

Are surrogate endpoints ready for HTA?

A statistical view

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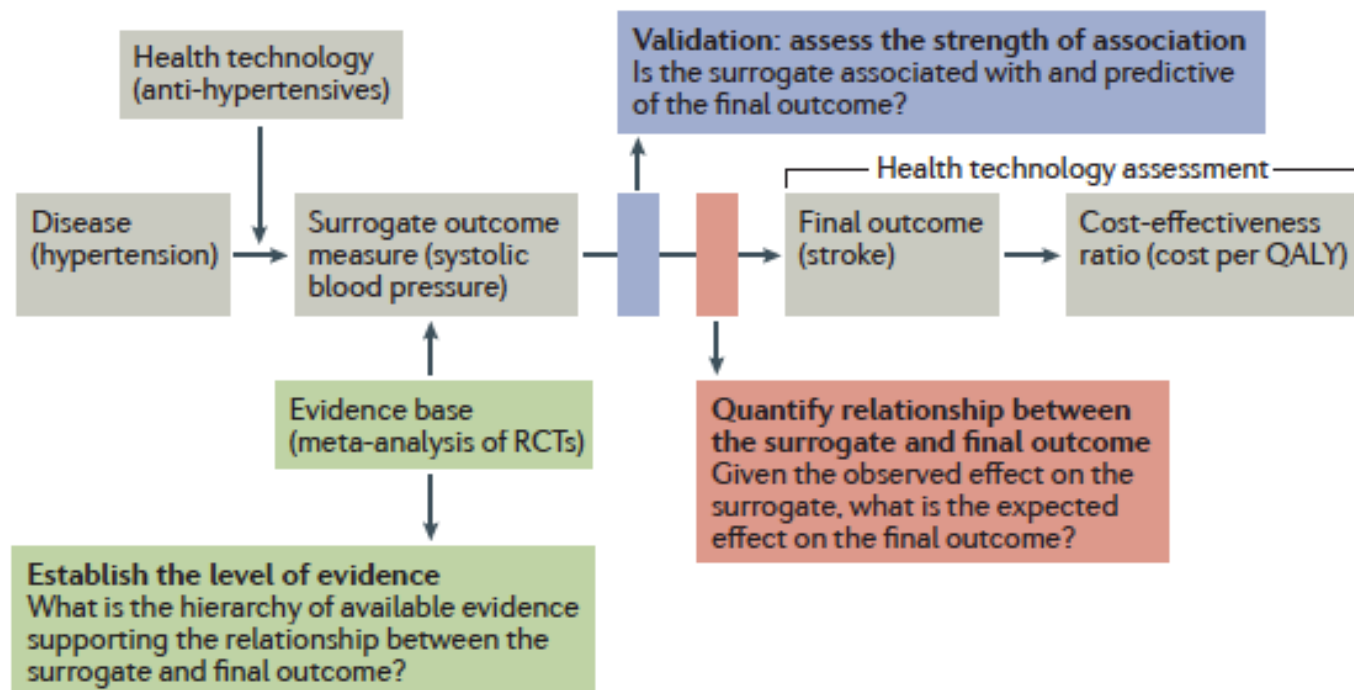
October 2022



