Author’s response to reviews

Title: Early Economic Evaluation of Emerging Health Technologies: Protocol of a Systematic Review

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Author’s response to reviews: see over
Comments and response

"1. I wouldn’t title this as being about "emerging health technologies". It’s about drugs, and at one point they even equate these two (where they say "e.g., a drug" on page 4). The whole phase I phase II phase II framework is about drugs, and would not apply to many things that I think - and I suspect most readers would think - as new technologies, particularly around diagnostic tests/imaging. Several of the 10 most rapidly rising costs for US Medicare are imaging, specifically advanced imaging of the head and advanced imaging of the lumbar spine. So the paper should probably say it is about drugs, or substantially revise the text to make it clear that it is about the broader concept of new technologies. I realize their methods state that they intend to include pharmaceuticals and biologics (I think many would consider the process of development and investigation and the regulatory requirements for these as being sufficiently similar that they can be all called "drugs"), but then also devices (which in the USA have a totally different regulatory process) and biomarkers (about which I don’t know the regulatory process). For the last two, I have never ever seen a paper entitled "A Phase II study of..." or "A Phase III study of..." whereas I see these titles for studies of drugs all the time. So they need to get in sync their intro and the methods, because right now the intro is all about drugs and the methods include other things.

For this systematic review, we’re interested in finding out which technologies can benefit from early economic evaluation. As suggested, we’ve revised the background section regarding our intent to include studies of different technologies (as specified in the Methods section).

Background

Economic evaluation is the comparative analysis of alternative technologies with respect to their costs and consequences.\(^1\) It is often used late in the evaluation of drugs, devices, and other technologies to inform coverage decisions.\(^2\) This is problematic because the evidence portfolio at the time of the reimbursement decision is often incomplete. Cost and preference data are often not gathered prospectively within clinical trials designed to evaluate effectiveness. This means that analysts cannot directly use trial data, and must struggle to assemble evidence from a variety of sources and settings to evaluate the cost effectiveness of new interventions.\(^3\) Published data suggest that considerable economic uncertainty existed in about half of the submissions for reimbursement decisions.\(^4\) Also, clinical trial design is rarely informed by ex-ante economic modeling. This means that optimal strategies and the full range of subgroups may not have been fully considered prior to commencing the clinical research program.
Economic evaluation can be used early in the process of technology evaluation. As an example, Vallejo-Torres et al. illustrate a 3-stage cost-effectiveness analysis of a new medical device: an early phase in which simple methods are used to estimate the maximum price attainable for the technology; a mid-stage which synthesizes data into a cost-effective model and identifies which information is most valuable to reduce decision uncertainty; and a late stage, in which all relevant information is synthesized.\textsuperscript{5} The results suggest that early and iterative economic evaluation could be useful to inform decisions along the technology development process.

Early evaluation can contribute to decision-making by both industry and government.\textsuperscript{20,21} From an industry’s perspective, early evaluation may be used for early market assessment, managing research and development portfolios, and informing pricing and reimbursement scenarios. From the policy perspective, decision-makers may benefit from information supplied by early evaluation. Thus, there is interest from both innovators and payers in early health technology assessment, and more specifically, early economic evaluation, to inform planning and development decisions by industry and to inform the potential of new technologies that may meet health system needs.\textsuperscript{6}

Though interest in early economic evaluation is considerable, much applied research is still at the pilot stage. There is uncertainty about which technologies can benefit from early evaluation, what methods are appropriate, and the contribution of early economic evaluation to health technology assessment.\textsuperscript{6} The aim of this systematic review is to describe the characteristics of early economic evaluation of emerging technologies and to understand current methods to early evaluation.

2. The authors make the point that an economic evaluation from a societal perspective can help inform the no/no go decision about further development. But how many of these are done from the societal perspective? I will not lose money betting that the pharmaceutical industry does its economic evaluations from a perspective different than a societal perspective, and even national health payment systems like the US Center for Medicare and Medicaid Services often requests that these CEAs be done from a payor perspective. I suppose that's one of the things they are going to find out.

According to a literature review of early economic evaluation studies, the studies were conducted to inform decisions by industry (e.g., innovators, investors, and manufacturers), government (e.g., economic...
development and innovation) and payers. By targeting different decision makers, broad consideration regarding costs and consequences of the technologies is necessary. We aim to find out any perspectives, stage-specific assumptions and methods (among others) that have been used in early economic evaluation.

3. How do the authors plan to assess whether or not the economic analysis was done prior to regulatory approval? I know how they might assess whether or not it was published prior to regulatory approval, but as to whether it was "conducted"...I just don't know.

Table 1 of the manuscript outlines how we will (attempt to) identify early economic evaluation studies. We anticipate studies taken place at different stages of the technology lifecycle, at different certainty with respect to the safety and efficacy data, and the extent to which the studies could inform the future effectiveness of the emerging technologies. As an example and aiming to inform investment decisions, McAteer et al. conduct a cost-effectiveness analysis at the development stage of a potential health technology involving tissue engineering of bladder and urethra (J Tissue Eng Regen Med 2007; 1: 343–349). We've revised the related sentence in the above comment to allow for different patterns to be discovered from our literature search and our review process.

Previous version: “This protocol describes a systematic review of economic evaluation studies (including both published and unpublished studies) of regulated health technologies such that the evaluation is conducted prior to regulatory approval.”

Revised: “This protocol describes a systematic review of economic evaluation studies that are conducted to inform the development and planning of early evaluation of emerging health technologies.”

4. Lastly, I wouldn't agree with the statement "technological innovations are infrequently discovered". At least in the context of this review (e.g. new drugs, new biologics, not to mention new biomarkers or new devices), dozens and dozens are approved or introduced - or at least attempted to be introduced - into practice every year.”

We were thinking about the drug screening process in writing the related sentence. However, it's not true in general, as indicated by the number of new submissions to regulatory agencies. This has been removed from the revised manuscript.

In addition to the above discussion, we have shortened the last paragraph of the Discussion section.

“The method outlined in this protocol is sometimes referred to as a meta-epidemiological investigation. In particular, there are well-established precedence regarding the use of systematic review to investigate factors affecting the conduct and reporting of trials, systematic reviews and economic evaluations of health interventions.35-42 By adapting a systematic approach to our
investigation, our aim is to collect relevant data from a representative sample of all early economic evaluation studies and therefore, reliably discern the contribution of early economic evaluation to product and policy development.”