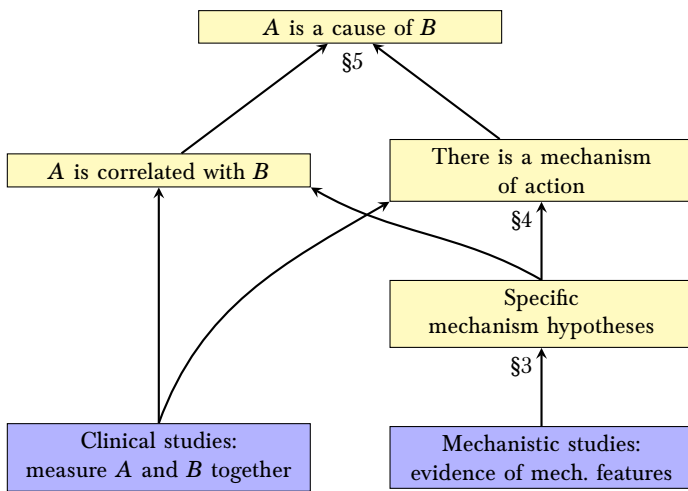


Evaluating Evidence of Mechanisms in Medicine: an Overview

This leaflet provides an overview of [Parkkinen et al. \(2018\)](#).

1. The flow of evidence

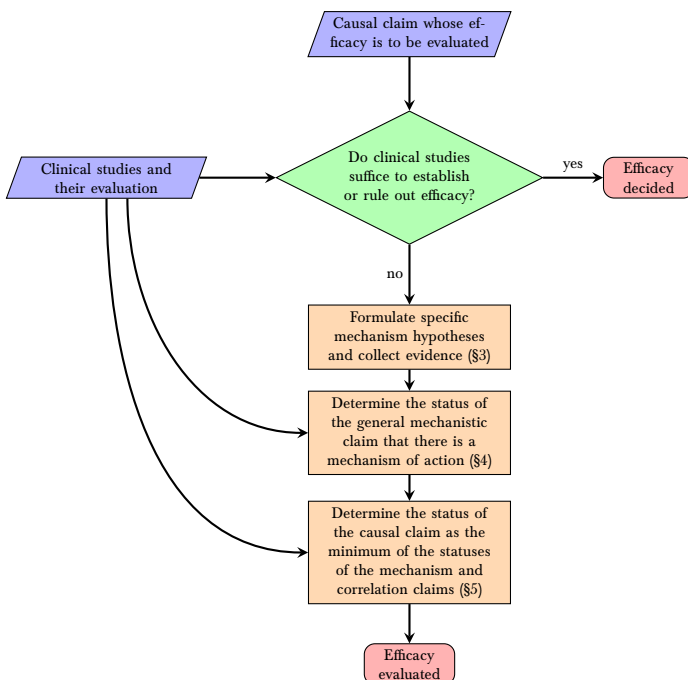
Clinical studies (especially large, well-conducted randomised studies) can suffice to establish causation. But mechanistic studies can raise or lower the credibility of a causal claim by supporting or undermining the existence of a mechanism of action:



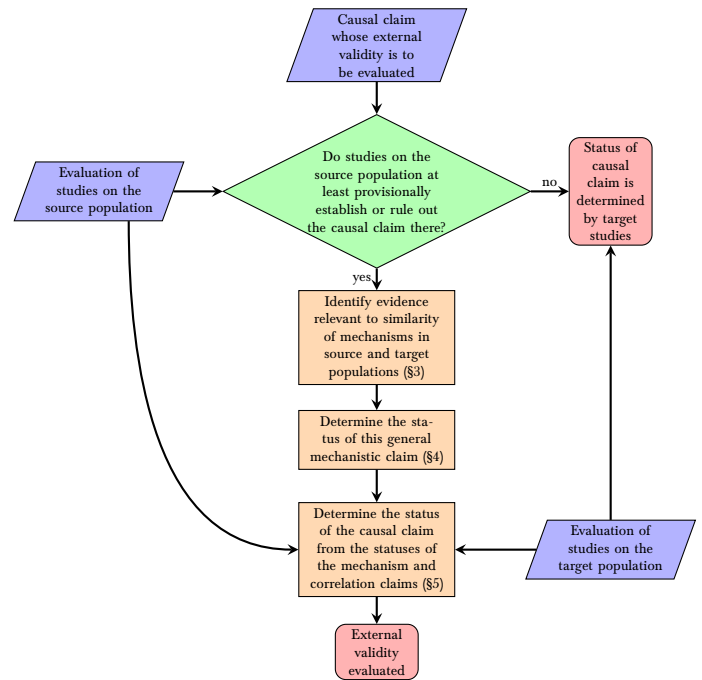
2. Efficacy and external validity

[Parkkinen et al. \(2018\)](#) develop a three-step process for systematically considering mechanistic studies.

