Surrogate Outcomes in Oncology: How Can They Be Used to Predict Overall Survival in Clinical Practice and Payer Decision-Making?: The Payer Perspective

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My Health Economist Perspective on Payers

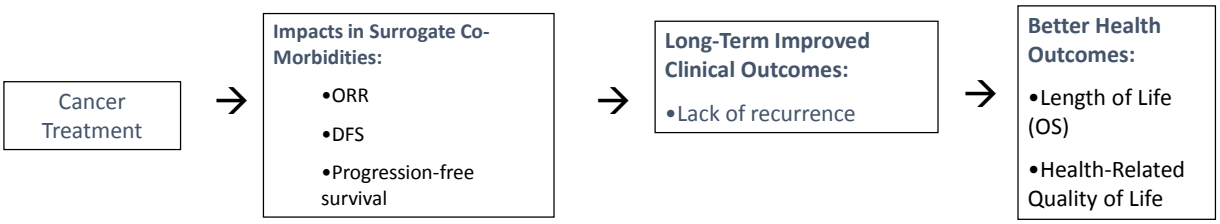
- Innovative medicines are global public goods.
- Role of regulator (FDA/EMA) is to approve if benefit-risk balance is acceptable.
- Pivotal trials are costly: their design should represent an informed trade-off among:
  - The monetary costs of trials
  - The practical realities of trial design and endpoint measurement: (a) lack of power for safety, (b) inability for complete follow-up, and (c) access for crossovers.
  - Potential health costs of regulatory delays on access to life-improving treatments
- The payer is the agent for the subscribers/patients.
  - But payer also wants to maintain good relations with providers who still maintain considerable power as an agent for the patient, including prescribing.

On the Inevitability of Surrogates and Modeling in Oncology

- Some payers (NICE, ICERs) have long understood the need to use surrogates and models.
- Some payers (IQWiG, US Commercial/P&T) review the comparative clinical evidence.

- Surrogates are increasingly being used for regulatory approval.

Bioclinical Health Outcomes Framework



Example: Oncology Disease-Treatment Model

"How Can Be Surrogate Outcomes be Used to Predict Overall Survival in Payer Decision Making?"

- Two ways:
  - As intermediate outcomes in cost-effectiveness models
  - As a qualitative justification for assuming a causal correlation

"Associations between surrogate outcomes and OS vary across disease, treatment setting, population, drug class and trial design/"

Regulatory Challenges

- Regulatory guidelines often are of high-level and lack clear and specific guidance
  - Food and Drug Administration (FDA) may grant accelerated approval based on an effect on a surrogate endpoint that is *reasonably likely* to predict clinical benefit [1]
  - European Medicines Agency (EMA) considers PFS and disease-free survival (DFS) as relevant measures of patient benefit if the magnitude of the treatment effect is sufficiently large to outweigh safety problems [2]
  - Neither guidelines provided details on what evidence needed to be provided to establish and justify a new surrogate outcome

Sources:
1. Food and Drug Administration. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics; May 2007. https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf
2. European Medicines Agency. Guideline on the Evaluation of Anticancer Medicinal Products in Man. London, United Kingdom: European Medicines Agency; December 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf

HTA Challenge: NICE

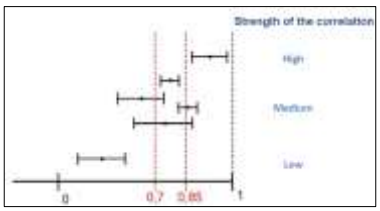
- **Health Technology Assessment (HTA) guidelines often vary by agencies**
  - National Institute for Health and Care Excellence (NICE)

