NICE National Institute for Health and Care Excellence

Surrogate endpoints in Health Technology Assessment

Exploration of the HTA Perspective

Professor Carole Longson, Life Science Adviser

Categories of Biomarkers

- Susceptibility/risk biomarker - *risk factor*
  - ❖ Indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.
- Diagnostic biomarker - *diagnostic*
  - ❖ Used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
- Monitoring biomarker - *staging*
  - ❖ Measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.
- Pharmacodynamic/response biomarker - *surrogate*
  - ❖ Used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.

Source: BEST (Biomarkers, EndpointS, and other Tools) Resource. FDA-NIH Biomarker Working Group

Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ctDNA) are proposed as new surrogate biomarkers in the development of anticancer agents

- Prognostic biomarker - *disease prognosis*
  - ❖ A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest
- Predictive biomarker - *response to treatment*
  - ❖ A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience an effect from exposure to a medical product or an environmental agent.

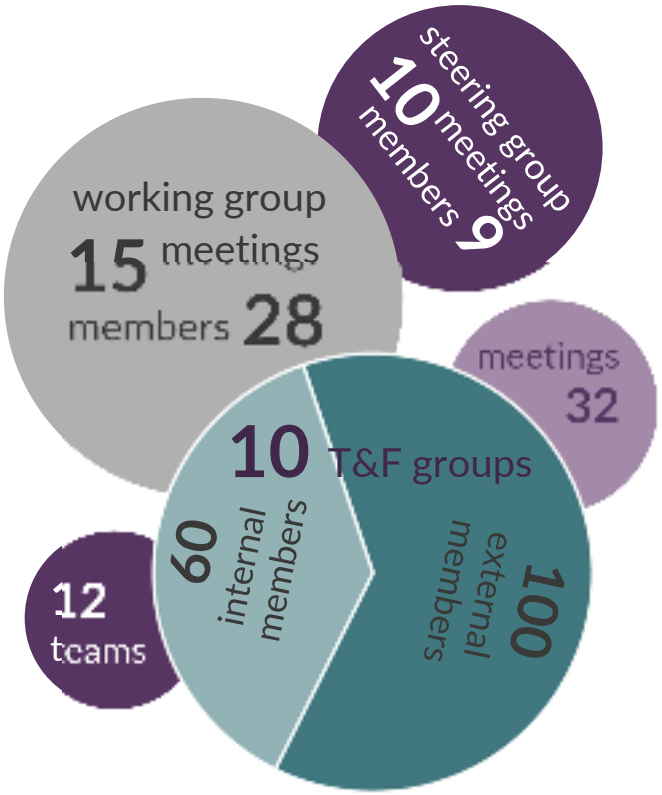
Source: BEST (Biomarkers, EndpointS, and other Tools) Resource. FDA-NIH Biomarker Working Group

Biomarkers as surrogates in HTA
A synopsis of the issues

- Increasing shift towards reviewing early evidence and immature data
- Increasing use of surrogate endpoints in regulatory approval
- **But** little attention is paid to the assumption that the effect of the drug on the biomarker surrogate is being considered as a proxy for its effect on clinically relevant endpoints
- **Usually** limited evidence is presented supporting the validity of the relationship between the biomarker surrogate endpoint and endpoints/outcomes of most interest to HTA decision-making - health-related quality of life (HRQoL) and survival
- **Whilst** expression of the biomarker may be associated with efficacy/survival it is not usually related to HRQL
- **This creates** high levels of uncertainty around the real incremental impact of innovative cancer drugs

NICE HTA Methods update 2022

Costs	Cost minimisation	Decision making
Discounting	Equality	HR-QoL
Modifiers	Sources and synthesis of evidence	Technology specific issues
	Uncertainty	