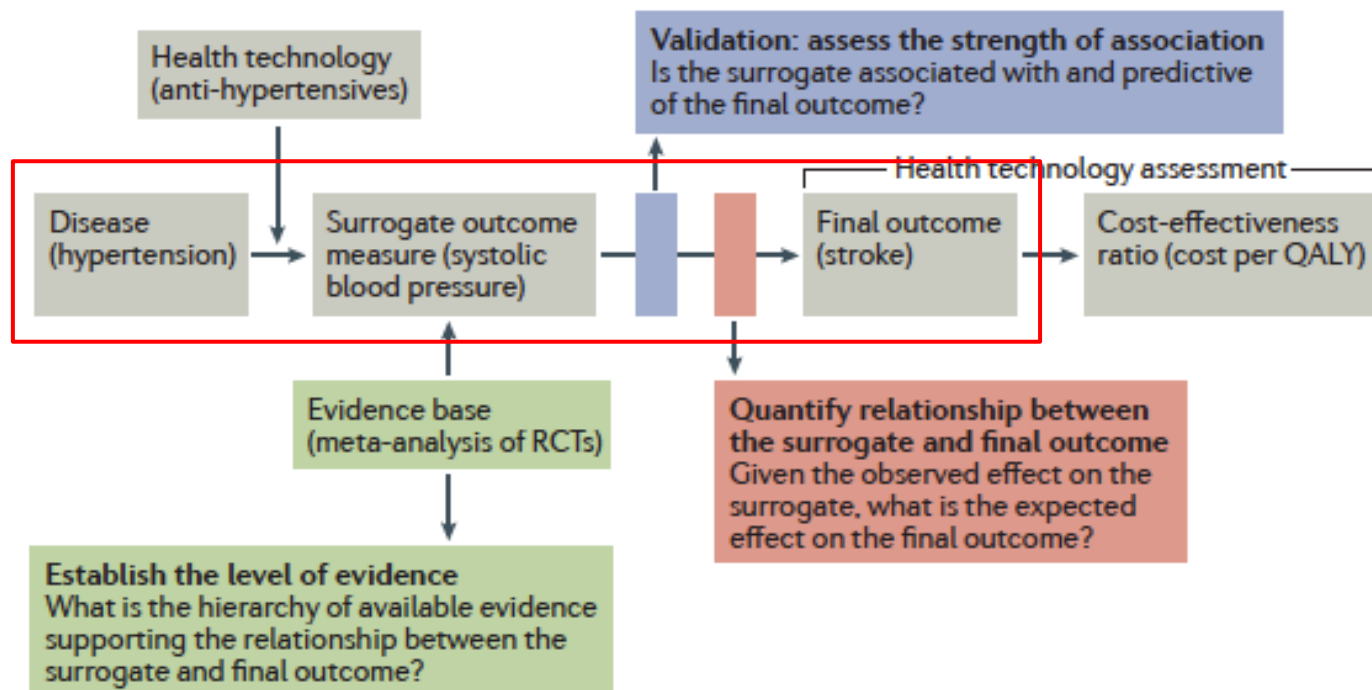
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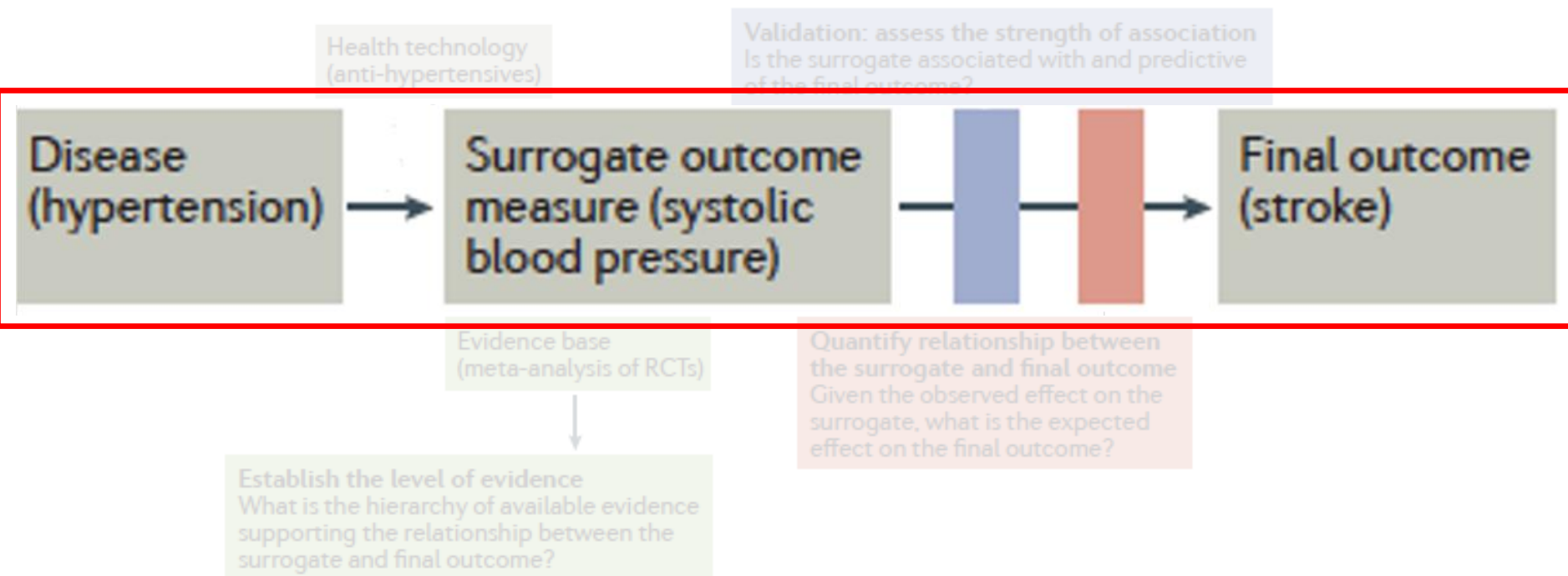
Statistical evaluation of potential surrogates



