

Peer Review Overview

Manuscript Title: Unified Ethical Principles and an Animal Research ‘Helsinki’ Declaration as Foundations for International Collaboration



Received	Apr 02, 2022
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1st Decision letter

Reference: CRNEUR-D-22-00032

Title: Unified Ethical Principles and an Animal Research ‘Helsinki’ Declaration as Foundations for International Collaboration

Journal: Current Research in Neurobiology

Dear Dr Petkov,

Thank you for submitting your manuscript to Current Research in Neurobiology.

I have completed my evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following major revision. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Sep 24, 2022.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully; outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission will need to be re-reviewed.

Current Research in Neurobiology values your contribution and I look forward to receiving your revised manuscript.

CRNEUR aims to be a unique, community-led journal, as highlighted in the [Editorial Introduction](#). As part of this vision, we will be regularly seeking input from the scientific community and encourage you and your co-authors to take the [survey](#).

Kind regards,

Yogita Chudasama
Associate Editor
Current Research in Neurobiology

Comments from Editors and Reviewers:

Reviewer #1:

Understanding both the history and current approach to the ethical principles for animal research is essential for any researcher conducting biomedical research. The aim of this paper, to review the different approaches from the 3Rs to the 6Ps in the context of the Helsinki declaration and attempt to integrate them while highlighting their important for international collaboration is long overdue and very welcome. This article has the potential to be essential reading for ALL researchers working with animals especially those working with non-human primates. The authors mostly do a great job of reviewing the different approaches to ethical animal research and they are perfectly placed to write this review as they constitute a group of esteemed veterinary and basic non-human primate researchers. Where I have comments they are mostly aimed at tightening up the arguments in favor of an international framework for ethical research principles, better defining the scope of the current manuscript, and more thoroughly integrating the history of animal research ethics into the manuscript.

Major comments

Introduction: Introduction starts by highlighting international collaborations as important for science before going onto discussing the necessity for animal models in research. This ordering felt backwards. The main message for the article is not to highlight the importance of these collaborations but to emphasize that ethical animal research is essential for human progress and international collaborations such as the human genome project are examples of such efforts. Consider refocusing.

Focus on non-human primates: The authors of this manuscript are primarily known for their work with non-human primates and this manuscript is part of a special issue on non-human primates. In that regard, it feels like it would make sense to focus this manuscript and its attention onto ethical non-human primate research across the globe. The point could be made that a unifying set of ethical principles for non-human primates is especially critical to help reduce the numbers of animals used to answer key questions of truly global importance.

Emphasis of why an international framework for ethical non-human primate research: The authors argue that international collaborations need a set of unifying principles to help foster collaboration. A good example of this is on page 18 but there are others throughout the manuscript: "The problem, however, is that without a global declaration for animal research there are tremendous hurdles for scientists who seek to collaborate or directly work in parallel with research groups conducting animal research in different countries.". The emphasis here doesn't feel quite right. For me the need for a unifying and internationally agreed set of ethical principles for animal research is that it would likely improve the reliability of findings across the world-wide research enterprise as well as helping international collaborations. Highlighting this point would, I think also help to convince stakeholders in countries with little oversight or applied ethical principles for animal research as to why it is in their best interests to sign up to such a set of principles. Chiefly, doing so would mean that their research findings would have added validity and possible reliability as their research is not being conducted in animals that are not in a normal, healthy state. I have a feeling that the authors might have been trying to get this point across, but it rather got lost. They could help bolster the point by highlighting situations where a lack of ethics in animal research lead to findings that could not be replicated etc.

The Basel Declaration is referenced repeatedly in the text without actually detailing what it is. Only after consulting the tables does it become clear what declaration is and why it is so important for the present manuscript. A little more of an introduction of this declaration and its history would be good to emphasize in the text for a reader. Related to this, many of the frameworks that are highlighted have a historical context and it would be useful, I think, to add a short discussion of the history of ethics in animal research and what tangible good it has led to.

Minor

The international brain lab could be highlighted as an example of an international research effort using animals that is trying to ensure replicability across multiple labs with different local laws for animals in research and ethical approaches. Similarly, international collaborations for the use of non-human primates could be highlighted. A good example of this was between Oxford and RIKEN (Mansouri et al., Science, 2009)

Page 7: Discussion of the 3V's waits until the end of the paragraph to actually detail what the 3V's stand for (somewhat like using an acronym repeatedly and only later telling a reader what it stands for). By structuring the paragraph this way, it rather makes the start of the paragraph hard to read or appreciate the thoughtful discussion and integration of this ethical framework with other approaches for animal research.

Reviewer #2:

This is a very constructive and useful article that is an important step towards unifying the principles governing animal research into a single declaration, possibly based upon the original Basel Declaration. The reviews draws a useful parallel to the original Helsinki Declaration for research involving humans and the developments that have occurred since its inception. The main point made by the authors is that international research needs a common set of principles to allow the research to progress in different countries. This is important because otherwise differences can be used by regulators or funders to create obstacles to high-quality international collaborations based on apparent differences in animal research/welfare regulations between contributing states. They also point out the enduring nature of the 3Rs as a set of principles, but argue that rather than replace these, a new animal research declaration should complement and extend the 3Rs to include a number of additional principles that have emerged since the 3Rs was introduced over 60 years ago.

I have no major criticisms to offer, rather this should be published as it will make a very useful contribution to the specific volume and to the debate more generally.

A few minor comments

the last bullet point of the 'highlights' might be better as ".....be amended to consolidate a single set of unified principles"

P11 line 7 : 'condone' or 'support' rather than consider?

P12 para 2 line 14 'is' rather than 'are'

P13 para 4 line 2 might read better as "....conducted across its different member states" (otherwise it

might read as if any other body could regulate research in the EU?

p14 oara 1 line 7 "animal research numbers by species..." and maybe add "...and by class of severity..."

1st Author Response Letter

Response to comments from Editors and Reviewers:

Comments from Reviewer 1

Understanding both the history and current approach to the ethical principles for animal research is essential for any researcher conducting biomedical research. The aim of this paper, to review the different approaches from the 3Rs to the 6Ps in the context of the Helsinki declaration and attempt to integrate them while highlighting their important for international collaboration is long overdue and very welcome. This article has the potential to be essential reading for ALL researchers working with animals especially those working with non-human primates. The authors mostly do a great job of reviewing the different approaches to ethical animal research and they are perfectly placed to write this review as they constitute a group of esteemed veterinary and basic non-human primate researchers. Where I have comments they are mostly aimed at tightening up the arguments in favor of an international framework for ethical research principles, better defining the scope of the current manuscript, and more thoroughly integrating the history of animal research ethics into the manuscript.

Reply. We sincerely appreciate the insightful comments and guidance and have addressed them as follows.

Major comments

Comment 1. Introduction: Introduction starts by highlighting international collaborations as important for science before going onto discussing the necessity for animal models in research. This ordering felt backwards. The main message for the article is not to highlight the importance of these collaborations but to emphasize that ethical animal research is essential for human progress and international collaborations such as the human genome project are examples of such efforts. Consider refocusing.

Reply. Thank you for noting a better organization of the introduction. We have switched the order to emphasize the importance of science (third paragraph promoted to first position) before discussing international collaboration as important for science. We have also added in this section the examples of nonhuman primate (Oxford and RIKEN) and rodent (International Brain Laboratory) international collaborations suggested by the reviewer (lines 89-94).

Comment 2: Focus on non-human primates: The authors of this manuscript are primarily known for their work with non-human primates and this manuscript is part of a special issue on non-human primates. In that regard, it feels like it would make sense to focus this manuscript and its attention onto ethical non-human primate research across the globe. The point could be made that a unifying set of ethical principles for non-human primates is especially critical to help reduce the numbers of animals used to answer key questions of truly global importance.

