carcinoma

- Avelumab is indicated as monotherapy for 'the treatment of adult patients with metastatic Merkel cell carcinoma.'
- Merkel cell carcinoma is a rare and aggressive cancer with limited treatment options.
- A conditional marketing authorisation was granted for first-line treatment.

TA517: Pivotal trial evidence

JAVELIN 200 trial - a single-arm non-randomised trial:

- Part A: 88 patients with relapse after at least 1 line of chemotherapy - 2nd-line + group
- Part B: 39 patients who had not had previous systemic therapy for metastatic disease -1st-line group

1st-line		2nd-line +	
ORR (3 months)	OS (median)	ORR (18 month)	OS (median)
62%	Not reached	33%	12.6 months

TA517 Uncertainty issues - 1st-line use

No head-to-head comparisons	Immaturity of data	Extrapolations
• Single arm trial with small N • Comparisons using observational study not robust • No adjustment for prognostic factors • Results from the indirect comparison were highly uncertain	• N=29 with 3-month follow-up • N=14 with 6-month follow-up	• OS and PFS derived from the second-line model by applying a HR based on assumptions, not using direct available evidence • Committee preferred direct extrapolation from the trial • PFS and OS estimates highly uncertain

TA517 Uncertainty issues - 2nd-line use

No head-to-head comparisons	Subsequent treatments	Extrapolations
• Comparisons using observational study not robust • Results from the naive indirect comparison were highly uncertain.	• OS data confounded by the use of subsequent treatments • No data on subsequent treatments were recorded	• OS and PFS were sensitive to method of extrapolation (spline-based vs Weibull approach) • Extrapolated from 18-months data to a 40-year time horizon

Options for bridging the evidence gap

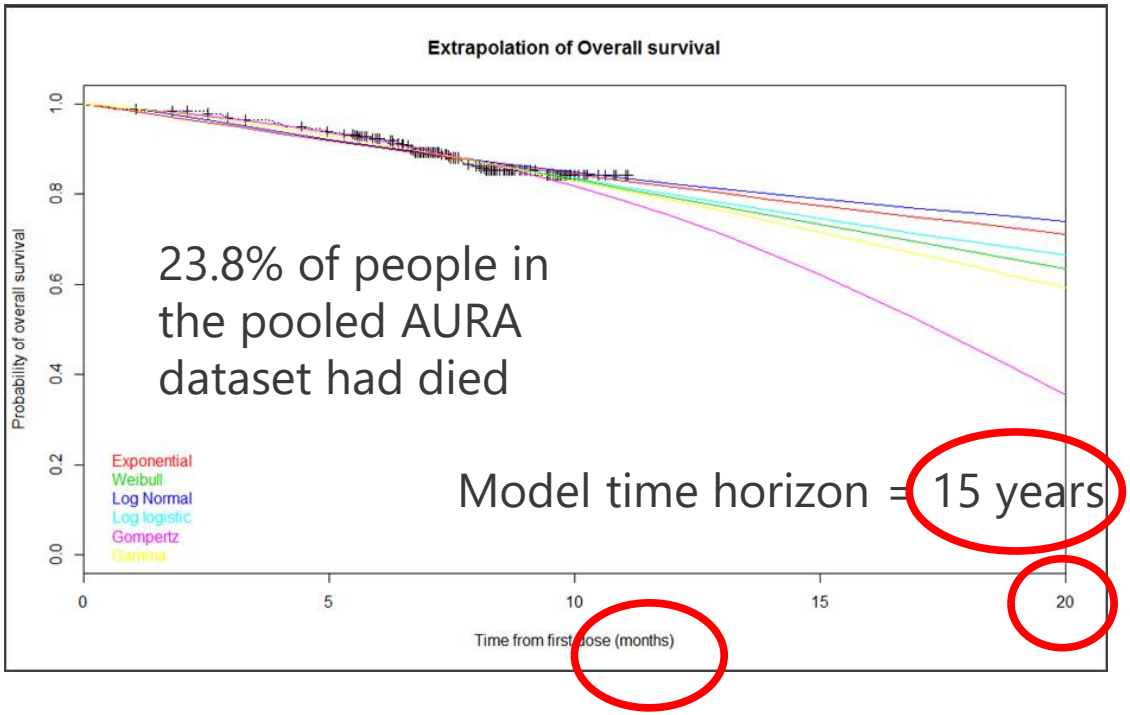
- Do nothing
- Quantitative
  - evidence synthesis, modelling
- Qualitative
  - dialogue, debate, interaction, consultation