NICE Methods Review - Approach

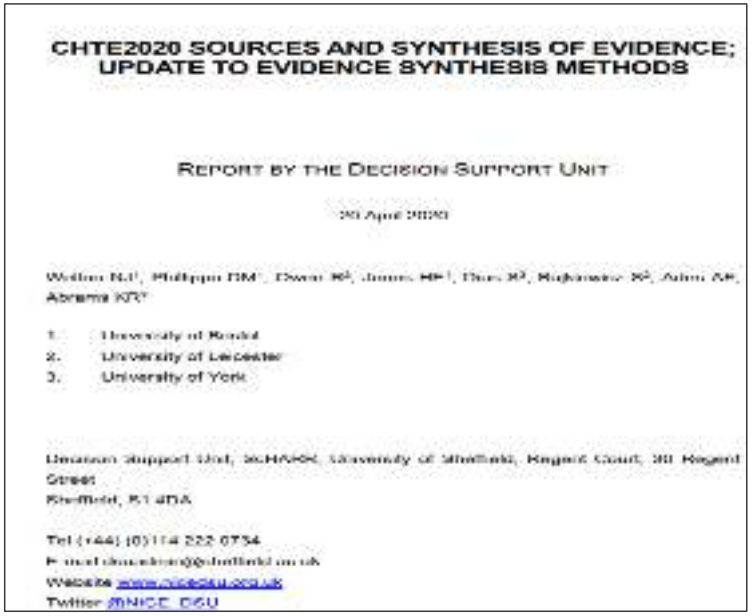
- Reviewing **current methods** used **across NICE programs**
- Reviewing **methods** used by **international HTA organisations**
- Reviewing **key literature: published papers** and NICE Decision Support Unit (DSU) technical Support documents (**TSDs**)
- **NICE Decision Support Unit (DSU) report on evidence synthesis methods for surrogates**

What other HTA Agencies say about surrogates

- The acceptability of a surrogate endpoint is based on its biological plausibility and empirical evidence
  EUnetHTA, CADTH
- Demonstrating a correlation between the surrogate endpoint and the final outcome is not sufficient for validation of the surrogate endpoint, as there also needs to be good evidence that an effect on the surrogate is predictive of an effect on the final outcomes
  EUnetHTA, IQWiG, PBAC, CADTH, HIQA
- It is preferred that this evidence comes from a meta-analysis of randomised controlled trials (RCTs)
  EUnetHTA, IQWiG
- Validation of the surrogate needs to be done in a population similar to the one in the trial or for whom the technology is indicated and is also technology class specific eg. Low-density lipoprotein cholesterol validated for statins but not for fibrates
  EUnetHTA, PBAC, IQWiG
- An attempt to extrapolate the validity of a surrogate to other technology classes within an indication should be thoroughly justified
  EUnetHTA, PBAC, IQWiG

Key Findings from the NICE Methods Review

"A correlate does not a surrogate make" Fleming and DeMets 1996



CHTE2020 SOURCES AND SYNTHESIS OF EVIDENCE; UPDATE TO EVIDENCE SYNTHESIS METHODS

REPORT BY THE DECISION SUPPORT UNIT

30 April 2020

Welton NJ[1], Phillippo DM[1], Owen RK[2], Jones HE[1], Dias S[3], Rutherford M[2], Ades AE[1], Abrams KR[2]

1. University of Bristol
2. University of Leicester
3. University of York

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street
Sheffield, S1 4DA

Tel (+44) (0)114 222 0734
E-mail dsu-admin@sheffield.ac.uk
Website www.nicedsu.org.uk
Twitter @NICE_DSU

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CHTE methods review

Sources and synthesis of evidence

Task and finish group report

July 2020

What NICE says about Surrogates - Updated NICE Methods Guide

General position on surrogates - Section 4.6.5

- For cost-utility analyses, clinical end points that reflect how a patient feels, functions, or how long a patient lives are considered more informative than surrogate outcomes. When using 'final' clinical end points is not possible and data on other outcomes are used to infer the effect of the technology on mortality and health-related quality of life, evidence supporting the outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling.

