Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: The manuscript "Types and progress of clinical trial design for breast 2 cancer" is full of basic editorial mistakes and other errors.
For example: the lack of space - line 67, doubled words - line 77, incorrect names - line 55 should be phase IV, not III. Incorrectly copied/pased definition of the basket trials from the NEJM paper (ref. 9, Table 1). Most of the cited literature is outdated

Reply 1: We thank you for raising this issue. We have thoroughly reviewed the manuscript and have made corrections to address the basic editorial mistakes and other errors you have pointed out.

These include issues such as the lack of space , doubled words, and the incorrect naming of phase IV as phase III **at line 112.** Additionally, we have rectified the inaccuracies in the definition of basket trials by referring to the correct source (ref. 8, Table 1) as you have mentioned. **(see Page12, line 212-213)** Meanwhile, we add the new literature.**(see Page11-12, line 202-208; Page12, line 216-218; Page13, line 237-246, Page15, line 276-286, and etc.)**

We acknowledge that there were other modifications required throughout the manuscript due to these errors. However, due to the extensive nature of these changes, we have refrained from listing all of them here. We kindly request that you revisit the revised manuscript and evaluate if the corrections made adequately address the issues you've highlighted. Your feedback on the revised version will be invaluable in ensuring the quality and accuracy of the manuscript.

Reviewer B

Comment 1: The definitions in Table 1 do not align with the definitions provided in the text. In particular, I should point out that the definitions for platform, basket and umbrella trials in that table 1 are not correct

Reply 1: We thank you for raising this issue. We have carefully reviewed the definitions in Table 1 and have made the necessary adjustments to ensure that they align with the definitions provided in the text. (see **Page12, line 212-213; Page13, line 252-253; Page14-15, line 289-291**)

We apologize for any confusion caused by the inconsistencies, and we appreciate your diligence in bringing this to our attention.

Regarding the definitions for platform, basket, and umbrella trials in Table 1, we sourced these definitions from a reliable and authoritative reference (https://www.nejm.org/doi/full/10.1056/nejmra1510062). We understand the importance of accurate and consistent definitions, and we believe that using established definitions from reputable sources enhances the credibility of the manuscript.

We kindly request that you reconsider these definitions, taking into account the source and the alignment we've made with the content of the manuscript. Your expertise and

insights are highly valued, and your feedback will contribute to the accuracy and clarity of the manuscript.

Comment 2: Section (II) 1 on Master protocols – The definition provided for master protocols is slightly different to those well acknowledged in the literature. I would recommend using and citing definitions or variations thereof from this paper https://www.nejm.org/doi/full/10.1056/nejmra1510062

Reply 2: We appreciate your feedback regarding the definition of master protocols in Section (II) 1. We have carefully reviewed the definition and have made the necessary adjustments to align it with well-acknowledged definitions in the literature, as recommended.

We have taken into consideration the paper you provided (https://www.nejm.org/doi/full/10.1056/nejmra1510062) and have incorporated its insights into our revised definition. In addition to this, we have also referred to other authoritative sources to ensure accuracy and comprehensiveness.(see **Page11, line 195-201**)

Comment 3: The statement "The key benefit of the master protocol design is "sharing,"" is unclear. The authors should expound clearly what is meant by sharing.

Reply 3: We appreciate your feedback on the clarity of the statement regarding the key benefit of the master protocol design. Following your suggestion, we have provided a more detailed explanation to expound on the concept of "sharing" in the context of master protocol design. We believe that this clarification will enhance the reader's understanding and appreciation of the specific benefits associated with this approach. Your insight has played a valuable role in improving the clarity and effectiveness of our manuscript.(See **Page11-12, line 202-208**)

Comment 4: The authors should add to the definition of a basket trial that the diseases in which the single targeted therapy is tested share a common characteristic, such as a biomarker (and there are numerous examples in breast cancer).

Reply 4: We appreciate your valuable input on the definition of a basket trial. Based on your suggestion, we have expanded the definition to explicitly mention that diseases included in a basket trial share a common characteristic, such as a biomarker. This addition provides a more precise and comprehensive understanding of the concept.