Uncertainty in overall survival gain is a big issue

CASE STUDY

TA416 Osimertinib - locally advanced/metastatic EGFR T790M mutation-positive NSCLC

Immature survival data = uncertain long-term benefit = uncertainty in clinical and cost-effectiveness estimates



Osimertinib vs platinum-doublet therapy

Assumptions	ICER (£/QALY)
Company's	£41,705
Committee's preference (alternative extrapolation)	Between £60,663 and £70,776[a]

[a]Dependent on utility estimates

Bridging the evidence gap- key issues to consider as early as possible

- Optimisation of pivotal clinical trial design for HTA ***and*** identification of robust data to compare it with established practice
- Understanding the relationship between surrogate outcomes and mortality/health-related quality of life
- Justifying proposed extrapolation modelling approaches - based on plausibility and using data available to date - to deal with uncertainty
- Developing evidence generation plans → ***increasing relevance of post-marketing authorisation studies*** including clinical effectiveness

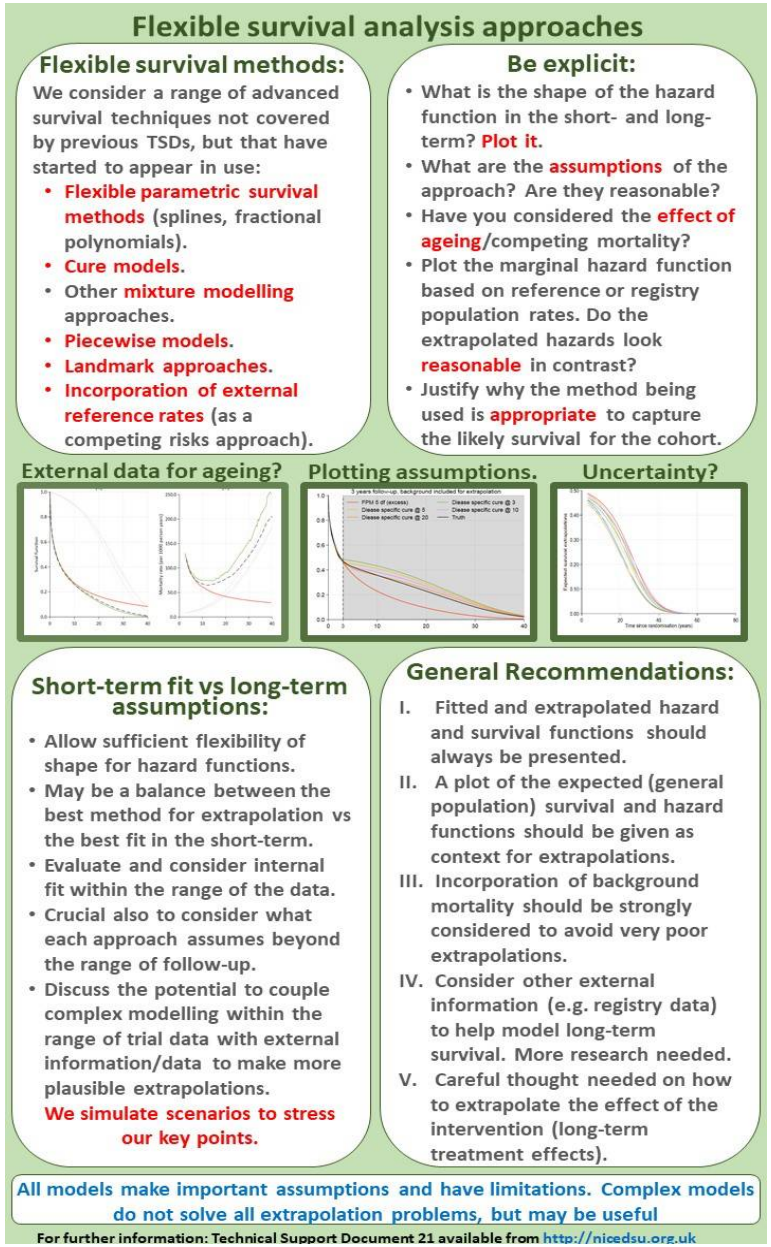
Guidance on key aspects of NICE methods

NICE Decision Support Unit
Technical Support Documents

Welcome to a series of Technical Support Documents (TSDs) produced by the NICE Decision Support Unit.

