The Use of Surrogate Endpoints in Regulatory and HTA Submissions: Methodological Considerations, Current Status and Best Practice Recommendations

Sylwia Bujkiewicz
Professor of Biostatistics

Huseyin Naci
Associate Professor of Health Policy

Oriana Ciani
Associate Professor of Practice

Dalia Dawoud
Scientific Adviser

UNIVERSITY OF LEICESTER www.le.ac.uk

Surrogate endpoints in HTA decision making: methodological considerations

Sylwia Bujkiewicz
Professor of Biostatistics
Biostatistics Research Group
University of Leicester

18 November 2020

Conflicts and disclosures

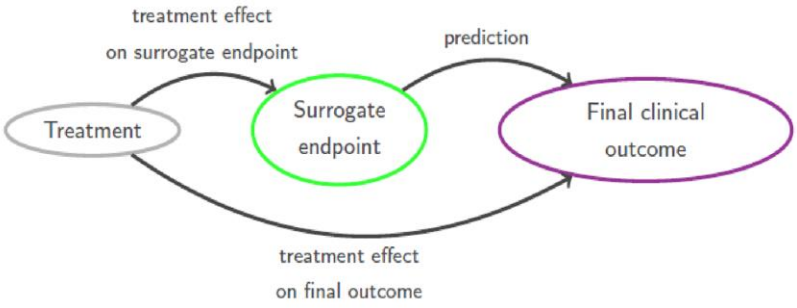
- I have served as a paid consultant, providing methodological advice, to NICE and Roche
- I have received research funding from European Federation of Pharmaceutical Industries & Associations (EFPIA) and Johnson & Johnson.
- I have received research funding from the Medical Research Council (MRC) , the National Institute for Health Research (NIHR) and EU Innovative Medicines Initiative (IMI).
- I have no financial or any other conflicts relating to specific products mentioned in my presentation

Surrogate endpoints: importance

- Modern trials of novel therapies bring a number of challenges for regulatory and HTA decision making, due to
  - trials of targeted therapies carried out in small subsets of the population
  - high success rates of new therapies reduce number of events (deaths) requiring long follow up time to measure effect on overall survival (OS)
  - This results in estimates of treatment effect on OS obtained with large uncertainty at early follow up.
- Regulatory agencies (EMA and FDA) carry out conditional licensing based on treatment effects measured on a short-term surrogate endpoint (PFS, TR).

Surrogate endpoints

Surrogate endpoints can be used to measure the effect of a new treatment earlier and with higher precision compared to OS.



Surrogate endpoint: A biomarker that is intended to substitute for a clinical (final) outcome. A surrogate end point is expected to predict clinical benefit
(Biomarkers Definitions Working Group. Clin Pharmacol Ther 2001.)

Advantages of surrogate endpoints

- Surrogate endpoints are of interest in drug development process if they can be measured
  - less costly
  - less invasively
  - or require shorter follow-up time

  compared to a final clinical outcome.
- They are increasingly important in HTA decision making
  - at the early stages of drug development
  - when conditional licensing based on a biomarker
  - evidence on treatment effectiveness on a target outcome limited

Surrogate endpoints: examples

- A number of putative surrogate endpoints have been investigated, in particular in disease areas where the final clinical outcome requires long follow up time.
- Examples include:
  - Progression free survival (PFS) as surrogate to overall survival (OS) in advanced colorectal cancer
    (Buyse et al. Journal of Clinical Oncology 2007, Ciani et al. Journal of Clinical Epidemiology 2015)
  - Relapse rate as surrogate for disability progression in relapsing remitting multiple sclerosis
    (Sormani et al, Multiple Sclerosis 2010)

Surrogate endpoint validation

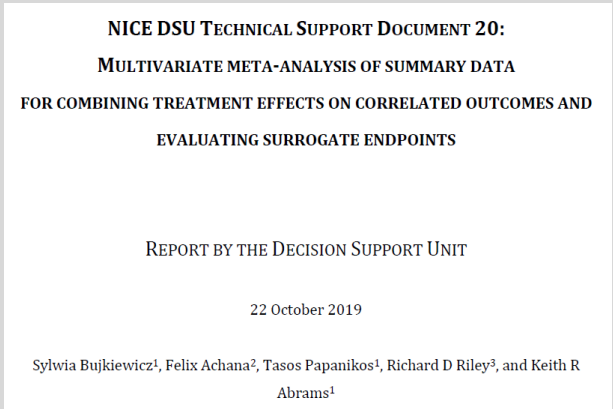
- Validation at three levels *(Taylor and Elston 2009, Ciani et al 2017)*
  - level 3: evidence based on biological plausibility alone
  - level 2: evidence of a strong association between the surrogate and the final endpoint at the individual patient level
  - level 1: evidence showing that health technologies improving the surrogate also improve the final clinical outcome across many randomized controlled trials; study level surrogacy.
- For HTA decision-making, a modelling framework is required
  - to establish the strength of the surrogate relationship between the treatment effects on the surrogate and the final outcome
  - and to predict the likely treatment effect on the final outcome for the new health technology

Methods for surrogate endpoint validation

- Relying solely on patient level association not sufficient when evaluating surrogate endpoints, in particular when individual level association evaluated based on data from a single trial *(Fleming and DeMets, Annals of internal medicine 1996).*
- A single trial validation cannot guarantee that an association between effects confirmed based on individual data under one treatment will hold in other interventions.
- A meta-analytic approach, based on data from a number of trials to establish the association between the treatment effects on the candidate surrogate endpoint and on the final outcome is more appropriate for evaluation of surrogate endpoints.