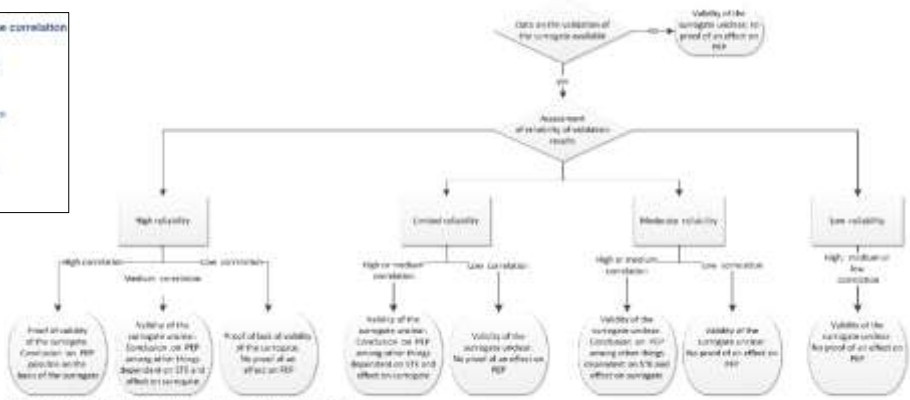
> Clinical end points that reflect how a patient feels, functions, or how long a patient survives are regarded as more informative than surrogate end points (such as laboratory tests and imaging findings). When the use of 'final' clinical end points is not possible and 'surrogate' data on other outcomes are used to infer the effect of treatment on mortality and health-related quality of life, evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling. 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 and/or survival. 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.

Source: National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013; April 2013. https://www.nice.org.uk/process/pmg9

HTA Challenge: IQWiG

- **Institute for Quality and Efficiency in Health Care (IQWiG) framework: reliability and correlation**





PEP: patient-relevant endpoint; STE: surrogate threshold effect

Figure A: Impact (of the reliability of validation studies and the correlation of the effects on the surrogate and patient-relevant endpoint) on the validity of the surrogate

Source: Institute for Quality and Efficiency in Health Care. Validity of surrogate endpoint in oncology; November 2011. https://www.iqwig.de/download/A10-05_Executive_Summary_Surrogate_endpoints_in_oncology.pdf

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

Analysis of endpoints used in marketing authorisations versus value assessments of oncology medicines in Germany

Jörg Ruof, Dietrich Knoerzer, Anja-Alexandra Dünne, Charalabos-Markos Dintsios, Thomas Staab, Friedrich Wilhelm Schwartz

Conclusions: Mortality endpoints are accepted by EMA and G-BA. EMA accepted well established and clinically relevant morbidity endpoints (e.g. progression-free survival and response rate), which were mostly excluded by G-BA from their value decisions. The applicability of methods used for benefit assessments to HRQoL differs from the mortality and morbidity categories, and requires further clarification.

HTA Challenge Australian Pharmaceutical Benefits Advisory Committee (PBAC) framework

Part	Summary
One	Definition, selection and measurement of the proposed surrogate measure (PSM) and the target clinical outcomes (TCO).
Two	Biological reasoning and epidemiological evidence supporting the relationship between the PSM and TCO (individual-level surrogacy).
Three	Randomized trial evidence using other drugs to show a comparative treatment effect on the PSM has satisfactorily predicted a comparative treatment effect on the TCO (trial-level surrogacy).
Four	Support for why the trial-level surrogacy with these other drugs is likely to apply to the proposed drug.
Five	Relevant considerations for incorporation of the comparative treatment effect based on the PSM into the economic evaluation.

Source: Report of the Surrogate to Final Outcome Working Group to the Pharmaceutical Benefits Advisory Committee: a framework for evaluating proposed surrogate measures and their use in submission to PBAC; 2008. http://www.pbs.gov.au/industry/useful-resources/pbac-technical-working-groups-archive/surrogate-to-final-outcomes-working-group-report-2008.pdf

ABSTRACT

Objective It is unclear how well different outcome measures in randomized controlled trials (RCTs) perform in predicting real-world cancer survival. We assess the ability of RCT overall survival (OS) and surrogate endpoints – progression-free survival (PFS) and time to progression (TTP) – to predict real-world OS across five cancers.

