Dear editors and reviewers,

Thank you for your insightful comments and feedback. Below we have addressed them (in Italics), referring to the relevant page and line numbers in the ***clean*** *version.*

Editor comments

1. Our analysis papers are 2000 word debates with data that are written in a journalistic style with academic heft. We recognise the importance of the messages in this paper but we feel work is needed to make this a more engaging read for our generalist audience. We appreciate you have already revised this once to improve the style but we still feel there is some way to go in terms of the style of the paper.

We revised the manuscript to make the text more engaging.

2. The piece is currently written as a walk through your reasoning as to why you believe screening programmes need to be evaluated alongside your proposed framework as to how this might happen in practice. We think the introduction needs to clearly outline the problems here, and put forward how you believe these could be addressed.

The introduction was restructured, with a stronger focus on both the current problems, the potential solutions and the strategy used to build the framework.

3. The conclusion must be clearer on the solutions and pave the way forward**.**

We incorporated our main messages and how they are addressed by our framework in our Conclusions section

4. The clinical examples you have selected to bring this to life are lacking in detail and are not well utilised to strengthen your arguments. Might you be clearer about why you have chosen these examples and further expand on them to illustrate your points? We also felt better quantification is required in some of these examples, for example you say “new targeted therapies “should” further lower mortality but without more detail despite seeming reasonable it remains quite speculative and more specifics might make this a more powerful tool to support your arguments.

We added some examples and adapted the text. E.g. we rephrased line 41-43, page 4, and added the specific reduction in mortality achieved. We added the example in line 68-70, page 4.

5. The section on the framework outlines very basic approaches to evaluation and could be more succinctly communicated as our readers will have a basic understanding of these principles.

We abbreviated this section.

6. The paper would benefit from a stronger focus on the content in box 4 which outlines the options for the final recommendations. This is of interest as it gives readers an idea of the potential solutions to the problems outlined and paves the way forward.

*We clarified the content of box 4 (page 8), and expanded the section that refer to it (line 160-162 page 8): ‘*These will depend on the quality of evidence, and value judgments of the stakeholders and Steering Committee on the balance of benefits, harms, and costs and the distribution thereof. Potential recommendations include no change, generate more evidence, or change current practice (Box4) ’.

7. We felt that the piece was weak on where the accountability lies here. Who is to be responsible for this? Who will enforce this and what will happen if it is not enforced? Are you arguing this should be built into all screening programmes at a particular time interval? What is the ideal here?

We discussed this with our author group and we agreed with your comment. This led to the following changes of text and box 2:

- *Section: proposed framework, line 112-114 page 5: ‘*A precondition for any re-evaluation is the political will to endorse the process and to act upon recommendations ’.

- *We abandoned a step in our framework (box 2, page 6) and focussed on an independent Standing Committee responsible to the Government in line 116-121. '*A standing independent government-recognised Steering Committee monitors key performance indicators and new evidence, and identifies the need for re-evaluation (Box 2). A secured budget for the work of this Steering Committee including funding for implementation of changes to screening practices and monitoring systems is essential. It is too resource-intensive to review all screening activities regularly. However, we propose that this independent Committee assesses screening practices to identify substantial changes (see Box 1) that would necessitate a full re-evaluation'.
- *Section: Challenges: line 173-175, page 8.'* Strong governance and leadership by national health authorities are necessary to ensure that the outlined framework will be followed and recommendations by the Steering Committee implemented; these may not always be readily accepted by stakeholders'.

Reviewer: 1

Recommendation:

Comments:

Thanks for asking me to review. I think it is an incredibly important subject (that of re-examining existing programmes) and it is useful for the readership to be reminded that things change, that harms are important as well as benefits. A systematic approach is to be welcomed and the views of the public important

8. But I think that the methods by which the evidence is generated and on which discussions take place are treated superficially.

Regarding the details of evidence synthesis and evaluation, we agree with the comment from the Editors that the general readership of BMJ would be familiar with the basic concepts of EBM, evidence synthesis, and evaluation.