These documents have been commissioned by NICE with the aim of providing further information about how to implement the approaches described in the current NICE Guide to the Methods of Technology Appraisal (2013).

The NICE Methods Guide does not itself provide detailed advice on how to implement and apply the methods it describes. This DSU series of Technical Support Documents is intended to help to fill that gap.



http://nicedsu.org.uk

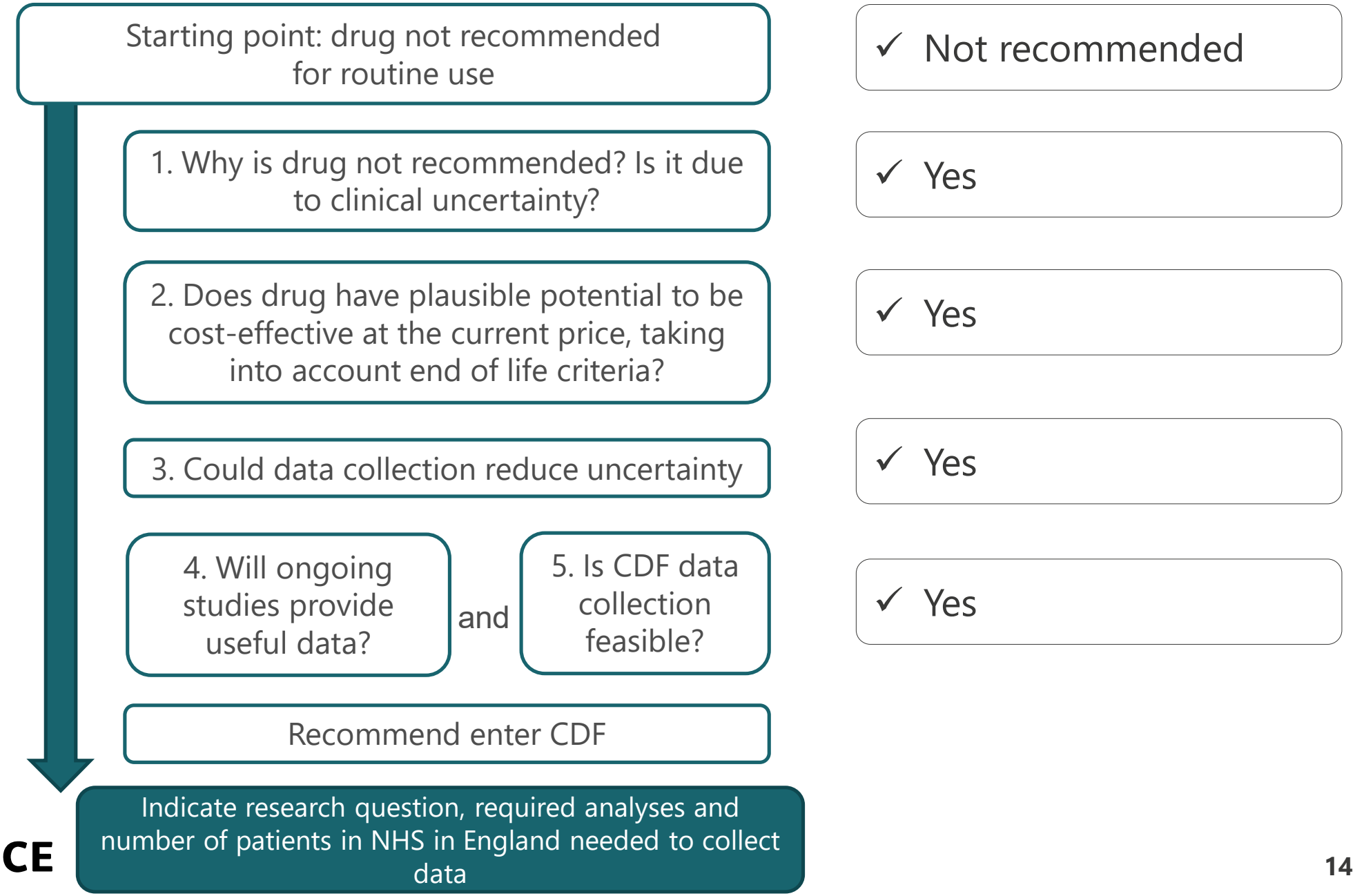
NICE

Bridging the evidence gap - the Cancer Drugs Fund and cancer drugs appraised by NICE