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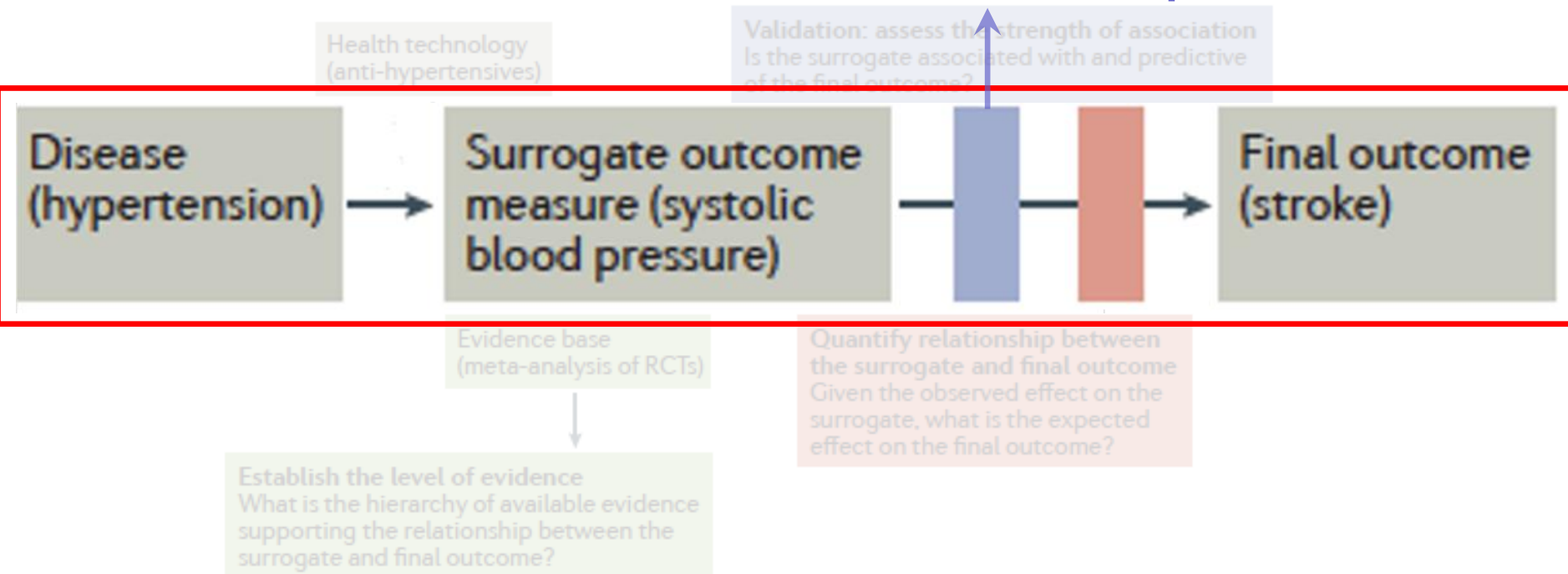
Statistical evaluation of potential surrogates



