BMJ-2021-064952.R1: Author Response to Editor Comments

Dear Dr. Doshi,

Thank you for sharing your additional comments on our revised article. We are grateful for the opportunity to submit a revised version of our article. Please see below our point-by-point responses to your comments.

We look forward to hearing your thoughts.

Kind regards,
Huseyin Naci

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.**

Authors: We have taken the editors' suggestions on board and substantially revised the structure of the manuscript, making our key arguments early and reinforcing these throughout the piece.

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.**

Authors: We have now further crystallised our argument. We are explicitly calling for more selective use of surrogate endpoints by regulators and HTA bodies, reserving them for chronic disease settings when measuring clinical outcomes may require unfeasibly long trials. In such cases, we have emphasised the need to evaluate the strength of the association between surrogate endpoints and clinical outcomes and fully take into account uncertainty in decision-making.

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

Authors: We agree. We have now revised our writing style and added several sentences to address this comment.

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).

Authors: Thank you. We have decided to delete this box and highlight the key changes in the article text as suggested (page 6, line 463).

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?

Authors: We agree. We no longer use the term "valid" surrogate in our revised article. Also, we have now added this statement to the paper to highlight the difficulty in defining what a "valid" surrogate endpoint is (page 5, line 223): "*There is little consensus for defining a "valid" surrogate, as it is difficult to set specific thresholds to grade the strength of association with the final clinical outcome*."

In addition, we have emphasised the importance of considering all relevant uncertainty associated with the use of surrogate endpoints rather than considering them as either "valid" or not (page 7, line 570): "*the strength (or weakness) of the surrogate will be reflected in the uncertainty around the predicted treatment effect on the final outcome. A weaker surrogate will yield a larger interval and hence greater uncertainty*."

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).**

Authors: Our revised article now refers to the widespread use of surrogate endpoints in cancer drug trials in particular (page 2, line 58): "*In cancer, for example, most drugs with promising effects on surrogate endpoints do not yield patient-relevant benefits in terms of improved quality of life or prolonged survival*."

We have also considerably expanded Table 1 with several additional examples of good and bad surrogates. We also included brief conclusions of each meta-analysis, demonstrating both "acceptable" and "weak" surrogates.

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.)

Authors: Thanks for letting us know. We have kept reference to aducanumab without expanding on it, as requested.

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?

Authors: We have now clarified that the implementation of the accelerated approval pathway in the US occurred at the height of the HIV/AIDS crisis in the early 1990s (page 3, line 18).

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

Authors: We have now removed one of these statements to avoid overlap.