

Surrogate endpoints in regulatory use: How many are actually statistically valid?

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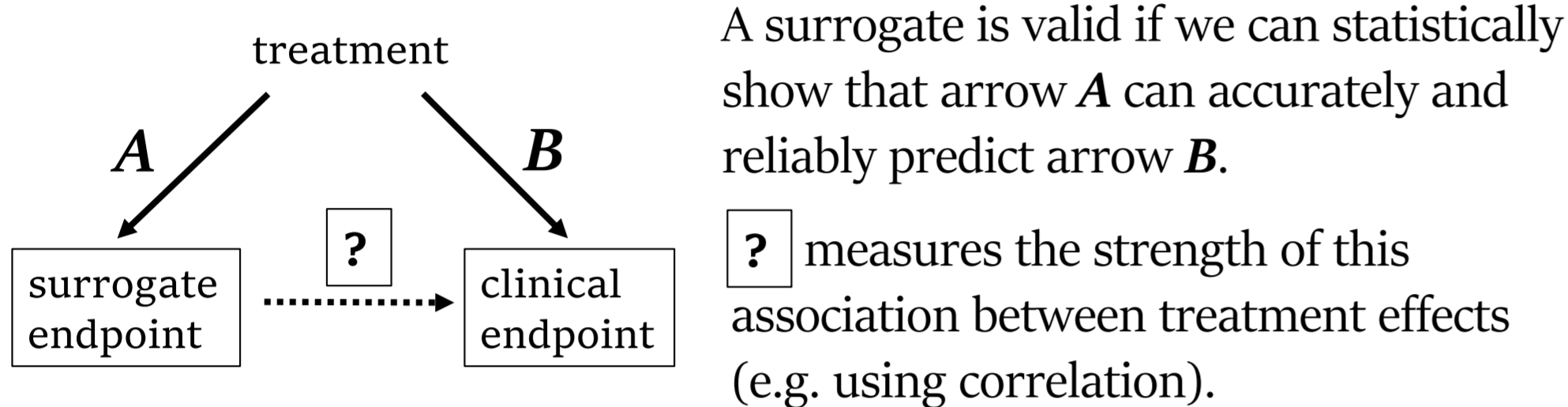
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Background

- A **surrogate endpoint** is an endpoint that is used in clinical trials as a **substitute** for a **direct measure of how a patient feels, functions, or survives**¹.
- Advantages of using surrogates include shortened trial duration (by measuring the endpoint earlier) and thus faster approval of drugs.
- Surrogate endpoints should ideally be *validated*.

Validation of a Surrogate



Use of Surrogate Endpoints by Regulators

- The US Food and Drug Administration (FDA) has an online **Table of Surrogate Endpoints**² that lists accepted surrogate endpoints to accelerate drug approval by disease area.
- The European Medicines Agency (EMA) publishes an assessment report for each approved drug from which we can identify the surrogate endpoints used.

Methodology

Objective:

To conduct a systematic review across all therapeutic areas which

- presents the status of validated surrogate endpoints;** and
- identifies non-validated surrogate endpoints that are currently in use** by the FDA and EMA regulators.

We searched five electronic databases between April 1989 and August 2021, and we included 1,528 articles for full-text screening. In the area of respiratory diseases, 44 articles were included and first results are presented in **Table 2**.