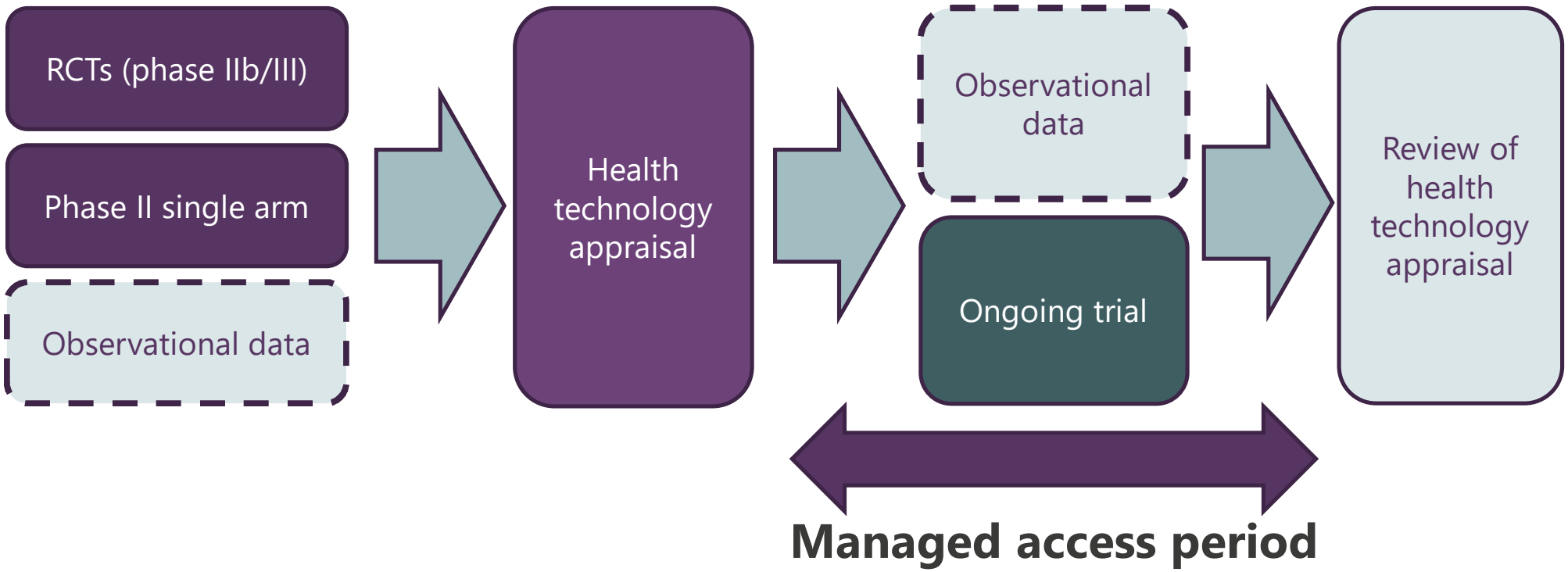
The NICE appraisal committee can make one of 3 recommendations for cancer drugs:

1. YES- recommended, the drug enters routine commissioning and will become available on the NHS
2. NO- NICE do not recommend the drug
3. Recommended for use within the CDF
    - The drug has **potential** to satisfy the criteria for routine commissioning but there is significant **clinical uncertainty** remaining which needs more investigation through real world data collection or clinical studies.

Cancer Drugs Fund recommendation criteria



What outcome data is collected whilst a drug is available on the CDF?



Conclusions

- HTA bodies are most interested in ‘final’ end points
- It is crucial to
  - ✓ demonstrate a predictive relationship between the ‘surrogate’ and ‘final’ end point
  - ✓ anticipate what data is required to bridge from expedited regulatory processes into HTA
- Early dialogue with HTA bodies essential
  - ✓ NICE Scientific Advice and Office for Market Access
  - ✓ EUnetHTA
- Need to plan to reduce uncertainty and decision risk
  - ✓ Plans for post launch evidence generation must take account of HTA requirements
  - ✓ Pricing strategies important

More information…

NICE Scientific Advice: www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice

Office for Market Access: www.nice.org.uk/OMA

Technology Appraisals: www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance

Cancer Drugs Fund: www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund