28-Jul-2021
BMJ-2021-064952.R1
Raising the bar for using surrogate endpoints in drug regulation and health technology assessment

Dear Dr. Naci,

Thank you for all the work you put into revising this which was obviously not trivial given the three reviews. It is definitely a substantially transformed piece, and the editors, who discussed it at the editorial meeting last week*** and via email, felt it was in a place now that we can make a provisional offer of publication if you are able to revise it to address the points made by the editors set out below.

1. There was still a fairly major concern from all the editors that the article is not sufficiently engaging. It reads (both in language and structure) very similar to a review article. For the Analysis section, we're looking for a scholarly argument - a position, a view - to be presented early and sustained in a way that is both authoritative and engaging to read. So the challenge is really an editing job - turning the piece on its head, so to speak, making the argument early and sustaining the argument from there.

2. Your argument - as I read it - is that the use of surrogate endpoints should be vastly limited, and that regulators & HTA bodies should work together and adopt higher standards for evaluating and using surrogate endpoints - but it's fairly buried and not sustained through much of the details. It would be easy for readers to assume the authors are saying that we just need to improve on our surrogate endpoint methods - when it seems the authors may in fact be saying that for many diseases, surrogate endpoints should not be used full stop.

3. In terms of writing style, I think it's fair to inject more urgency into it. This is not a dull academic issue, this is affecting people's lives in a very serious way. So less things like 'In this article, we first review the benefits and harms

4. We are not sure about Box 1 (on NICE). It is very dense and probably would end up as supplemental material if left as-is, which means vastly reduced readership. Please decide whether you want it in the piece (in which case it will need to be simplified substantially), or prefer online supplemental file. Whatever you do, it would help in the main manuscript text if you could highlight for readers what the big, if any, implications there might be from NICE's new proposed changes (around line 206).

5. On substance, it would be helpful to make really clear just what a "validated surrogate" is - and whether "validated surrogate" is the right term - as doesn't the FDA use the term "validated surrogates" quite often but some of these are surrogates that actually aren't predicting clinical benefit for some drugs?

6. We also think readers will want more specifics, to know about more specific therapeutic areas, to learn about which classes of drugs and therapeutic areas are actually built on a mountain of possibly false hope thanks to the use of unproven surrogate endpoints, to know for which types of drugs we should toss surrogate endpoints altogether. We hear about Alzheimers via aducanumab but not a ton more. So something summarizing where we are for a slew of the most common surrogates would make for a useful table. It's not clear if this is what you were trying to achieve with Table 1? If so, we felt this table was missing the punchline (the conclusions, in a sentence, of each meta-analysis as to the relationship between surrogate and clinical outcome).

7. (Just to let you know, we are covering the aducanumab story in more detail elsewhere in the journal - you definitely should keep aducanumab in your piece, but no need to expand on it greatly.)

Other specific points

8. Line 107. You say that pharmaceutical company lobbying led to use of surrogates, but isn't is also caught up in AIDS activism that led to our various expedited pathways?

9. Lines 102-103 seem to overlap with 118-120.

Please note that the BMJ might choose to shorten content or replace or re-size images for the print issue.

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I hope you will find the comments useful.

Best wishes,

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*** Present at Analysis meeting: Kamran Abbasi, Paul Simpson, Emma Rourke, Henry Scowcroft

Date Sent: 28-Jul-2021