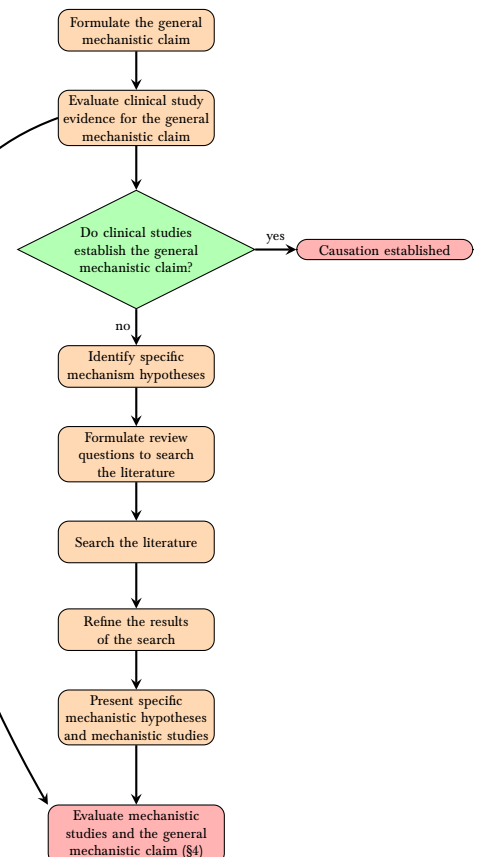
Efficacy. Does the causal relationship hold in the study population?



External validity. Can the causal relationship in the study population be extrapolated to a target population of interest?

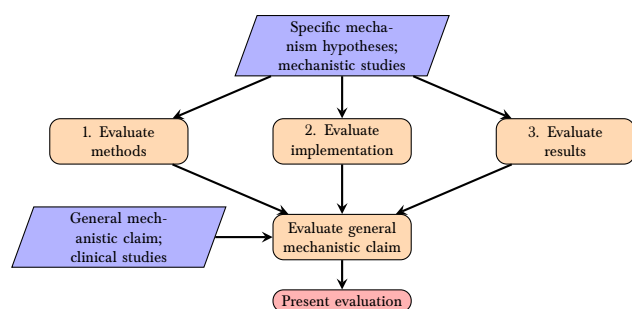


3. Gathering evidence of mechanisms



4. Evaluating evidence of mechanisms

Each specific hypothesised mechanism of action is assessed by analysing the methods, implementation and results of mechanistic studies:



The status of the general mechanistic claim (GMC) depends on evidence from both mechanistic and clinical studies:

	Established	Provisionally established	Arguable	Speculative	Arguably false	Provisionally ruled out	Ruled out
Established	Established	Established	Established	Established	Established	Provisionally established	Speculative
Provisionally established	Established	Established	Provisionally established	Provisionally established	Arguable	Speculative	Arguably false
Arguable	Established	Provisionally established	Provisionally established	Arguable	Speculative	Arguably false	Ruled out
Speculative	Established	Provisionally established	Arguable	Speculative	Arguably false	Provisionally ruled out	Ruled out
Arguably false	Established	Arguable	Speculative	Arguably false	Provisionally ruled out	Provisionally ruled out	Ruled out
Provisionally ruled out	Arguable	Speculative	Arguably false	Provisionally ruled out	Provisionally ruled out	Ruled out	Ruled out
Ruled out	Speculative	Arguably false	Ruled out	Ruled out	Ruled out	Ruled out	Ruled out

5. Using evidence of mechanisms

Efficacy. Status of causal claim = minimum of status of correlation claim and status of general mechanistic claim.

External validity. The status of the causal claim in the target population depends on the status of the causal claim in the source population, the status of the claim that the mechanism of action in source and target is similar, and the status of the causal claim in the target population on the basis only of studies carried out on the target population:

	Established + established	Provisionally established + established; or Established + provisionally established	Other combinations	Provisionally ruled out + established; or Ruled out + provisionally established	Ruled out + established
Established	Established	Established	Established	Established	Provisionally established
Provisionally established	Established	Provisionally established	Provisionally established	Provisionally established	Arguable
Arguable	Established	Provisionally established	Arguable	Speculative	Speculative
Speculative	Established	Arguable	Speculative	Arguably false	Ruled out
Arguably false	Speculative	Speculative	Arguably false	Provisionally ruled out	Ruled out
Provisionally ruled out	Arguably false	Provisionally ruled out	Provisionally ruled out	Provisionally ruled out	Ruled out
Ruled out	Provisionally ruled out	Ruled out	Ruled out	Ruled out	Ruled out

Appendices

In several appendices, Parkkinen et al. (2018) provide further discussion of the above approach.

A. A critical appraisal tool for evidence of mechanisms. A checklist of questions to ask when evaluating evidence of mechanisms.

B. GRADE-style tables with mechanism assessment. Shows how GRADE tables for the assessment of clinical studies can be extended to incorporate the assessment of hypothesised mechanisms of action.

C. Databases for evidence of mechanisms. Some examples of databases that can assist the search for relevant mechanistic studies.

D. Assessing exposures. How the framework applies to the assessment of exposures to possible harms, and its relation to other approaches, such as SYRINA and that of IARC.

E. Assessing mechanisms in public health. Considerations to bear in mind when applying the framework to public health interventions.

F. Particularisation to an individual. How to apply the framework to the treatment of an individual.

G. A probabilistic interpretation of quality and status. Shows that the general approach is compatible with a more quantitative Bayesian framework.

H. Glossary. Definitions of key terms.

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Bibliography

Parkkinen, V.-P., Wallmann, C., Wilde, M., Clarke, B., Illari, P., Kelly, M., Norrell, C., Russo, F., and Williamson, J. (2018). *Evaluating Evidence of Mechanisms in Medicine: Principles and Procedures*. Springer Briefs. Springer. Available at <http://ebmplus.org/about/papers-articles/>.