

223: Surrogate Endpoints Under Attack

Is It Still Worth Performing Surrogacy Validation?
Lessons from NSCLC

Introduction of the panel and the panelists by Silvia Paddock, PhD
May 2022



Disclosures and acknowledgements

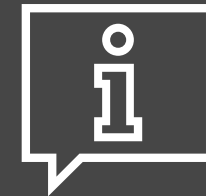


Amgen sponsored this issue panel



The analyses shown in this presentation were planned by Amgen and Certara and conducted by Certara Evidence and Access

Shuai Fu, PhD; Agnieszka Kopiec, MSc; Noemi Hummel, PhD



Opinions of all panelists reflect their personal opinions and not necessarily the official opinion of their employers.

What is a surrogate endpoint?

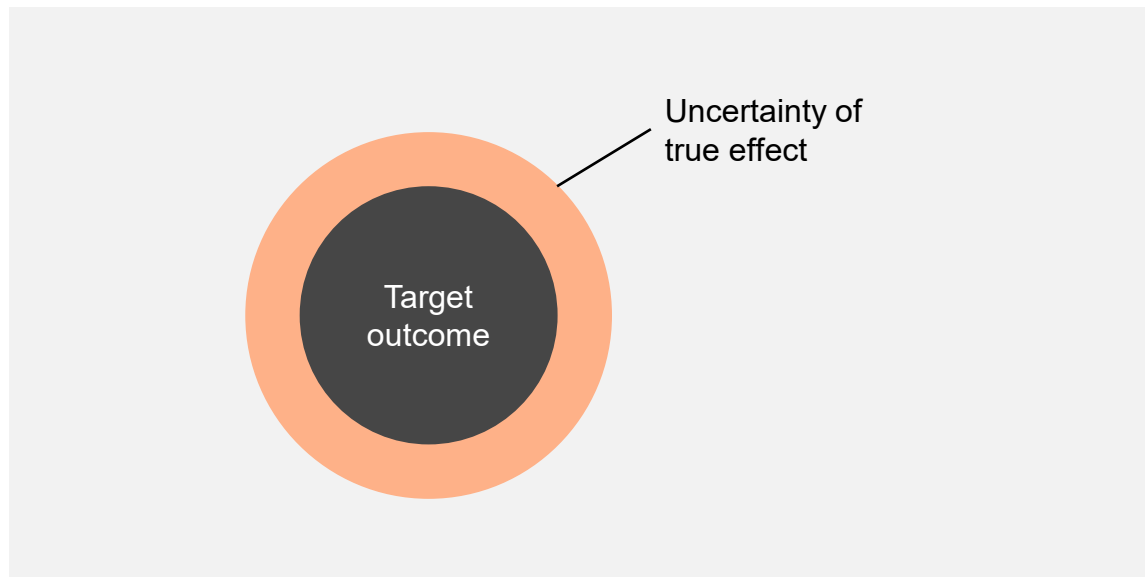
‘Surrogate’ means ‘replacement’

We may want to talk about ‘intermediate’ endpoints instead and will use the terms interchangeably

Scenario 1

Direct measurement of target outcome is possible.

The uncertainty of the results is caused by the variability of this outcome.