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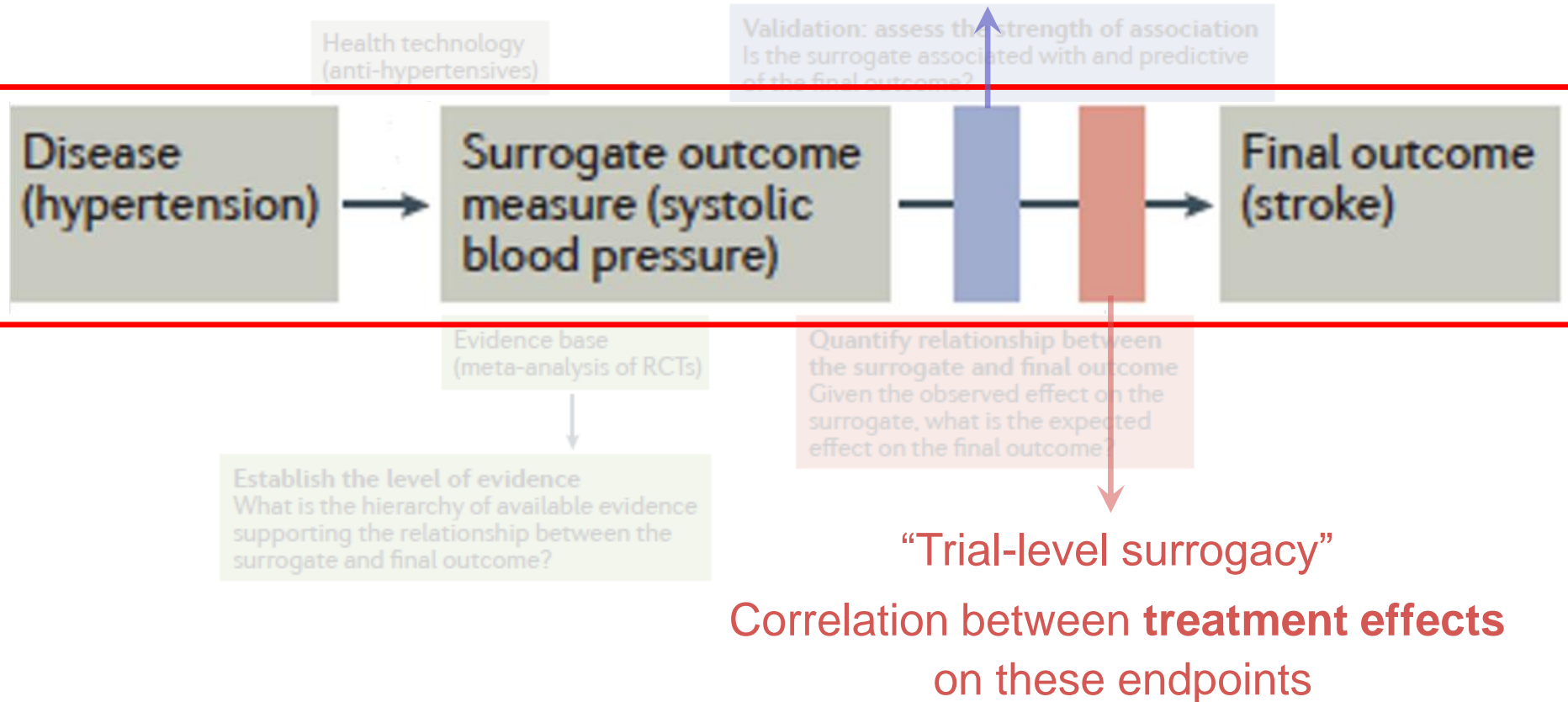
“Individual-level surrogacy”

Correlation between **endpoints**



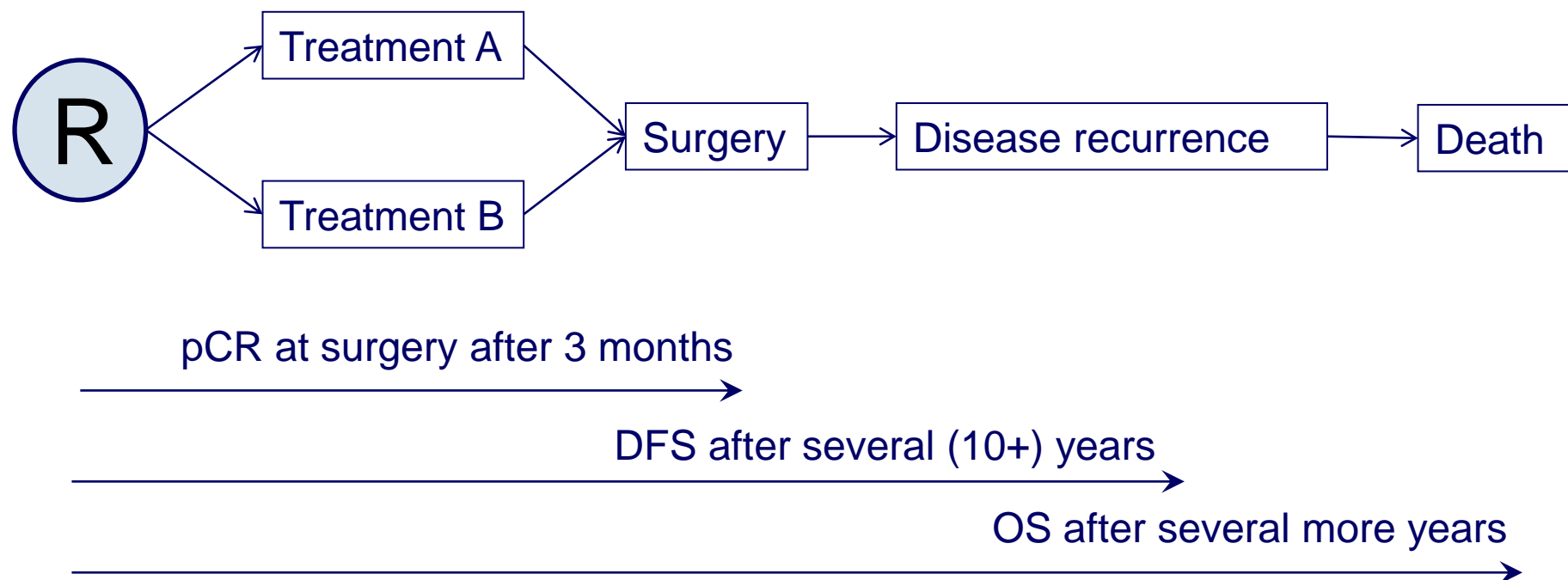
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pCR as surrogate for OS in early breast cancer

Is pathological complete response (pCR) an acceptable surrogate for overall survival (OS) for patients receiving treatment before surgery of early breast cancer?