*In line 120-121, page 6, we underline the importance of monitoring programmes. '*However, we propose that this independent Committee assesses screening practices to identify substantial changes (see Box 1) that would necessitate a full re-evaluation'.

9. It is OK to say examine the cost effectiveness of the programme but (as I have found when asking economists to do such work) **the comparator is very difficult to agree**. Without agreed alternatives to the programme as is and a method of working out what outcomes each including current screening programme might yield) then this is likely to yield opinions (of which there are legion) and not evidence.

When evaluating current screening programmes or practices, it is important to recognise that current practice represents "the comparator" and that any change to that practice (expanding, contracting, or ending screening) is the "intervention", the effects of which are to be assessed. Re-evaluations of screening practices therefore differ from standard economic evaluations prior to introduction, and from stand-alone evaluations of the cost-effectiveness of current practice. We feel that there are more pressing issues to explain in this outline of our framework but will return to this important issue in a later paper in this series.

8.. So…I think the paper is important and should be published. But I think the authors should be asked how such evidence will be generated. They are intentionally best placed to answer (*see answer under point 8 above).*

Reviewer: 2

Recommendation:

Comments:

The manuscript presents a framework to reevaluate established health screening practices and thus fills an important gap in this area. It is well written and the presented framework is comprehensive and duly justified. Importantly, the framework is based on similar processes in other settings and at the same time considers important issues unique to the context of screening such as documented biases in clinicians and the general public (e.g., the generally high enthusiasm for screening, positive beliefs etc.), which could play an important role in the evaluation process, along with other important aspects such as conflicts of interest and citizen involvement. My opinion is that the framework is generally well elaborated, will be a useful tool and hence this manuscript should be published.

Below I list several issues that I thought may benefit from some clarification. I hope that the authors will find these comments useful.

10. Introduction: regarding the four major reasons to reevaluate screening practices. It should be specified whether this is meant to be an exhaustive list of possibilities or this framework could be potentially applied to situations where the need for reevaluation comes due to other unforeseen issues.

In line 25 page 3 after "We outline four major reasons to re-evaluate existing screening practices (Box 1*).', we have added*: "This list is not exhaustive'.

11. In addition, in reason 2, the authors consider change in test performance as one basis for reevaluation. It seems that the availability of new tests should be considered under this heading too but the way that the issue of test performance is currently introduced does not specifically spell it out.

We agree and have added ' new test methods*' to reason 2 (now reason 1) in box 1 (page 3) and changed the title of reason 2 (now reason 1) into '* Change in the incidence of the target condition, new test methods, or therapeutic advances*' and adjusted the text in line 43-45 page 4* 'Similarly, improvements in conventional tests or development of new tests may impact performance and change the benefit, the burdens or costs of screening.'

12. There is perhaps one issue that I found to be inconsistent and where further elaboration may be needed: the citizen involvement and in particular **the recommendation for exclusion of citizens who have undergone screening.** First, this recommendation directly contradicts the principle mentioned in Box 2

("Members of a community to provide an **inclusive sample** of citizens (ensuring no relevant group is systematically excluded)), so the text should be revised to avoid this contradiction. Second, it may be worth reconsidering this recommendation or at least specifying the conditions under which it may be meaningful. My initial hunch was that it makes sense because the public in general is not very knowledgeable of screenings and how they should be evaluated etc, and hence one would think that having participated will only increase some existing biases in favor of screening (e.g., I had the test and it saved my life etc…or the higher tolerance to harms that the authors cite). However, people who have participated are also those who have experienced the perceivable harms of screening, so in fact biases can go both ways. Anyway, this group IS eventually included in the process, in particular in the form of an advisory board to the Steering committee (p. 7), so again the recommendation for their exclusion stands in contradiction to what is mentioned later.