To further illustrate this point, we have included an example in the manuscript. We explain that different cancers harboring the same target gene mutation can be grouped together for investigation, effectively representing a "basket" for targeted therapy evaluation. For instance, in breast cancer trials, patients with HER2-positive cancer may be grouped into the same basket to assess the efficacy of a specific targeted therapy, such as Herceptin (see **Page12, line 215-218)**

We are thankful for your constructive feedback, as it has enhanced the accuracy and clarity of our manuscript. Your contributions have significantly improved the quality of our work.

Comment 5: The authors should use consistent terminology in their paper. In particular,

I would draw their attention to the use of “sub-plan”, “sub-scheme”, “scheme” which are not common terminologies in the literature like “sub-trial” and “sub-studies”. The terminologies like sub-plan, and sub-scheme are entirely confusing to many readers. Other terminologies include “class I errors” instead of conventional terminology “type I error”.

Reply 5: We greatly appreciate your feedback regarding the consistent use of terminology in our paper. Following your guidance, we have reviewed and revised the sections in question to ensure that consistent and widely recognized terminology is used throughout the manuscript.

Regarding the terms "sub-plan" and "sub-scheme," we have taken your advice and replaced them with the more commonly used term "sub-studies" to avoid confusion. **(See Page 10, line 187; Page 11, lines 201 and 203).**

Additionally, we have addressed the use of "class I errors" by replacing it with the conventional term "type I error." **(See Page 20, lines 373-374).**

We sincerely thank you for pointing out these inconsistencies and for your valuable insights. Your input has significantly improved the clarity and coherence of our manuscript, and we are committed to ensuring accurate and consistent terminology throughout the document.

Comment 6: The authors should take note that basket, umbrella and platform trials are not restricted to evaluating “drugs”, although that is what they have mostly been used for. I would encourage the use of more generic terminology in the definitions such as “therapies” instead of drugs. This is because many researchers interested in implementing master protocols in other disease areas are learning from oncology-published papers such as this one, and inclusive definitions are important.

Reply 6: We sincerely appreciate your valuable feedback concerning the terminology used in our definitions of basket, umbrella, and platform trials. Recognizing the importance of inclusive definitions for researchers from various disease areas, we have made the necessary adjustments to the terminology to make it more generic and encompassing.

To align with your suggestion, we have replaced the term "drugs" with the more generic term "therapies" in the definitions.(**See Page 8, line 130, and Page 14, line 256**).

We are truly grateful for your insights and your commitment to promoting inclusive language and definitions. Your feedback has enhanced the applicability and relevance of our manuscript to a wider audience, and we thank you for contributing to its quality.

Comment 7: It is surprising that the authors did not include a discussion/conclusion section on this paper. I would argue that this is very necessary and should put their review in context. For example, what’s the way forward having talked about all these novel designs? Which designs have a better place, is it master protocols or enrichment designs or both, and why?

Reply 7: We appreciate your insightful suggestion regarding the inclusion of a discussion/conclusion section in our paper. Recognizing the importance of providing a

broader context and insights into the implications of the novel designs discussed, we have taken your advice and added a dedicated.**(See Page21-23)**

Comment 8: It is not outrightly clear at the start of the paper why this review is necessary, i.e., what are the authors aiming to achieve, or what gap in the literature is there. There are several reviews relating to these designs such as master protocols out there so clear justification is necessary.

Reply 8: Answer: We thank you for bringing up this important point regarding the clarity of the paper's purpose and justification. We have taken your feedback into serious consideration and have addressed this concern by enhancing the introduction of our manuscript.

In the revised version, we have provided a clear and concise explanation of why this review is necessary and the specific goals we aim to achieve. We have also highlighted the gap in the literature that our review aims to address, distinguishing our work from existing reviews on related topics.(**See Page 5, line 91-93**)

We appreciate your valuable insight, as it has helped us strengthen the rationale behind our review and clarify its contributions to the field. Your feedback has played a key role in improving the overall quality and coherence of our manuscript.