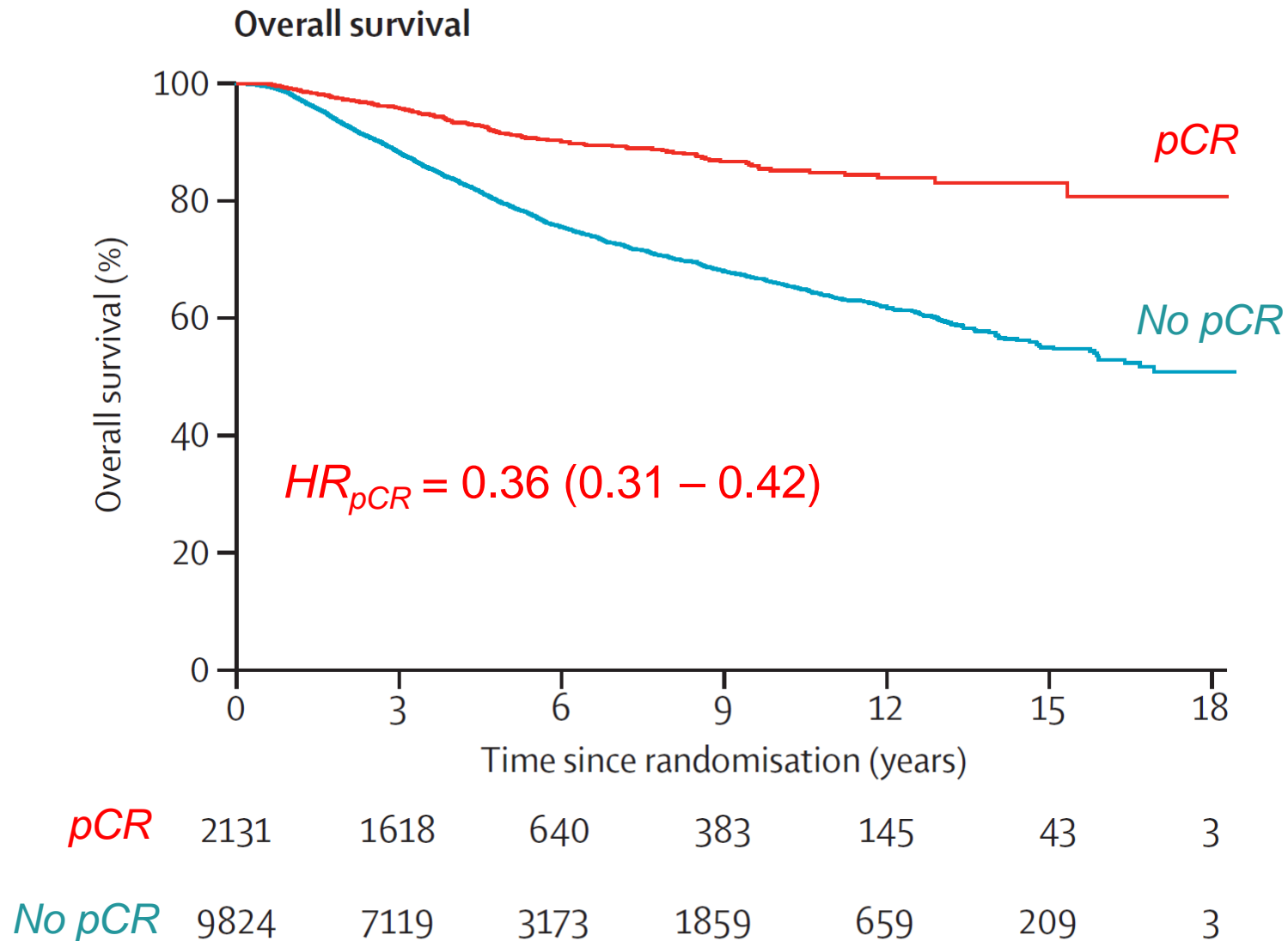


pCR as surrogate for OS in early breast cancer

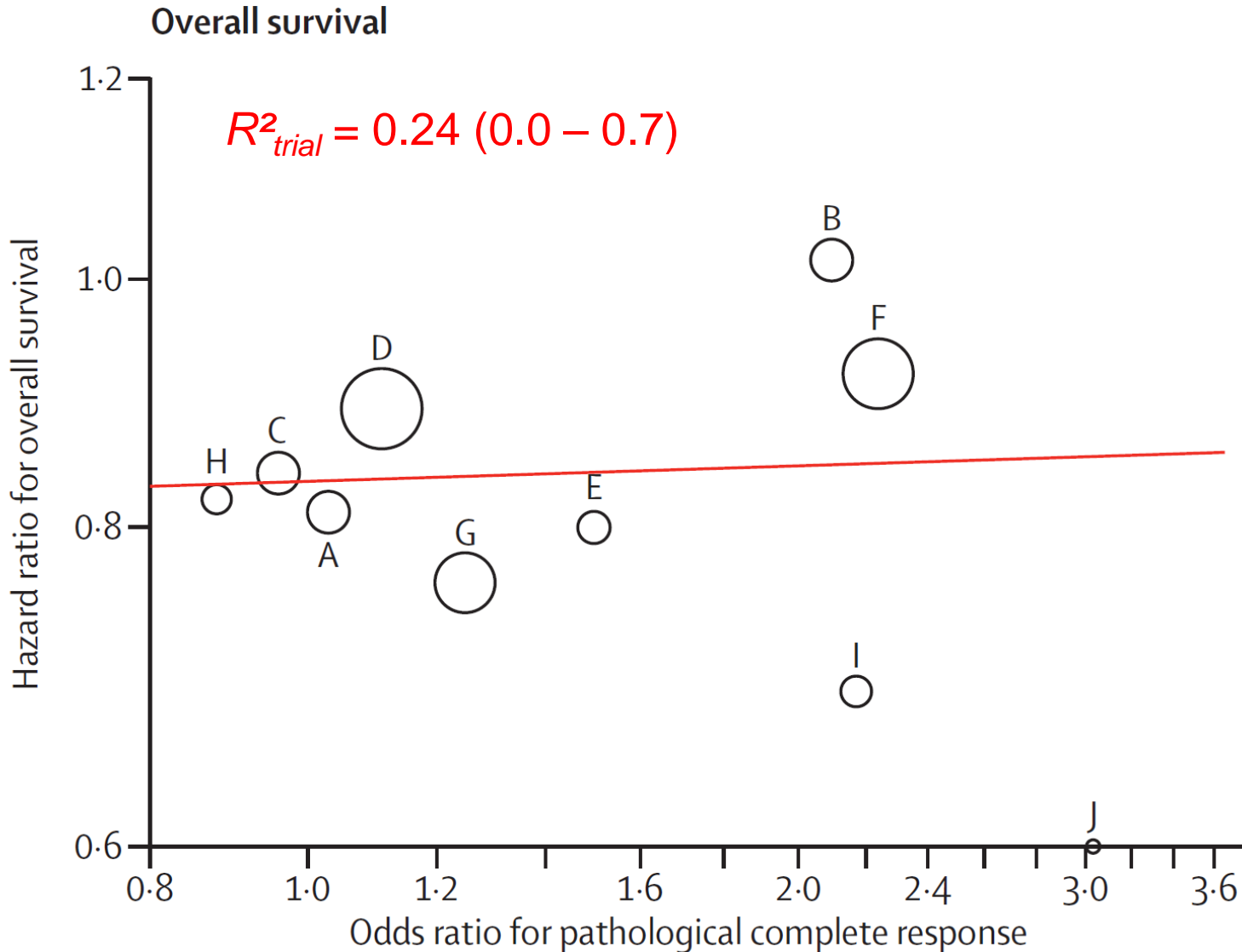
FDA performed a meta-analysis of 12 randomized trials (11,955 patients) submitted for approval

All trials compared an experimental therapy given before surgery to immediate surgery