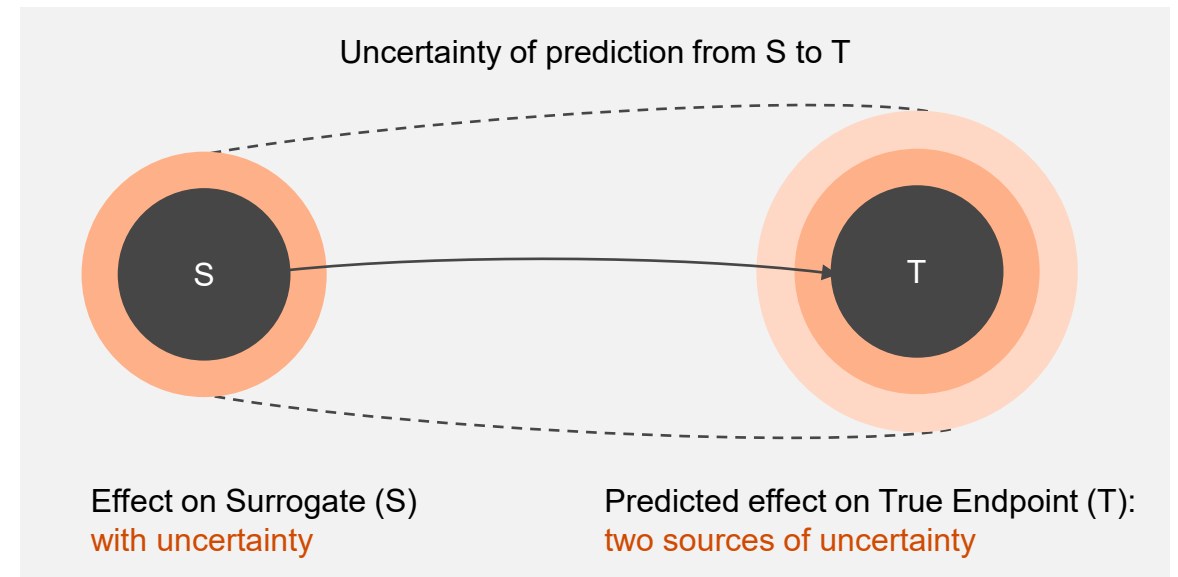


Scenario 2

Direct measurement of the target outcome is not possible.

The total uncertainty is the sum of:

- The uncertainty of the measurement of the intermediate endpoint
- The uncertainty of the correlation between this endpoint and the target outcome



It is difficult to make predictions...

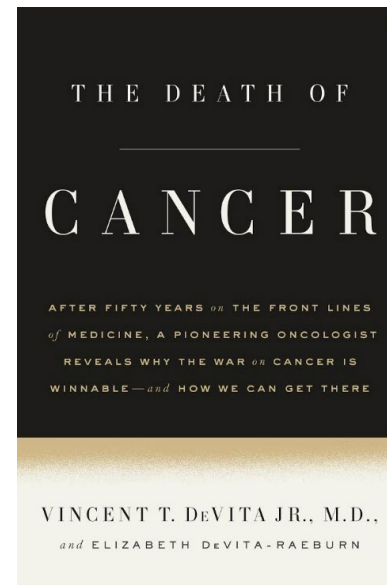
... especially about the future

How much uncertainty are we willing to accept and when?

Examples of 'failed' intermediate endpoints in the past that were found to be harmful to patients include arrhythmias, cholesterol levels, and hormone and vitamin levels. There is no such thing as a 'no brainer', yet a good biological rationale is important.

Reasons to accept uncertainty include:

- Trials being prohibitively long when measuring the target outcome
- Equipoise being violated (e.g., if patients in the control arm are not allowed to cross over)



“[...] according to the FDA, we needed to show that using PLX4032 increases survival compared to dacarbazine. That’s nonsense. [...] Patients should have refused to enter the control arm, and doctors should have refused to offer it.”

If it looks like a surrogate endpoint and quacks like a surrogate endpoint, it may still not be a valuable surrogate

Surrogate (intermediate) endpoints



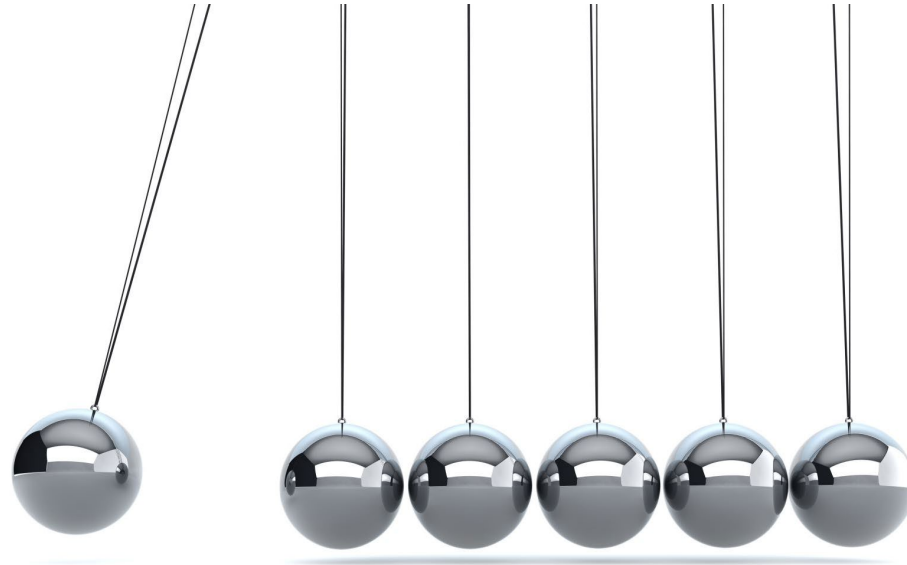
Somewhere
between absolutely
vital and completely
unacceptable

(quote from 2011 IQWiG
symposium)

