Surrogate Endpoints Under Attack: Is It Still Worth Performing Surrogacy Validation? Lessons from NSCLC

Using Surrogate Endpoints in HTA Submissions: NICE Methods Update

Dalia Dawoud

Senior Scientific Adviser

@drddawoud

NICE National Institute for Health and Care Excellence

Declaration

No conflicts of interest to declare

Views expressed my own and not those of NICE

NICE

Why surrogates?

- ❑ Continued shift towards reviewing **early evidence and immature data**
- ❑ Continued increase in **using surrogate endpoints** in **regulatory approval**
- ❑ **Limited evidence**, if any, presented **to support the validity** of the **relationship** between the **surrogate endpoints** and **outcomes** required for decision-making (health-related quality of life (**HRQoL**) and **survival**)
- ❑ **Uncertainty** around the **long-term impact** of many of the innovative technologies assessed particularly those for **cancer and rare diseases**

The 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**)
- **DSU report on evidence synthesis methods for surrogates**

NICE

Key Findings: NICE methods guidance and other HTA agencies'

There is a need to make the evidence requirements for more explicit.

In particular:

- ❑ Describing the **levels of evidence**
- ❑ The expectations for **evidence of validation**
- ❑ How to properly account for **uncertainty** in surrogate relationships

- IQWIG Guidance most detailed
  - ❑ Recommends using Surrogate Threshold Effect to define the minimum level of association required
  - ❑ Also includes considerations for small populations

NICE

Key Changes

Addition

Three levels of evidence for surrogate relationships can be considered in decision making [1]:

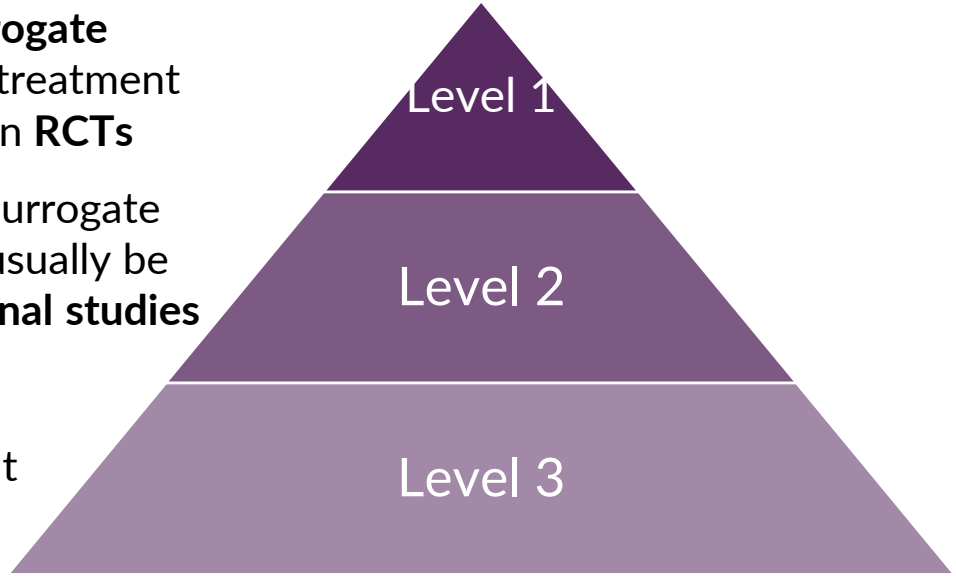
Level 1: Treatment effect on the **surrogate endpoint** corresponds to commensurate treatment effect on the **final outcome** as shown in **RCTs**

Level 2: consistent association between surrogate endpoint and final outcomes. This would usually be **derived from epidemiological or observational studies**

Level 3: biological plausibility of relation between surrogate endpoint and final outcomes

Rationale

Need for clarity regarding the different levels of evidence for a surrogate relationship.



NICE

Key Changes

Addition

For a surrogate endpoints to be considered **validated**, there needs to be good **evidence** that the **relative effect of a technology on the surrogate** endpoint is **predictive** of its **relative effect on the final outcome**.

This evidence should be obtained 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 TSD20** [2] (bivariate meta-analytic methods/joint modeling).

If **other levels of evidence** are used to support the surrogate relationship, this will need to be **justified**.

Rationale

Robust meta-analytic **methods are currently available** to conduct such analysis including the **Bivariate NMA** method proposed by the DSU (**TSD20** [2]).

NICE

[2] Welton, N.J., Phillippo, D.M., Owen, R., Jones, H.J., Dias, S., Bujkiewicz, S., Ades, A.E., Abrams, K.R. DSU Report. CHTE2020 Sources and Synthesis of Evidence; Update to Evidence Synthesis Methods. March 2020

Key Changes

Addition

The validation of a surrogate endpoint is specific to the population and technology type under consideration.

- **Extrapolation** of a surrogate to final relationship to a **different population or technology** of a different class or with a different mechanism of action **needs thorough justification**.

It should be undertaken using the **recommended meta-analytic methods** that allow borrowing of information from sufficiently similar treatment classes, populations, and treatment settings, as outlined in TSD20 [2] and [3]

Rationale

Methods developed by the DSU facilitate borrowing of information between closely similar classes (TSD20 [2], [3])

NICE

[2] Welton, N.J., Phillippo, D.M., Owen, R., Jones, H.J., Dias, S., Bujkiewicz, S., Ades, A.E., Abrams, K.R. DSU Report. CHTE2020 Sources and Synthesis of Evidence; Update to Evidence Synthesis Methods. March 2020
[3] Papanikos T, Thompson JR, Abrams KR, et al. Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data. Stat Med. 2020;39(8):1103-1124. doi:10.1002/sim.8465

Key Changes

Amendment

"In all cases, the **uncertainty** associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified."

To

"In all cases, the uncertainty associated with the relationship between the surrogate endpoint and the final outcome should be quantified and presented. It **should also be incorporated* through probabilistic sensitivity analysis** and can be further explored in **scenario analysis**."

Rationale

Sensitivity analyses submitted to NICE **rarely include the uncertainty around the surrogate to final relationship.**

NICE

*In the economic model

Conclusions

- More **explicit guidance** relating to **the evidence requirements** when using surrogate endpoints is required

- Although NICE seeks the **highest level evidence** possible, it is acknowledged that the methods manual should include a **degree of flexibility** to ensure being relevant for a wide range of scenarios.

References

[1] Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward. Value Health. 2017;20(3):487-495. doi:10.1016/j.jval.2016.10.011

[2] Welton, N.J., Phillippo, D.M., Owen, R., Jones, H.J., Dias, S., Bujkiewicz, S., Ades, A.E., Abrams, K.R. DSU Report. CHTE2020 Sources and Synthesis of Evidence; Update to Evidence Synthesis Methods. March 2020, https://www.sheffield.ac.uk/sites/default/files/2022-02/CHTE-2020_final_20April2020_final.pdf

[3] Papanikos T, Thompson JR, Abrams KR, et al. Bayesian hierarchical meta-analytic methods for modeling surrogate relationships that vary across treatment classes using aggregate data. Stat Med. 2020;39(8):1103-1124. doi:10.1002/sim.8465

NICE National Institute for Health and Care Excellence

Acknowledgments

- **Jeanette Kusel** (Director, NICE Scientific Advice)
- **Micah Rose** (Senior Technical Adviser, NICE Scientific Advice)
- **Ian Watson** (Senior Technical Adviser, Methods, NICE CHTE)
- **Sources and Synthesis of Evidence Task and Finish Group**
- **CHTE Methods Update Team**
- **NICE DSU Team**

Dalia.Dawoud@nice.org.uk