Methods We identified 20 treatments and 31 indications for breast, colorectal, lung, ovarian, and pancreatic cancer that had a phase III RCT reporting median OS and median PFS or TTP. Median real-world OS was determined using a Kaplan–Meier estimator applied to patients in the Surveillance a… of RCT OS an… prediction err…

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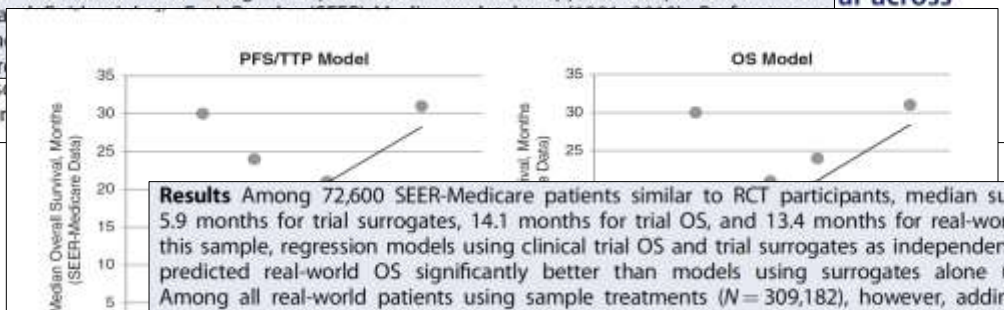
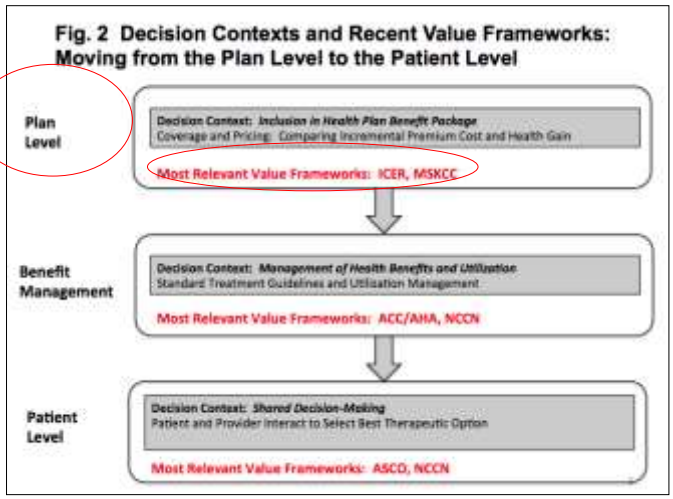


Results Among 72,600 SEER-Medicare patients similar to RCT participants, median survival was 5.9 months for trial surrogates, 14.1 months for trial OS, and 13.4 months for real-world OS. For this sample, regression models using clinical trial OS and trial surrogates as independent variables predicted real-world OS significantly better than models using surrogates alone ($P = 0.026$). Among all real-world patients using sample treatments ($N = 309{,}182$), however, adding trial OS did not improve predictive power over predictions based on surrogates alone ($P = 0.194$). Results were qualitatively similar using median absolute prediction error and R^2 metrics.

Conclusions Among the five tumor types investigated, trial OS and surrogates were each independently valuable in predicting real-world OS outcomes for patients similar to trial participants. In broader real-world populations, however, trial OS added little incremental value over surrogates alone.

Figure 1. PFS/TTP … vival, TTP = time …

Decision Contexts and Value Frameworks



Source: STF Final Report, Section 2 (Garrison, Pauly, et al, Value Health, Feb. 2018)

Are we ready for a consensus? How important is it?

- "Call for Action": "clear evidence-based aligned guidance on surrogacy by regulatory and reimbursement agencies"

Lesson:
Have worked (with many others) for over 10 years on encouraging regulators to use quantitative benefit-risk analysis, progress has been slow but noticeable.

Persistence and patience are essential—along with having many fellow travellers.

Thanks!

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