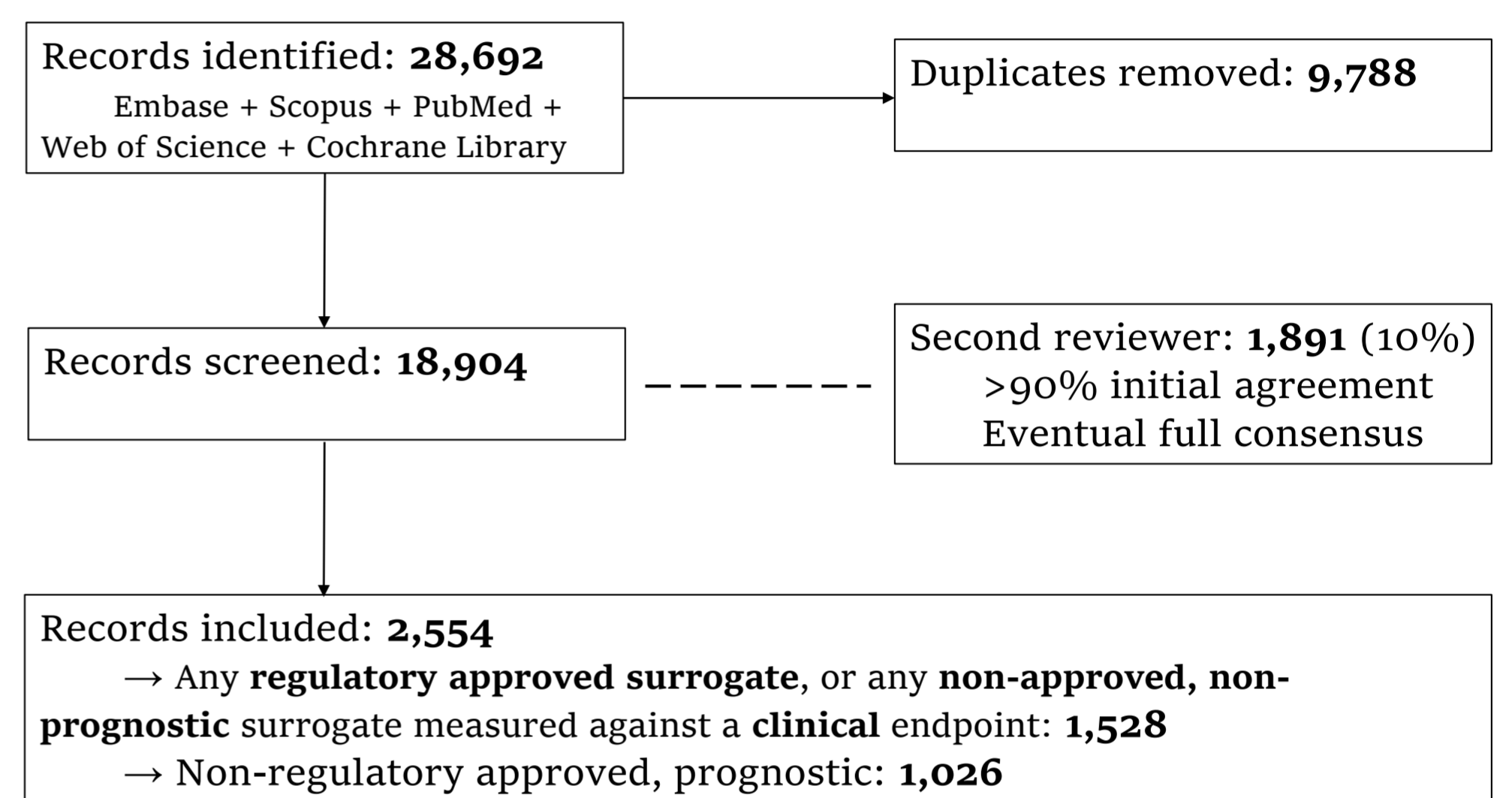


Figure 1. PRISMA flow diagram of number of articles in each phase of the systematic review.

Case Study: Surrogate Endpoints Accepted by FDA/EMA in Respiratory Disease Settings

To illustrate some results from this review, **Table 2** below presents the level of validity of FDA/EMA-accepted surrogate endpoints in respiratory diseases.

- Each sub-column represents one study (e.g. meta-analysis or RCT). We use three different frameworks^{3,4,5} to rank each component of validation.
- For each surrogate, we then pool the results from each sub-column to obtain an overall rank, which is shown in the second row.

Surrogate:		Forced Expiratory Volume in 1 Second			Forced Vital Capacity			Pulmonary Vascular Resistance		Sputum Culture Conversion	
Overall Conclusion		needs further evidence			disputed					trial supported EMA decision	
Authors' Conclusion											
Framework	Ciani Hierarchy ³										
	IQWiG ⁴ : Reliability										
	IQWiG: Correlation										
	BSES ⁵ : Study Design										
	BSES3: Target Outcome										
	BSES3: Statistical Score										
	BSES3: Generalisability										
		0: lowest level of evidence			1: borderline/satisfactory			2: reasonable		3: highest level of evidence	

Table 2. Heatmap of surrogate endpoints that are accepted by FDA or EMA. Colour-coded on a scale from 0-3 based on statistical and clinical evidence.

Discussion: Systematic Review and Ways Going Forward

- This review will be the first to assess the status of surrogate endpoints across all therapeutic areas. We illustrated above a small snapshot of this in the context of respiratory diseases.
- On the whole, generalisability was difficult to achieve, and statistical rankings for many respiratory studies were not applicable due to the use of statistical methods other than correlation. The highest level of validity was not reached for any of the respiratory surrogates.
- There is a need for further validation studies to assess surrogate endpoints that are accepted by regulatory authorities.

¹FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools) Resource. <http://www.ncbi.nlm.nih.gov/books/NBK326791/> [Accessed 18 October 2022]

²U.S. Food and Drug Administration. Table of surrogate endpoints that were the basis of drug approval or licensure. URL: <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure> [Accessed 19 October 2022]

³Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to review the role of surrogate endpoints in health policy: state of the art and the way forward. *Value in Health*. 2017 Mar 1;20(3):487-95.

⁴Institute for Quality and Efficiency in Health Care. Validity of surrogate endpoints in oncology. Executive summary of rapid report a10-05, version 1.1.

⁵Lassere MN, Johnson KR, Schiff M, Rees D. Is blood pressure reduction a valid surrogate endpoint for stroke prevention? An analysis incorporating a systematic review of randomised controlled trials, a by-trial weighted errors-in-variables regression, the surrogate threshold effect (STE) and the Biomarker-Surrogacy (BioSurrogate) Evaluation Schema (BSES). *BMC medical research methodology*. 2012 Dec;12(1):1-21.