Absolutely
vital



Completely
unacceptable



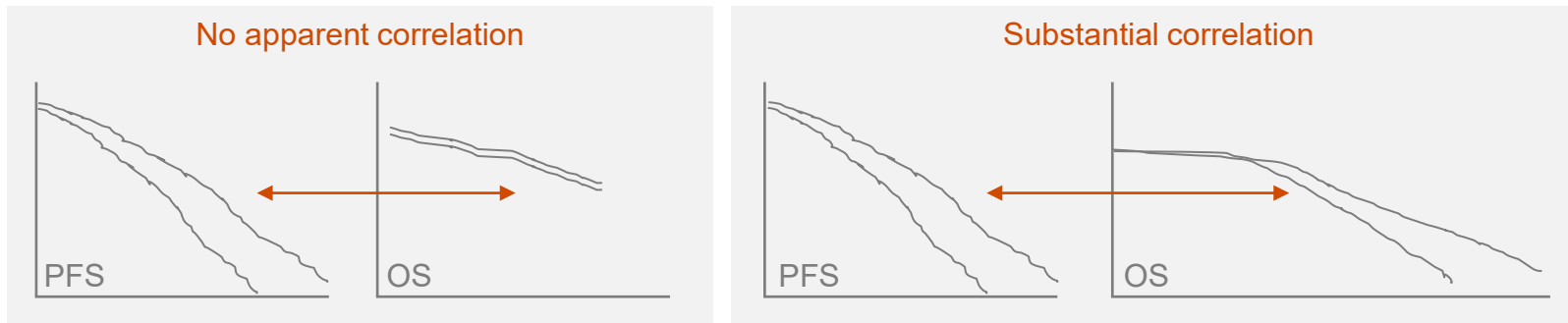
At least 50 years of this pendulum swinging back and forth in oncology

Source: https://www.iqwig.de/veranstaltungen/11-11-25_glaeske_surrogatendpunkte.pdf?rev=117386

Non-small-cell lung cancer (NSCLC)

Why has it been difficult to establish valid surrogate outcomes (e.g., PFS for OS)?

- Some studies that aimed to prove surrogacy included trials with immature survival data



- Hyperprogression (it looks as if the cancer is progressing, especially seen after using immunotherapies)
- Substantial cross-over into treatment arm
- Multiple later lines of treatment that 'dilute' the effect of the initial treatment

The rationale for 'progression' being a surrogate for survival for this specific cancer seems strong

- The lung is a vital organ
- Patients with NSCLC frequently die from lack of function of the lung (in contrast, to other cancers that need to spread to other vital organs)

Our panel

Dalia Dawoud, PhD

National Institute for Health and Care Excellence, NICE, UK

Update on recent requirements for surrogacy validation at NICE and the implications for future HTAs.

Billy Amzal, MSc, MPH, PhD

Quinten Health, France

Advanced statistical methods can reduce the uncertainty around predictions from the surrogate to the final outcome. Progression-free survival can serve as potential surrogate for overall survival in NSCLC. Billy also discusses options to transfer the findings into a real-world setting.

Jeff Allen, PhD

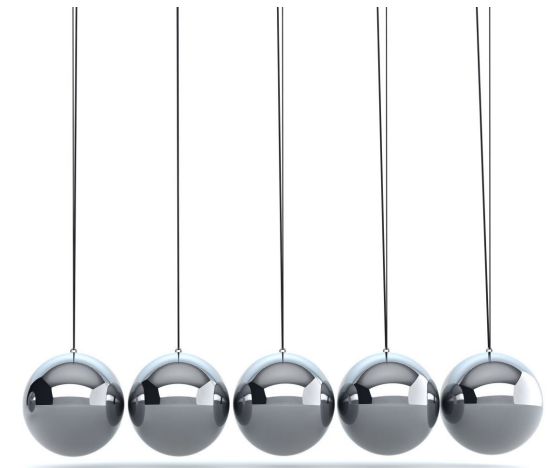
Friends of Cancer Research, FOCR, USA

Overview of the potential benefits of using surrogate endpoints for people living with cancer and recent initiatives on surrogacy validation in NSCLC at Friends of Cancer Research.

Moderator: **Silvia Paddock, PhD**

PwC Switzerland

Is it possible to move toward a 'stable equilibrium'?



Thank you

This publication has been prepared for general guidance on matters of interest only, and does not constitute professional advice. You should not act upon the information contained in this publication without obtaining specific professional advice. No representation or warranty (express or implied) is given as to the accuracy or completeness of the information contained in this publication, and, to the extent permitted by law, PricewaterhouseCoopers AG, its members, employees and agents do not accept or assume any liability, responsibility or duty of care for any consequences of you or anyone else acting, or refraining to act, in reliance on the information contained in this publication or for any decision based on it.

© 2022 PwC. All rights reserved. In this document, “PwC” refers to PricewaterhouseCoopers AG which is a member firm of PricewaterhouseCoopers International Limited, each member firm of which is a separate legal entity.