Author’s response to reviews

Title: Umbrella and basket trials in oncology: ethical challenges

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Author’s response to reviews:

Dear Editors,

Thank you for the opportunity to revise our manuscript. We are also grateful to reviewers for a helpful comments and suggestions. Please find our responses below.

Reviewer reports:

Rieke Van Der Graaf (Reviewer 1): The authors have written an interesting paper on various challenges to umbrella and basket trials. These novel trial designs are on the rise, and are sometimes promoted for ethical reasons (assigning fewer patients to the seemingly inferior drug). Hence a paper that critically evaluates these designs from an ethical perspective is timely. The authors list eight challenges, which sound reasonable at first sight. But there are some major and minor issues that need to be clarified.

1. It is not entirely clear how they arrive at these challenges. Although the challenges seem to derive from their analysis of the NCI-MATCH and Lung-MAP trial, not all challenges refer to these trials (for example 5 and 7 don't).

Response:
Thank you for this remark. We have rearranged manuscript and keep on challenges specific to basket and umbrella trials. We have also added information about other challenges that are not specific to these trial designs and we mention it in the manuscript. NCI-MATCH and Lung-MAP trials serve as examples to support our claims.

2. It is also questionable whether all of them are fair and/or should be merged with others. I will explain this comment below in a more detail.

Response:
We have rearranged the discussion section and we divided it into three main sections: scientific validity, risks and benefits and informed consent.
3. Another problem is that the title and research aim of the paper suggests that this paper presents an overview of risks and benefits of these novel trial designs, but the paper is actually primarily about the risks (or challenges, as I see it).

Response:
We have created a “Benefit” section and provided analysis.

4. A final major issue is the structure. It has been submitted as a debate article. I do understand that the structure of debate articles is less strict than for a research article. However, I believe it strengthens the paper when the methods are clear. The paper now hinges on an analysis and a discussion. What is called discussion is actually an analysis of problems of these designs. Sometimes these 8 challenges are concluded with a claim (for example in line 254/255 "We claim that…), but not always. At the same time, the research aim of this paper is "to discuss risks and benefits…..". I think that the main part of the paper is in fact an analysis.

Response:
Thank you for the comment. We have rebuilt the structure of the manuscript, added more arguments and arranged it more into discussion/debate mode. Since it was not a systematic analysis there was no specific methodology involved.

5. The scope of the paper is a discussion of these trial designs in general whereas they discuss them in the specific context of oncology (and not e.g. in the context of disaster research). The scope should be part of the title, but also be discussed as a limitation of this paper. It is not clear to me whether their analysis would be different when applied to the use of these designs in other contexts.

Response:
We narrowed down the scope of our paper to oncology, described limitation and we clarify this in the title of our manuscript.

Minor

1. Pages 3/4. The authors state in line 76 that a basket trial is focused on testing one treatment against a specific target. Please clarify how this is consistent with assigning patients to 30 subtreatment protocols (line 86) or "drugs being studied" (94) and (97/98).

Response:
We have added explanation. We believe, that now it is clearer.
“It can be a single- or multiple-arm trial, in which one arm is a separate “basket”, that assigns small cohorts of patients and focuses on testing one treatment against a specific target, regardless of disease types”.
2. Lines 162-171: it is not immediately clear how these lines are related to the main theme of this section (reliability). It may be better to start this section with line 172.

Response:
Thank you for this remark. We decided to rearrange sections and remove some parts.

3. Line 177/178: the authors address reliability in this section but also point at substandard treatment. It may be better to merge substandard treatment with e.g. section 3 on harms.

Response:
We mentioned allocation to a substandard treatment in both scientific validity and risks and benefits section as it is a threat to both of these ethical requirements.

4. Line 180: chemotherapy. I think the authors mean care as usual? Please clarify.

Response:
Actually, we mean here chemotherapy. A care as usual can be a targeted therapy (e.g., S1400E sub-trial in Table 2) or a chemotherapy. In the case of some Lung-MAP sub-studies (e.g., S1400B) patients are randomized to receive either chemotherapy, (which we agree is a care as usual), but it attacks both malignant and non-malignant cells, or experimental targeted therapy which targets only one genetic change. The flaw of this design is that no matter how many genetic changes the patients' tumor harbor, they are assigned to chemotherapy or targeted therapy, which may be harmful to the patient and the trial findings may be unreliable. We described it as an example and we now referred to the example of Lung-MAP trial.