Reply. This is also an excellent point and we have ensured a clearer focus on nonhuman primates for the reasons stated and have also integrated the reviewer's excellent statement as follows, (lines 108-114: *"Although the ethical issues are relevant for all animal research, this paper and the special issue topic that it is a part of focus on nonhuman primates. Use of non-human primates in research is generally considered to require greater justification than use of other species. In addition, the greater resources needed for non-human primate research often involve global collaboration and these may require incorporating multiple national standards into study designs. All animal research needs to utilise optimal study designs and combine scientific rigor with appropriate ethical standards. However, these may be considered particularly important to improve reliability and reduce animal numbers when using non-human primates as model systems."* .

Comment 3. Emphasis of why an international framework for ethical non-human primate research:

The authors argue that international collaborations need a set of unifying principles to help foster collaboration. A good example of this is on page 18 but there are others throughout the manuscript: "The problem, however, is that without a global declaration for animal research there are tremendous hurdles for scientists who seek to collaborate or directly work in parallel with research groups conducting animal research in different countries.". The emphasis here doesn't feel quite right. For me the need for a unifying and internationally agreed set of ethical principles for animal research is that it would likely improve the reliability of findings across the world-wide research enterprise as well as helping international collaborations. Highlighting this point would, I think also help to convince stakeholders in countries with little oversight or applied ethical principles for animal research as to why it is in their best interests to sign up to such a set of principles. Chiefly, doing so would mean that their research findings would have added validity and possible reliability as their research is not being conducted in animals that are not in a normal, healthy state. I have a feeling that the authors might have been trying to get this point across, but it rather got lost. They could help bolster the point by highlighting situations where a lack of ethics in animal research lead to findings that could not be replicated etc.

Reply. We appreciate the reviewer raising this point which we directly address in the revised manuscript, as follows (lines 550-563): *"Another issue is that a mutually agreed upon global declaration could help to provide common guidance to ensure better replicability of animal research findings and improve the quality of the scientific data while also reducing animal numbers when groups work in isolation or under substantially varying welfare conditions, animal oversight and regulation. One reason why the 3Rs are being widely adopted is that they not only promote good welfare, but also good science. There are valid concerns where animals in poor health, stressed unnecessarily and undergoing poorly conducted procedures generate poor data quality [17, 40]. The effects of the laboratory environment on research outcomes has been highlighted by several authors (e.g. [41, 42]). Addressing these concerns brings together improved welfare, often by reducing uncontrolled stress, and optimal study design. There is an argument to be made about scientifically introduced heterogeneity in animal results [43], but that is different from heterogeneity that is introduced because of welfare issues leading to poor quality science. Working towards agreement on a global declaration does not need to impinge on geographical and cultural sensitivities, and this effort can establish common ground to increase rigor and reproducibility [44] while reducing animal numbers."*

Comment 4. The Basel Declaration is referenced repeatedly in the text without actually detailing what it is. Only after consulting the tables does it become clear what declaration is and why it is so important for the present manuscript. A little more of an introduction of this declaration and its history would be good to emphasize in the text for a reader. Related to this, many of the frameworks that are highlighted

have a historical context and it would be useful, I think, to add a short discussion of the history of ethics in animal research and what tangible good it has led to.

Reply. We have created a section after introducing the Helsinki Declaration entitled: “What is the Basel Declaration on animal research?” (starting on line 163). The manuscript has a brief introduction to the rich history of animal research ethics that developed in the UK, USA, Canada and Australia. This starts on line 488 in the section on Incorporating ethical principles into the fabric of legislation and points the reader to further reading.

