FIVE IDENTIFIED HURDLES ASSOCIATED WITH SURROGATE ENDPOINT VALIDATION

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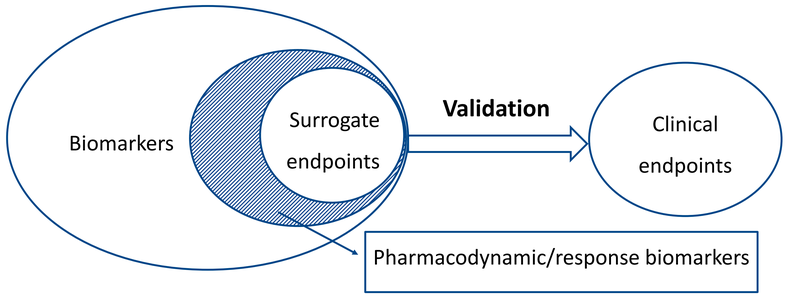
Background

Surrogate endpoints are adopted in clinical trials when final clinical endpoints are difficult or costly to be measured within the timeframe of clinical studies. The suggestion to establish the correlation between surrogate and final endpoints was proposed in 1996[1] and a conceptual approach based on the recommendation was published. In 2008, the US FDA set up Biomarker Qualification Program[2] to validate surrogate endpoints. Health technology assessment bodies also released principles on surrogate endpoint evaluation[3]. However, there are very few surrogate endpoints that are validated.

Objective

The objective of this research is to explore the challenges associate with surrogate endpoint validation.

Figure 1. Relationship between biomarkers, surrogate endpoints and clinical endpoints.



Methods

- A literature search was conducted on electronic databases including PubMed, EMBase, Web of Science, and Medline (Figure 2). Published articles and grey literature after 2010, together with official guidance on surrogate endpoints validation in the US and UK were also reviewed.

  Keywords:

  (surrogate endpoint OR surrogate marker OR surrogate endpoint OR biomarker) AND (validation OR qualification OR evaluation) AND (regulatory OR health technology assessment OR HTA OR industry) AND (perspective OR view OR aspect OR opinion)

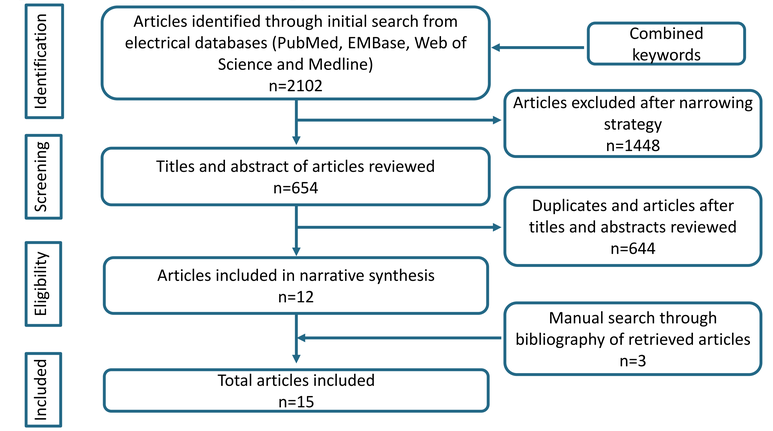
  Filter: "full-text", "10 years", "English" and "journal article"

- Three interviews with experts from regulatory and health technology assessment bodies were held to supplement the findings from the literature search

Results

Fifteen articles were included, 11 adopted the regulatory perspective and 4 the pharmaceutical industry perspective. No specific recommendations on essential evidence for surrogate endpoint evaluation was found in official technical guidelines. The main challenges in surrogate endpoint validation are limited knowledge of diseases, lack of incentives and harmonised criteria, costly and time-consuming from stakeholders' point of view. Expert opinions aligned with the literature findings. Resolutions on establishing a harmonized framework, collaborative work between stakeholders, and data sharing to accelerate surrogate endpoint validation were discussed.

Figure 2. Study selection strategy



Discussion and conclusion

Stakeholders suggested solutions to resolve the difficulties. Recommendation for each category is presented in Table 1.

In conclusion, 5 categories of challenges associated with surrogate endpoint validation: 1. Lack of physiopathology knowledge; 2. Lack of harmonised criteria for validation; 3. Lack of incentives; 4. Cost and time barriers; 5. Lack of collaboration between stakeholders.

Categories	Detail	Recommendation
Lack of physiopathology knowledge	Abundant data needed for sufficient power	Collaborative work lead by medical society
Cost and time barriers	Time needed to follow-up to collect data of correlation	
Lack of collaboration between stakeholders	Very few collaborative work is recognized	
Lack of harmonised criteria	Diverse patient population and study design	Separate validation framework for each disease area
Lack of incentives	Absence of harmonised framework	

Table 1. Surrogate endpoint validation challenges and recommendations

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Reference

[1] Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med. 1996 Oct 1;125(7):605-13. doi: 10.7326/0003-4819-125-7-199610010-00011. PMID: 8815760.

[2] US Food and Drug Administration. Biomarker Qualification Program. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program. Accessed on June 10th ,2020.

[3] European network for Health Technology Assessment (EUnetHTA). Endpoints used in relative effectiveness assessment of pharmaceuticals: Surrogate Endpoints. Feb 2013.