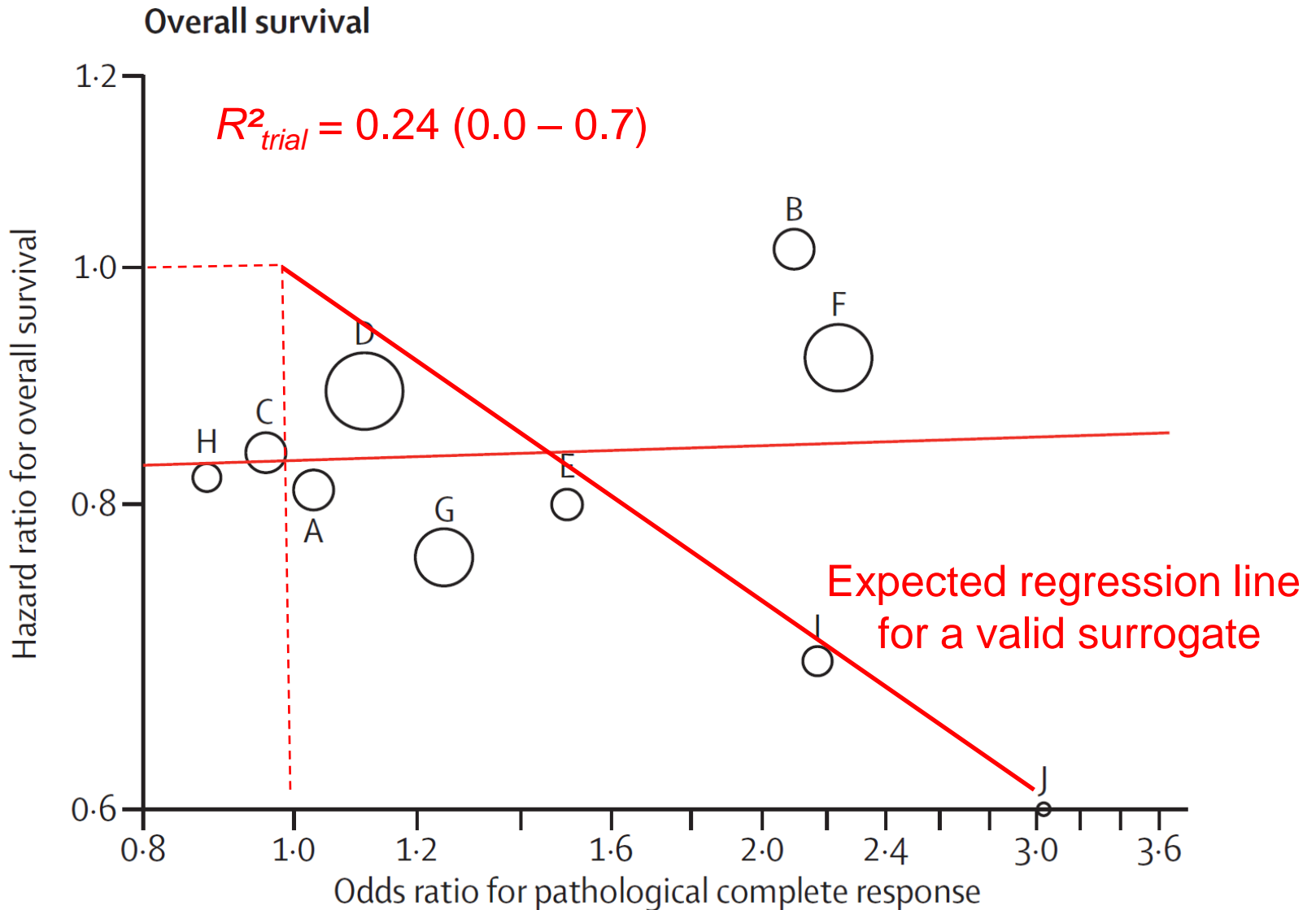
pCR is an individual-level surrogate



pCR is **NOT** a trial-level surrogate !



This would be expected of a trial-level surrogate



What does this example show?

The fact that pCR has a huge impact on OS (« individual-level surrogacy ») does not imply that a **treatment-induced change** in pCR will induce a **treatment-induced change** in OS (« trial-level surrogacy »).

What does this example imply for HTA?

Intermediate outcomes or biomarkers that have a big impact on the final outcome may or may not be valid surrogates.

Real-world or epidemiological evidence, regardless of size and quality, only address individual-level surrogacy.

We need **large-scale, randomized evidence** to assess the validity of a surrogate in terms of trial-level surrogacy.



Pathological Complete
Response in Neoadjuvant
Treatment of High-Risk
Early-Stage Breast Cancer:
Use as an Endpoint to
Support Accelerated
Approval
Guidance for Industry

July 2020
Clinical/Medical
Revision 1

[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/
Guidances/UCM305501.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf)