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A Better Way to Evaluate Evidence of Mechanisms in Medical Decision-Making

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ABSTRACT

A common criticism of Evidence-based Medicine (EBM) is that the guidance it provides tends to put too much weight on evidence from randomized trials, and too little on evidence of mechanisms.1-5 Nonetheless, the general advice regarding evidence of mechanisms and mechanistic reasoning provided within EBM has changed little since its inception.6 This is partly due to ongoing concerns regarding the appropriate role of mechanisms in the evaluation of medical evidence,7,8 and partly due to the absence of agreed frameworks for evaluating evidence of mechanisms and implementing this evidence into decision-making. *Evaluating Evidence of Mechanisms in Medicine*: Principles and Procedures seeks to address these issues. EBM has been successful in implementing the explicit evaluation of clinical research into practice, guideline development, and policy. *Evaluating Evidence of Mechanisms in Medicine* provides the resources to achieve a similar outcome for the explicit evaluation of evidence of mechanisms.

KEYWORDS

Causality; Clinical guidelines; Evidence-Based medicine.

1. Introduction

Evaluating Evidence of Mechanisms in Medicine is Open Access and freely available online (references to the book throughout this review refer to the PDF available online). The author team includes philosophers of science (Veli-Pekka Parkkinen, Christian Wallmann, Michael Wilde, Brendan Clarke, Phyllis Illari, Charles Norell, Federica Russo, Jon Williamson) and experts in evidence evaluation in policy development (Michael P. Kelly, Beth Shaw). The book articulates a framework for explicitly evaluating evidence of mechanisms and provides tools for implementing the framework during critical appraisal and the development of guidelines and policy. The focus on implementation means the book will be of interest to clinicians, guideline developers, and policy-makers as well as philosophers of science in practice.

The organization of the book is something of a challenge given the varying interests of different groups of readers. Part I provides a broad overview of the philosophical framework (Chapter 1) and discusses the need

to better incorporate evidence of mechanisms into assessments of efficacy and external validity (Chapter 2). Chapter 3 provides an evaluation framework for judging the quality of evidence and the overall status of a claim. The overview provided in these chapters is introductory and relatively brief. Philosophers and philosophyinclined practitioners unfamiliar with recent work by the authors would likely benefit from reading key papers and recent work from the team alongside this overview.9-12 Part II provides six tools for assessing evidence of mechanisms. The tools are styled in the same way as critical appraisal tools provided within EBM. Part III focuses on core principles for applying the framework. This includes the procedures for gathering and evaluating evidence of mechanisms (Chapters 5 and 6) and using this evidence to assess efficacy and external validity claims (Chapter 7). The authors present Part III as additional detail, but it is essential (I think) for understanding how the authors intend the framework and associated tools to be implemented. Finally, Part IV considers particular applications of the framework.

Evaluating Evidence of Mechanisms in Medicine makes a positive and practical contribution to the evaluation of mechanisms in medicine. "Medicine," it should be noted, is interpreted broadly throughout the book. In addition to clinical medicine, the authors seek to apply the approach to public health and social policy. The overall approach is an excellent example of translating philosophy of science into practice. The book provides the resources necessary for initiating a more comprehensive discussion of evidence of mechanisms and the ways in which that evidence can be evaluated. Section 2 examines the approach of the book in more detail. Opportunities for further work are considered in Section 3.

2. The Approach of the Book

The philosophical framework advocated in the book is explicitly causal. This is important—appeal to explicit causal accounts in the biomedical literature is relatively rare outside specific areas. This is despite the fact that medical and policy decisions rely on the assessment of specific causal claims: In population P, does intervention I (when compared to comparator C) improve outcomes O? The key idea driving the book is that the assessment of causal claims in the biomedical sciences requires explicit consideration and evaluation of evidence of correlation and evidence of mechanisms. This idea, labelled the Russo-Williamson Thesis, has been defended by authors of the book in other work.

Evidence of correlation refers to evidence for the claim that there is a genuine correlation between exposure to intervention I, rather than comparator C, and change in a clinical outcome measure O in population P. Well-conducted randomized trials provide excellent evidence of correlation. Evidence of mechanisms refers to evidence for the claim that there is a genuine mechanism that links the intervention with the outcome. Evidence regarding the mechanism of action of the intervention is important in this assessment, but so too is evidence regarding additional mechanisms. Depending on the context, this will include evidence of the mechanisms by which the intervention gets to and remains at the site of action, and evidence regarding the action of any additional mechanisms at play that might mask the mechanism by which intervention brings about its effect. Evidence of correlation and evidence of mechanisms sit on equal footing according to the Russo-Williamson Thesis. Evidence regarding the two claims—that there is a correlation and that there is a mechanismcis amalgamated in order to assess an overall causal claim that an intervention works (efficacy) or is likely to work in a particular practical context (external validity). A strength of the approach is that it highlights the amalgamation of evidence, as opposed to mere ranking. Evidence of mechanisms helps to inform judgements regarding whether an observed correlation is genuine rather than due to confounding, and high quality evidence of correlation provides evidence of the existence of a mechanism producing that correlation.

Evaluating Evidence of Mechanisms in Medicine provides resources for the identification and evaluation of evidence of mechanisms as well as procedures for combining the evaluation of evidence of correlation and

evidence of mechanisms into an overall evaluation of the causal claim. Quality of evidence is assessed for a body of evidence and is defined in a similar way to the definitions provided in the original development of the GRADE.15 Quality levels range from "very low" to "high"—the key determinant is consideration of the likelihood that future research would have a significant impact on our confidence in the claim under review. The status of a claim is determined by the quality of evidence for the claim and the degree of confidence the scientific community has in the claim. The status of a claim can be described as "established," "provisionally established/provisional," "arguably true/arguable," "speculative," "arguably false," "provisionally ruled out," and "ruled out." A claim is considered established "when community standards are met for adding the claim to the body of evidence".

The authors focus on the evaluation of two overall causal claims: efficacy claims and external validity claims. "Efficacy claims" are defined in terms of the beneficial or harmful effect of an intervention in the study population. "External validity claims" are defined as claims regarding whether a particular causal relationship holds in a population other than the study population. The status of an efficacy claim is determined by combining the status of the correlation claim and the status of the general mechanistic claim. The overall efficacy claim is assigned the lower status level of the correlation claim and the general mechanistic claim (p. 92). External validity claims are determined on the basis of combined status of (1) the efficacy claim in the study population, (2) the efficacy claim in the target population, and (3) the similarity of mechanisms in the study and target population (see Section 7.2 and Table 7.1). Critical appraisal tools and GRADE-style tables for mechanism assessment are provided to support the evaluation and communication of evidence of mechanisms.

3. Further Work

Evaluating Evidence of Mechanisms in Medicine provides a framework and resources for the explicit evaluation of evidence of mechanisms. The conceptual framework provided by the book is an important contribution. The framework, informed by the Russo-Williamson Thesis, is able to incorporate many of the key insights of EBM into the rigorous assessment of evidence of correlation while at the same time addresses a limitation of EBM by better recognizing the role that evidence of mechanisms plays. The tools and evaluation framework are fit-for-purpose as they are. The next step is implementing the framework and the tools it provides into decision-making in medicine, public health, and policy. Opportunities for improving the tools and the evaluation framework will come from widespread implementation in range of contexts. The two suggestions outlined below are provided in this context: Opportunities for further work as the framework is implemented by decision-makers.

3.1 Broaden the Philosophical Framework

The book focuses on developing and applying the philosophical work of the authors. While recognizing the fruits of this work, there is an opportunity for further engagement with other philosophical work on the evaluation of evidence in medicine. I think the ambitious goals of the project would be well served by broadening the philosophical base and utilizing some of the resources provided by related work. Reiss provides a theory of evidence that seeks to address to the same problems identified by the Russo-Williamson Thesis — an overreliance on randomized trials.1 Reiss' theory provides an account of evidential support and warrant. In short, evidence supports a hypothesis to the extent that the evidence is a pattern in the data that is compatible with the truth of the hypothesis (or incompatible with the truth of one or more valid alternatives to the hypothesis). A body of evidence warrants a hypothesis to the extent that there is direct support for the hypothesis and the body of evidence eliminates relevant alternative hypotheses. Reiss recommends four grades of warrant based on the extent that the body of evidence supports a specific claim and eliminates relevant alternative accounts of the evidence. In my view, this account of warrant has some benefits over the evaluation framework provided in the book. In particular, the focus on the relevant alternative hypotheses

that have been considered within a body of evidence and either ruled-out or still in contention provides an explicit and useful criterion for judging the status/ warrant of a claim. This approach is consistent with the approach to assessing research in the clinical and biomedical sciences and can be usefully specified as part of the evaluation. In the biomedical sciences in particular, evaluation of research depends on the extent to which the researchers have eliminated relevant alternative explanations for their data. Researchers may have to perform additional experiments to meet this requirement.

Cartwright's work on external validity highlights the argument that needs to hold to apply the results of a randomized trial into a practical setting.16,17 A key premiss in this argument is that the support factors necessary for the intervention to work in the experimental environment are present in the practical setting. In most situations, there are many different support factors that either need to be present or take a value within a particular range for the intervention to bring about an effect in the practice setting that is similar to the effect observed in the experimental setting. Cartwright's account emphasizes the need to identify these supporting factors and to assess their likely effect when judging effectiveness/external validity. Support factors may be related to the mechanism of action of the intervention, the systems in which the intervention is acting, and any aspect of delivering the intervention to, or maintaining the intervention at, the site of action. While Cartwright's account is largely consistent with the approach to external validity detailed in the book, the book tends to place a greater focus (sometimes unintentionally, I suspect) on the mechanism of action of the intervention as opposed to the complex of systems and factors that are interacting and influencing the outcome of the intervention. In this way, Cartwright's account supplements the approach articulated in the book.

3.2 More Mechanisms

Many mechanisms in addition to the mechanism of action of an intervention are important to the evaluation of an intervention. Different areas tend to provide different levels of detail regarding these additional mechanisms. Within clinical medicine and clinical drug development, there is frequently a considerable amount of mechanistic evidence regarding ADME—the absorption, distribution, metabolism, and elimination of drugs. Increasingly, there is also mechanistic evidence available regarding pharmacogenetic influences on ADME and the actions of the drug. The importance of additional mechanisms is recognized throughout the book and related work by the authors.9 Nevertheless, there are opportunities in the book to better recognize the importance of these additional mechanisms. Fleshing out the details of these additional mechanisms and the roles that they play is an important part of the evaluation of efficacy and external validity. A better characterization of these mechanisms would assist implementation of the framework into critical analysis, guideline development, and policy.

An efficacy claim is assessed according to the combined status of a general mechanistic claim and a correlation claim. The authors emphasize that in some circumstances the general mechanistic claim can be supported on the basis of clinical study evidence alone (see pp. 15 – 16). This is, in part, due to the recognition that clinical study evidence can also provide evidence of mechanisms. A series of well-conducted clinical studies can provide compelling evidence that treatment is correlated with improved outcomes and this same body of evidence can provide compelling evidence of the existence of a mechanism between treatment and the outcome. The inference is correct, but it is misleading to suggest that this inference is supported on the basis of clinical study evidence alone. For a series of well-conducted clinical studies to provide sufficient evidence for the existence of a mechanism linking treatment with the outcome, there will need to be a supporting body of additional mechanistic evidence. Evidence regarding ADME processes frequently plays this role in clinical drug development. Even if evidence regarding the mechanism of action of a drug is incomplete, there will often be a considerable amount of evidence regarding the absorption of the drug, distribution of the drug to the proposed site of action, and the metabolism and eventual elimination of the drug from the body that can be combined with what is known about the mechanism of action of the drug and the available evidence of

correlation. For the efficacy claim to go through, evidence regarding additional mechanisms needs to support the general mechanistic hypothesis in addition to the evidence provided by clinical studies. ADME evidence that does not support the drug being efficacious will undermine the evidence provided by the clinical studies. This could be because the drug fails to absorb or distribute to the site of action, or is extensively metabolized or eliminated before it could bring about the proposed effect.

By the end of clinical drug development, the evidence regarding the drug includes the mechanism of action, evidence regarding the absorption, distribution, metabolism, and elimination of the drug (including predictors of exposure), evidence regarding possible mechanisms of drug harm, evidence of correlation between exposure to the drug and the intended clinical outcome, evidence linking different levels of exposure to variance in clinical outcomes, and some evidence regarding how exposure in different groups of patients might influence outcomes (e.g., older patients, sicker patients, and patients with less severe disease). Very little of this evidence will be certain, but by the same token, very few drugs will reach the end of clinical drug development without a considerable amount of actionable evidence in many of these domains. Assessing the external validity of trials conducted for regulatory approval requires the navigation of this complex of mechanistic and correlational evidence. Key questions regarding external validity include the following: Which patients are likely to benefit most from treatment? Which patients are more likely to experience adverse events? What patient factors might influence exposure to the drug? What is the average size of benefit and harm in the kinds of patients treated in routine care?—what influences these estimates? The framework provided in the book has the resources to accommodate judgments such as these—and provides superior advice to the typical advice provided within EBM regarding external validity—however, to make best use of these resources, there needs to be a clear characterization of evidence regarding additional mechanisms and the role that this evidence plays in the assessment of external validity. The examples provided in the book tend to focus on public health or social policy in which the detail and extent of evidence regarding additional mechanisms is substantially different and a focus on the mechanism of action may be defended.

4. Conclusion

Evaluating Evidence of Mechanisms in Medicine addresses an important gap in the literature and provides actionable guidance through the development and dissemination of practical resources for the explicit evaluation of mechanisms by decision-makers. Opportunities for further work include the evaluation (and subsequent update) of the resources implemented in a range contexts, and further development of the kinds of mechanistic evidence that plays important roles in different contexts.

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