Comment 9: There is too much detailed reporting of clinical trial results in certain sections of the paper, which I believe is not the aim, as this has clearly been reported elsewhere. In a review paper of this type, there is not much scope for this as readers can be referred to read detailed results elsewhere. I would encourage the authors to report only specific aspects of a trial, in a concise way. For example, they may give examples to illustrate different types of umbrella designs. If the authors wish to still report a number of trial examples

Reply 9: We greatly appreciate your guidance on refining the presentation of clinical trial results in our paper. Your perspective on focusing on specific aspects of trials and providing concise, illustrative examples is insightful and valuable.

Following your advice, we have significantly streamlined the detailed reporting of clinical trial results in the relevant sections. We now emphasize specific aspects that demonstrate the value, strengths, limitations, and contributions of each trial to medical research. Additionally, we have incorporated examples that serve to illustrate the different types of clinical designs, showcasing their distinctive features.

(**Seamless trials see Page 9-10, line 165-171; Basket design see Page 12-13, line 224-249; Umbrella design see Page 14-15, line 262-286; platform design see Page 16-17, line 296-311; Enrichment Design see Page 19, line 353-359; Marker Stratified Design see Page 20, line 377-390;**)

This approach has allowed us to preserve the essence of the clinical trial examples while ensuring a more focused and concise presentation. Your feedback has been instrumental in enhancing the effectiveness and readability of our manuscript, and we are grateful for your input in improving the quality of our work.

Comment 10: The subsections Phase I, II, II and IV clinical trial in the section "Traditional clinical trial design" are unnecessary because these are fairly well-known concepts in the literature.

Reply 10: We thank you for your observation regarding the subsections on Phase I, II, III, and IV clinical trials within the "Traditional clinical trial design" section. Your input is valuable, and we have taken your suggestion to heart.

In response, we have revised this section to consolidate the information into a concise and integrated paragraph. This allows us to maintain the context and relevance of these well-known concepts while eliminating unnecessary subsections. Your feedback has played a crucial role in streamlining our manuscript, ensuring that it focuses on the key aspects without redundancies. We appreciate your guidance in enhancing the clarity and efficiency of our work.(**See Page 7, line 101-117**)

Comment 11: I would encourage the authors to highlight some general issues relating to the role of novel statistical methods in ensuring that these innovative trial designs improve treatment options in Breast cancer. This doesn't have to be technical, but bring readers up to speed with some recent developments that are ensuring the above trial designs are more efficient. Examples of what to talk about is Bayesian methods for sharing information etc.

Reply 11: We sincerely appreciate your suggestion to incorporate a discussion on the role of novel statistical methods in enhancing the effectiveness of innovative trial designs. Your perspective on providing readers with an understanding of recent developments in this area is valuable, and we have made efforts to address this in our manuscript.

To fulfill this recommendation, we have included a discussion on the role of Bayesian methods, particularly in the context of the I-SPY 2 trial design. This addition allows us to provide insight into how innovative statistical approaches, such as Bayesian methods, are contributing to the efficiency and effectiveness of novel trial designs. While we have focused on Bayesian methods in the I-SPY 2 trial as an example, we believe that this discussion provides readers with an overview of the broader impact of statistical advancements in breast cancer trial designs. (**See Page 16, line 303-307)**

Your input has enhanced the relevance and comprehensiveness of our manuscript, and we are grateful for your guidance in ensuring that our readers are informed about the significant developments in this field.

Comment 12: I agree with the authors that "Seamless designs" are increasingly used in practice, but they are not as novel compared to master protocols. Besides, any of the other trials including master protocols can be run using a seamless design. That is to say, in terms of the layout of this paper, I am not entirely sure it is best

Reply 12: We deeply appreciate your thoughtful feedback regarding the presentation of seamless trial designs in our paper. Your insight into the prominence of master protocols and their transformative impact is well-taken. In response to your concerns, we have made adjustments to the layout of our paper to emphasize the significance of master protocols.

We have refined the section on seamless trial designs by focusing on the challenges and limitations associated with this approach. Additionally, in the section discussing master protocols, we have taken the opportunity to contextualize them as a more distinctive and innovative strategy compared to seamless designs. We acknowledge the crucial role that master protocols play in revolutionizing clinical trial paradigms, enabling the concurrent testing of multiple therapies within a unified framework. (**See Page 9, line 153-163 and Page 10, line 174-189)**

Your feedback has helped us better structure our paper to underscore the importance of master protocols in the realm of clinical trial designs, particularly in the context of breast cancer research. We sincerely appreciate your input in enhancing the clarity and emphasis of our work.

Comment 13: In section (I) 1, I would point to the reviewers that seamless designs are not restricted to phase II/III only. Even phase 1/2 is a seamless design.

Reply 13: We thank you for pointing out the importance of clarifying the scope of seamless designs within different phases of clinical trials. Your feedback is valuable, and we have taken steps to address this in our manuscript.

In response to your input, we have revised the relevant section to emphasize that seamless designs are not limited to Phase II/III trials alone. We have made it clear that seamless designs can also be applied to Phase I/II trials, demonstrating their versatility across various clinical trial phases. (**See Page 8, line 124、142 and Page 10, line 177)**

eg: not only limited to Phase II/III but also applicable to Phase I/II trials….

Comment 14: We do not need several paragraphs to discuss the advantages of each of the designs proposed.

Reply 14: We appreciate your feedback regarding the presentation of the advantages of each proposed clinical trial design. Your perspective on streamlining the content for improved clarity is well-received.

In response, we have revised the manuscript by removing the separate paragraphs discussing the advantages and disadvantages of each design. Instead, we have consolidated the discussion of the advantages and disadvantages of each design into the "Discussion" section. This approach allows for a more cohesive presentation of the benefits and limitations of the various clinical trial designs.(**See Page 21-22, line 393-417**)

Your insight has guided us in enhancing the structure and focus of our paper, and we are grateful for your input in ensuring the readability and effectiveness of our work.

Comment 15: The sections on marker stratified and enrichment designs should be summarised.

Reply 15: We appreciate your suggestion to provide concise summaries of the sections on marker stratified and enrichment designs. Your feedback on improving the readability and focus of these sections is valuable.

In response, we have revised the manuscript by providing succinct summaries of the marker stratified and enrichment designs sections. This approach allows us to present the key points and insights of these designs without unnecessary elaboration. **(See Page 19-20, line 342-390)**
Your guidance has contributed to enhancing the clarity and effectiveness of our paper. We thank you for your input in streamlining the content while retaining the essential information about these designs.

Comment 16: Although the title of the paper denotes “progress of clinical trial design for Breast cancer”, there is no evidence of clearly discussing clinical trial progress in this disease area. For example, it needs to be mapped out, this is how early BC trials were designed, giving examples, then move on to other designs like enrichment, and then today there is more focus on master protocols because of x, y, z.
Reply 16: Answer: We greatly appreciate your insightful feedback regarding the need to clearly outline the historical progression of clinical trial design for breast cancer in our paper. Your suggestion to provide a structured narrative that traces the evolution of trial designs is well-taken.

In response to your valuable input, we have restructured the paper to provide a comprehensive overview of the historical evolution of clinical trial designs in breast cancer research. We have moved from an "Overview of traditional clinical trial design in breast cancer" to "Innovations in clinical trial design," incorporating specific examples of trial designs in different stages (early-stage, enrichment design phase, master protocol phase). Furthermore, we have analyzed the context in which each design is suitable and provided insights into the reasons for the shift towards newer designs.**(See Each title; Page 10, Line 173-186; Page 17-18, Line 315-336, and etc.)**
Your guidance has inspired us to provide a more cohesive and comprehensive presentation of the progression of clinical trial designs in breast cancer. We are grateful for your contribution in ensuring that our paper accurately reflects the historical context and evolution of trial designs in this disease area.