Minor

Comment 5. The international brain lab could be highlighted as an example of an international research effort using animals that is trying to ensure replicability across multiple labs with different local laws for animals in research and ethical approaches. Similarly, international collaborations for the use of non-human primates could be highlighted. A good example of this was between Oxford and RIKEN (Mansouri et al., Science, 2009)

Reply. We highlight these as examples of international research using animals that ensure replicability across labs with different laws for research animals and ethical approaches (lines 89-94), as follows: “*Other examples of scientists working internationally with different local laws for animal research and ethical regulation abound, including successful collaborations between international groups working with nonhuman primates to advance scientific knowledge [8, 9], and with rodent behavior and neurobiology aiming to ensure replicability and support joint work across multiple laboratories around the world (e.g., the International Brain Lab [10]).*”

Comment 6. Page 7: Discussion of the 3V's waits until the end of the paragraph to actually detail what the 3V's stand for (somewhat like using an acronym repeatedly and only later telling a reader what it stands for). By structuring the paragraph this way, it rather makes the start of the paragraph hard to read or appreciate the thoughtful discussion and integration of this ethical framework with other approaches for animal research.

Reply. We have corrected the structure of the 3Vs paragraph to define the 3Vs from the beginning (now on line 233-246).

Comments from Reviewer 2

This is a very constructive and useful article that is an important step towards unifying the principles governing animal research into a single declaration, possibly based upon the original Basel Declaration. The reviews draws a useful parallel to the original Helsinki Declaration for research involving humans and the developments that have occurred since its inception. The main point made by the authors is that international research needs a common set of principles to allow the research to progress in different countries. This is important because otherwise differences can be used by regulators or funders to create obstacles to high-quality international collaborations based on apparent differences in animal research/welfare regulations between contributing states. They also point out the enduring nature of the 3Rs as a set of principles, but argue that rather than replace these, a new animal research declaration should complement and extend the 3Rs to include a number of additional principles that have emerged since the 3Rs was introduced over 60 years ago. I have no major criticisms to offer, rather

this should be published as it will make a very useful contribution to the specific volume and to the debate more generally.

Reply. We thank the reviewer for their assessment and support for the potential usefulness of the article. We made all of the modifications below.

A few minor comments

Comment 1. the last bullet point of the 'highlights' might be better as ".....be amended to consolidate a single set of unified principles"

Reply. We have revised it as follows "*The Basel Declaration could, if there is interest, be amended to consolidate a single set of unified principles and documents*" (see Highlights). We have included 'documents' in the phrase because there are several documents that the declaration could point to, as we have here, or usefully integrate into the next amendment if there is interest to do so.

Comment 2. P11 line 7 : 'condone' or 'support' rather than consider?

Reply. Replaced 'consider' with 'support' (now on line 380).

Comment 3. P12 para 2 line 14 'is' rather than 'are'

Reply. Typo corrected (now on line 421).

Comment 4. P13 para 4 line 2 might read better as "....conducted across its different member states" (otherwise it might read as if any other body could regulate research in the EU?)

Reply. Corrected as suggested (now on line 478).

Comment 5. p14 para 1 line 7 "animal research numbers by species..." and maybe add "...and by class of severity..."

Reply. Changed as noted (now on line 494).

Accept Letter

Dear Dr Petkov,

I am pleased to inform you that your manuscript has been accepted for publication. My comments, and any reviewer comments, are appended below.

Your accepted manuscript will now be transferred to our production department. We will create a proof which you will be asked to check, and you will also be asked to complete a number of online forms required for publication. If we need additional information from you during the production process, we will contact you directly.

We appreciate you submitting your manuscript to Current Research in Neurobiology and hope you will consider us again for future submissions.

We encourage authors of original research papers to share the research objects – including raw data, methods, protocols, software, hardware and other outputs – associated with their paper. More information on how our open access Research Elements journals can help you do this is available at https://www.elsevier.com/authors/tools-and-resources/research-elements-journals?dgcid=ec_em_research_elements_email.

Kind regards,

Yogita Chudasama
Associate Editor
Current Research in Neurobiology

Editor and Reviewer comments:

Reviewer 1: The authors have done a great job responding to my concerns and the manuscript is significantly improved. In its present form it should be mandatory reading for all researchers conducting brain research work with non-human primates.

Reviewer 2: The authors' responses to the points that I raised are all satisfactory

----- *End of Review Comments* -----