My second concern was that this recommendation (to exclude people with experience with screening) may introduce other biases and/or be unrealistic for some screenings. To give an example, in the context where I live, it would be difficult to find a woman who has not had cervical screening (because compliance is generally high, the screening has been in place for a long time, and encompasses a wide age range). So citizen representatives could either be women with more abnormal healthcare usage, too young or old to be eligible, or men, which would not make a very meaningful citizen panel. **So my recommendation is to reconsider or reformulate this recommendation, so that 1) there are no contradictions in the text, and 2) it is flexible enough to be realistic and/or does not exclude relevant groups.**

Thank you for pointing out this inconsistency and the implications of our suggestions on in/exclusion of certain groups of citizens. Under the section: Involving the Public', we changed the last sentence from ' Preferably, citizens that have not (yet) participated in screening should be involved' *to line 96-97 page 5 '*Care is required to ensure an inclusive sample not skewed towards or against screening. *'. This way we believe that we have corrected the inconsistency with box 2 and ensured flexibility.*

13. Proposed framework: Consider adding a brief description of the process followed to elaborate the framework and the field of expertise of those involved in its generation.

We have now briefly described that the framework is the result of deliberations in a broad international group over three years in line 17-19, page 3.

14. Step 1: Establish a Steering Committee: Consider revising and adding more detail to the following recommendation: “we suggest that Steering Committee members should not be directly involved in screening but may have a relevant background in an adjacent field of medicine.”. I wondered what exactly this would mean, as anyone who possesses relevant expertise regarding screening may be considered as involved in screening somehow. For the tasks performed by the steering committee, such as defining thresholds for acceptable levels of benefits, harms, and their balance, acceptable costs…, it is clear that Steering Committee members need relevant expertise in the context at hand. In that sense, this exclusion criterion should be better specified to avoid conflicts of interest but also allow for the necessary expertise (for instance, specify “not directly involved in the initiation and execution of the program being evaluated” ???).

*We agree that we should be more specific about what is meant by involvement in screening. We now write in line 122-125 page 6: ‘*To minimize influence of vested interests while maintaining relevant input, we suggest that Steering Committee members have relevant expertise, but should not be involved in screening interventions under review through practice or research.’

In line 126-129 page 6: Instead, the Steering Committee may consult with professionals involved in the screening under review, and people with the target condition to inform how screening works in practice, how aspects of service delivery may affect the interpretation of evidence, to what extent international findings are applicable to local context, and the experience of participating in screening.

15. Step 3: Deliberative engagement with citizens: In some health systems, and for some screening programs, informed decision making is recommended, whereby citizens are first informed about the nature, extent and probability of different benefits and harms of screening, before they decide to participate or not. The process of deliberative engagement with citizens could be used to reevaluate this aspect of screening as well. For instance, the reevaluation of screening practices could necessitate the inclusion of an informed decision making process that did not exist before (e.g., sending a leaflet with information as done by NHS UK for instance). Input from both professionals and citizens, based on the information from the Technical committee, could be used to make recommendations regarding such changes to screening practices. Have the authors considered informed decision making as part of the screening practice? Perhaps this is out of scope of the current framework, but if not, it may be a suggestion worth considering.

We agree that informing potential participants is a prerequisite for any screening programme. We address this in several places in the manuscript. Under the heading ‘Involving the public’ we write in line 89-93, page 5: ‘ The public should be included in decisions because screening aims to improve public health,

uses resources, and generates opportunity costs (17). If public views are incorporated into recommendations on screening and how to inform future participants, this may increase acceptability, reduce negative reactions from affected communities (4), and increase legitimacy and trust in health systems '.

Also in the section on the final recommendations we stress the importance of adequately informing potential participants in line 168-171, page 8.

"Additional recommendations could focus on monitoring to facilitate future re-evaluations or research, or randomisation to different screening strategies when there is important uncertainty (21). Recommendations regarding information for potential participants should focus on improved understanding rather than increased participation.'

We will address this topic further in future manuscripts of this series.

16. "To involve everyday people": sounds awkward. Shouldn't it be "laypersons" for instance?

We agree. In box 2, page 6, under step 3, and changed 'everyday people' to ' members of the general public*'.*

17. "Though our proposal involves financial investment": unclear what this means.

We changed this into ' requires resources', line 176 ,page 8 to do justice to the fact that re-evaluation depends on the will to allocate both money, time and intellectual resources, and political commitment to this endeavour..