Levels of Evidence - Section 4.6.6

Three levels of evidence for surrogate relationships can be considered in decision making (Ciani et al. 2017):

- Level 3: biological plausibility of relation between surrogate end point and final outcomes.
- Level 2: consistent association between surrogate end point and final outcomes. This would usually be derived from epidemiological or observational studies.
- Level 1: the technology's effect on the surrogate end point corresponds to commensurate effect on the final outcome as shown in randomised controlled trials (RCTs).

Rationale

- Improvement in clarity regarding the acceptability of the use of surrogates and the different levels of evidence for a surrogate relationship

What NICE says about Surrogates - Updated NICE Methods Guide

Validation of surrogates - Section 4.6.7

- For a surrogate end point to be considered validated, there needs to be good evidence that the relative effect of a technology on the surrogate end point is predictive of its relative effect on the final outcome. This evidence preferably comes from a meta-analysis of level 1 evidence (that is, RCTs) that reported both the surrogate and the final outcomes, using the recommended meta-analytic methods outlined in technical support document 20 (bivariate meta-analytic methods). Show biological plausibility for all surrogate end points, but committees will reach decisions about the acceptability of the evidence according to the decision context. For example, for certain technologies indicated for rare conditions, and some diagnostic technologies and medical devices, the level of evidence might not be as high.

Rationale

- Robust meta-analytic **methods are available** to conduct such analysis including the **Bivariate NMA** method proposed by the DSU (**TSD20**)

What NICE says about Surrogates - Updated NICE Methods Guide

Validation of surrogates - Section 4.6.8, 4.6.9, 4.6.10

- The validation of a surrogate outcome is specific to the population and technology type under consideration.
- Thoroughly justify extrapolating a surrogate to final relationship to a different population or technology of a different class or with a different mechanism of action.
- Extrapolation should be done using the recommended meta-analytic methods that allow borrowing of information from similar enough classes of technologies, populations, and settings, as outlined in technical support document 20. Existing relevant meta-analytical models may be used. However, when historical models are based on data collected in a different setting, then development of a new model using appropriate meta-analytic techniques is recommended. This may include network meta-analysis or hierarchical methods reflecting differences in mechanism of action between classes of technologies or for first-in-class scenarios.4.6.8,

Rationale

- Methods developed by the DSU facilitate borrowing of information between closely similar classes (TSD20)

What NICE says about Surrogates - Updated NICE Methods Guide

Exploring Uncertainty- Section 4.6.11

- In cost-utility analyses, the usefulness of the surrogate end point for estimating QALYs will be greatest when there is strong evidence that it predicts health-related quality of life or survival. In all cases, the uncertainty associated with the relationship between the surrogate end points and the final outcomes should be quantified and presented. It should also be included through probabilistic sensitivity analysis and can be further explored in scenario analysis.

Rationale

- The exploration of the uncertainty around the surrogate to final relationship is crucial in understanding the contribution of use of surrogates to overall decision uncertainty.

Surrogate endpoints in Health Technology Assessment
Conclusions and suggestions

- Validation of new biomarkers as predictive surrogates requires much scientific endeavour and careful planning and execution.
- Keep in mind the phrase ‘a little learning is a dangerous thing’ ....

Alexander Pope, 1709

.... it is particularly apt in relation to the validation of new biomarker surrogate end points for use in HTA as it will be scientifically complex and technically challenging.

- As a consequence, companies seeking to use new biomarkers as predictive surrogates for outcomes of interest in HTA should plan to validate this relationship as early as possible in clinical development.
- Seek concurrent scientific advice from ***both*** the regulatory and HTA perspective on how best to validate the biomarker as a surrogate

Acknowledgements

- Dalia Dawoud Senior Scientific Adviser, Science, Policy and Research Programme, NICE
- Ian Watson Senior Technical Adviser, Methods, Centre for Health Technology Evaluation, NICE
- Francois Maignon, Principal Scientific Adviser, NICE Scientific Advice
- Sources and Synthesis of Evidence Task and Finish Group
- NICE CHTE Methods Update Team
- NICE DSU Team

And a useful read

Dawoud et al. Raising the bar for using surrogate end points in drug regulation and health technology assessment

https://www.bmj.com/content/374/bmj.n2191