Methods for surrogate endpoint validation

- Putative surrogate endpoints are validated by estimating the pattern of association between the treatment effects on surrogate and final endpoints across trials.



NICE DSU TECHNICAL SUPPORT DOCUMENT 20:

MULTIVARIATE META-ANALYSIS OF SUMMARY DATA FOR COMBINING TREATMENT EFFECTS ON CORRELATED OUTCOMES AND EVALUATING SURROGATE ENDPOINTS

REPORT BY THE DECISION SUPPORT UNIT

22 October 2019

Sylwia Bujkiewicz[1], Felix Achana[2], Tasos Papanikos[1], Richard D Riley[3], and Keith R Abrams[1]

Methods for surrogate endpoint validation

- Putative surrogate endpoints are validated by estimating the pattern of association between the treatment effects on surrogate and final endpoints across trials.
- Bivariate meta-analysis methods, that take account of the correlations between the average treatment effects on surrogate and final outcomes, are suitable tools for modelling surrogate endpoints
  (Bujkiewicz et al, NICE DSU Technical Support Document 20; October 2019).
- Individual patient data hierarchical methods can be used to evaluate surrogate endpoint at both patients and study levels
  (Buyse et al. Biostatistics 2000, Burzykowski et al. Journal of Royal Statistical Society A 2004).
- Bivariate methods for summary data can be used to model study-level surrogacy
  (Daniels and Hughes, Statistics in Medicine 1997, Bujkiewicz et al. Stat Methods in Med Res 2018).

Novel methods for surrogate endpoint validation

- Bayesian meta-analytical methods to evaluate jointly multiple surrogate endpoints
  (Bujkiewicz et al, Statistics in Medicine 2016)
- Bivariate network meta-analysis for surrogate endpoint evaluation.
  (Bujkiewicz et al. Statistics in Medicine 2019)
  - allows modelling of surrogate relationships in greater detail
  - can help to disentangle information about surrogate relationships in data scenarios where such relationships vary across treatment contrasts
- Bayesian hierarchical meta-analytic method for modelling surrogate relationships that vary across treatment classes *(Papanikos et al. Statistics in Medicine 2020)*
  - allows for borrowing information about surrogate relationships between treatment classes whilst evaluating them within each treatment class

Discussion

- Use of putative surrogate endpoint – careful evaluation is needed.
- Rather than using pre-specified criteria, considering a balance between the strength of the surrogate relationship and the need for the decision to be made about the effectiveness of the new treatment may be important, in particular in the high priority disease areas.
- Uncertainty is key. The strength of the surrogate relationship will be reflected in the level of uncertainty around the predicted treatment effect on the final outcome.
- Predicted treatment effect (along with the uncertainty) may be used in HTA decision making framework.
- Novel methods may help improve predictions.

References

- R. S. Taylor and J. Elston. The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of uk health technology assessment reports. Health Technology Assessment, 13(6), 2009.
- O. Ciani, M. Buyse, M. Drummond, G. Rasi, E. D. Saad, and R. S. Taylor. Time to review the role of surrogate end points in health policy: state of the art and the way forward. Value in Health, 20(3):487-495, 2017.
- Thomas R Fleming and David L DeMets. Surrogate end points in clinical trials: are we being misled? Annals of internal medicine, 125(7):605{613, 1996.
- M. J. Daniels and M. D. Hughes. Meta-analysis for the evaluation of potential surrogate markers. Statistics in Medicine, 16(17):1965-1982, 1997.
- M. Buyse, G. Molenberghs, T. Burzykowski, D. Renard, and H. Geys. The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics, 1(1):49-67, 2000.
- Bujkiewicz S, Achana FA, Papanikos T, Riley RD, Abrams KR, NICE DSU Technical Support Document 20: Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints; 22 Oct 2019.
- Bujkiewicz S, Thompson JR, Riley RD, Abrams KR, *Bayesian meta-analytical methods to incorporate multiple surrogate endpoints in drug development process, Statistics in Medicine, 2016; 35 (7): 1063–1089.*
- Bujkiewicz S, Jackson D, Thompson JR, Turner R, Städler N, Abrams KR, White IR, *Bivariate network meta-analysis for surrogate endpoint evaluation, Statistics in Medicine 2019;38:3322–3341.*
- Papanikos T, Thompson JT, Abrams KR, Städler N, Ciani O, Taylor RS, Bujkiewicz S, *A Bayesian hierarchical meta-analytic method for modelling surrogate relationships that vary across treatment classes, Statistics in Medicine 2020;39:1103–1124.*