5. Page 10, section 2 risk of unrepresentativeness. This challenge may be fair, but the content on this page does not substantiate this claim: lines 198/199: if it is impossible to obtain a sufficient amount of tissue and if this is a general feature of these trials I think it is part of section 1 on reliability (which could also be given a more general heading of scientific validity).

Response:
Thank you for suggestion. We have changed the general heading.

Furthermore, in lines 201/202 the authors show that only a limited geographical region of tumor is analyzed. At the same time, many oncology trials focus on parts of the tumor. It is not clear to me how this is different for basket trials. What I can imagine is that patients are misled, or that results are misinterpreted, but the authors are not clear in this respect.

Response:
The insufficient amount of tissue and testing only a limited part of the tumor is not a specific feature, but it may contribute to the allocation to the substandard treatment. This refers also to the general problem of tumor complexity, which may be neglected in treatments targeting only one genetic change.
6. Lines 205/206. The authors rightly claim that there should be a positive risk-benefit balance. Accordingly the "however" in line 206 is unclear. That harms may occur does not imply that the risk-balance is unreasonable in general.

Response:
Thank you for this remark. We have removed “however” and we discussed the risk-benefit balance in these trial designs.

7. Section 4 on page 11/12 on screening is somewhat heterogeneous running from large numbers to be screened to coping with incidental findings. Some parts can be merged with other sections (e.g. reliability).

We have rearranged and merged sections.

8. Line 227/228. I don't understand the claim that inability to participate in a study is a problem (moreover, which is not specific for this trial design)

Response:
Thank you for this notice. We do not claim that inability to participate in a study is a problem. We are curious why some trials offer a default arm and some not. We think that patients are not aware of the prospects of being included into the study and they also do not know that after screening they may be treated with already approved drugs. We clarified this.

9. Lines 277-279: please clarify why the problem of such misunderstandings can be intensified in these trials with non-match substudy.

Response:
We have clarified this.

10. Line 346: that FDA encourages implementing innovative clinical trial designs is presented as the main conclusion: 1. this cannot be the conclusion, 2. it is new information that should not be part of the conclusion.

Response:
Thank you. We have transferred this information into the background.
Anna Höglund, Ph.D. (Reviewer 2): This is an interesting discussion paper on an important matter. However, I think the authors need to do some major revisions in developing the ethical aspects further, in order to make the manuscript suitable as a debate in BMC Medical Ethics.

1) Background: The background section is focused on describing the difference between "umbrella trials" and "basket trials". This is necessary and interesting, but the background also needs to include text on important ethical aspects, such as autonomy, integrity, informed consent, do no harm, beneficence, non-maleficence etc., which could thereafter be used in the discussion.

Response:
We included now ethical aspects into background based on Levine et al. framework ("What makes clinical trials ethical"). We selected three elements of the framework which seem to be the most challenged in umbrella and basket trials in oncology: scientific validity, risks and benefits and informed consent.

2) The discussion is focused around risks and benefits in umbrella and basket trials, but the text concerns mainly practical matters and lacks conceptual clarity. Please relate the discussion of risks and benefits to ethical concepts, such as the ones mentioned above. What ethical values are threatened due to lack of reliability, unrepresentativeness etc.? Please develop this throughout the discussion section.

Response:
Thank you for this comment. We developed the discussion section and included analysis of scientific validity, risk-benefit balance and informed consent.

3) The concluding remarks are very scarce. Also in this section, the authors need to specify what ethical values that are at stake in the different trials the manuscript concerns. The last sentence is very vague: "We believe that the ethical issues and challenges described above need more theoretical and practical approaches… etc." This is too vague. What theoretical and practical approaches? Please explain and develop.

Response:
Thank you. We keep our conclusion short but we added more information about principles which are challenged in basket and umbrella trials.