

Author's response to reviews

Title: Ethical approval and informed consent: analysis of biomedical publications originating from Sri Lanka

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Author's response to reviews: see over

Response to reviewers

We are grateful to all three reviewers' for their comments.

We have accommodated almost all the points made by this reviewer. We have reanalyzed the results and have gone through all the hard copies and almost re written the paper along the lines of suggestions. We have concentrated on human subject research and documentation of Ethics Review Committee approval and consent.

Reviewer: Adnan Hyder

Major Compulsory Revisions

Comment

The major issue relates to the organization of the paper, and an inconsistent use of key terms which makes the paper somewhat confusing. In the first instance, the authors assert the basis of the paper is to assess current trends in adherence to guidelines regarding ethical approval of research in Sri Lanka. They assert that there are two essential elements of the approval process: rigorous scientific evaluation of protocols, and informed consent. The authors inconsistently lump these two things together and sometimes call it “ethical approval”, while at other times in the paper referencing the two things – review of protocols and informed consent – separately. The authors reference international guidelines for their claim but do not specifically state how they narrowed down human subject protection to just these 2 activities? The references do not do this for sure and so the authors have to defend their claim.

Response

We have accepted this comment in full and done the necessary revisions. We have removed ‘rigorous scientific evaluation of protocols’ and the term ethical approval is replaced by ERC approval. We now concentrate on two issues documentation of Ethical review Committee (ERC) approval and consent. Accordingly we have revised the introduction and were re written.

Comment

A second source of confusion - in the paper, the authors evaluate three separate sources of research: graduate theses from PGIM, scientific articles in the Ceylon Medical Journal, and articles by Sri Lankan authors in international medical journals. However – the methods section specifically mentions only review of PGIM thesis and generally mentions a Medline search. The METHODS section should be expanded to specify each specific area of the work (thesis, CMJ, international journals) and how it was done for the reader to understand issues such as selection bias.

Response

We have revised the methodology section and presented each specific area of the work: thesis, CMJ, international journals, separately in the methods section and also present the results accordingly.

Comment

A third source of confusion – the authors review three sources of research, and in describing this use different phrases and terms to explain the results of their review. For instance, in the RESULTS section the authors describe reviewing PGIM theses and calculating the % of those mentioning or providing evidence of “ethical approval”. There is no mention of informed consent.

Then when CMJ articles are discussed, the authors reference both ethical approval and informed consent. The analysis of results needs to be consistent across sources and if there are differences, then they need to be explained.

Response

We have now rectified this by including this information to that ‘One hundred and seventy nine (58.6%) theses had documented obtaining informed consent, and twelve stated that informed consent was not relevant’. All three surveys present results on ERC approval and consent separately.

Comment

Importantly, only in the discussion of the Sri Lankan articles in International journals do the authors, prior to discussing the issue of consent, first define the number of articles that involved human subjects – in the discussion of the other sources of research papers the authors are silent on this point, leading to the inference that ALL papers from those sources (PGIM and CJM) involved human subjects --- possible but not likely and in any event this issue needs to be specifically described --- 'X of the 305 theses involved human subjects', for example. This last comment is a weakness throughout the paper – the lack of distinction between the number of total research pieces (theses, CMJ articles, international articles) vs. the subset of those involving human subject research. So, first, this distinction (% of research involving human subjects) should always be made and presented – otherwise the denominators may be incorrect and it is generally confusing, and second in each area of analysis both key components of ethical review (as these authors identify them – scientific review of protocols and informed consent) should be addressed. Again, see RESULTS section.

Response

We have now reanalyzed all the three components to rectify this deficiency and all the calculations are done based on human subject research

Comment

The authors have not indicated the basis of their “proxy indicator” as “good enough” except for their ‘opinion’? Moreover, it is unclear what the proxy is a proxy for. What if

any is the empirical basis? Are there other opinions that support this choice? It is important to understand the underlying basis of this decision.

Response

We have revised this section and justified why we decided to survey documentation of IRB approval and informed consent also using reference.

Accordingly we have included this paragraph in the introduction.

‘In the guidelines by the International Committee of Medical Journal Editors (ICMJE) in its 1981 edition required researchers to indicate that the research had IRB review;[and, in 1991, the ICMJE added that when "informed consent has been obtained by authors, this should be clearly stated in the article."[13](#). Previous studies have shown that documentation of IRB review and IC is not consistently done, even in journals that state it as a requirement.[14–19](#)’

Comment

Of 367 you downloaded only 131 – why – you did not explain?

Response

We have explained this in the methods sections as below

A Medline search was carried out with MeSH major and minor heading using ‘Sri Lanka’ as the search term to find all published research originating from Sri Lanka, between 1st January 1999 and 1st September 2004. We downloaded full text papers published in open access journals and those available in Athens an access management system of academic articles. For those not available in open access or through Athens we downloaded only the abstracts. We could not obtain the full text hard copies of those abstracts as the printed journals were not available in Sri Lanka.

Comment

What does this create in scientific terms? Does this not affect the validity of your result?

You need to refer to methods for bibliometric analysis and then present your findings.

There needs to be a full discussion of your limitations and threats to validity based on your methods and results. There is both selection and non-sample bias in your methods and thus the nature of your recommendations has to be affected (and frankly made more humble and toned down).

Response

We have addressed most of the above issues.

There is a paragraph on the limitations in the discussion section.

We are ignorant about this **bibliometric analysis** so has not done that part. Apologies.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Response

These were done

Comment

What were the rules for student theses in academia in Sri Lanka for 1999-2005? Have they changed during this time? Was ethical approval essentially required or by choice of advisor? Also, over the course of this time period there was a sharp increase in the number of theses – even if this sharp increase is utterly irrelevant to this paper, it is striking and the authors may want to provide a brief comment.

Response

We have included this paragraph in the discussion.

There is no reference to ERC approval or consent in PGIM examination rules and regulations. However each board of study are responsible for ensuring these standards. Board of study in community medicine has made it a requirement for candidates to obtain ERC approval (personal communication chairman board of study) since 1991. Regulations and guidelines of board of study in family medicine states that the protocol for a research project should include approval of the project by a relevant ERC. We were unable to find information about necessity for ERC approval in other disciplines. Instruction to authors in CMJ [27] states that ethical committee approval should be mentioned in the text in 'intervention studies' with photocopy of approval letter attached in all submissions.

Comment

The discussion section actually reads in large part like a series of recommendations, not a discussion of the findings of this study. The authors need to first discuss their findings, especially their limitations, and then make recommendations. The authors need to include some comparison with other types of empirical work from South Asia or the developing world on this issue.

Response

Discussion has been revised in the light of the comments

Comment

The papers lack a good review of the literature of this type. Review papers by the following authors to see if you can use any: Kumar N et al; Jafarey A et al; Raja A et al; Moazam F et al; Hyder AA et al; Ahmad A et al; Indian Council for Medical Research; etc.

Response

We have done this part. However we could not find specific work on documenting ERC approval and consent in published research in South Asia.

Discretionary Revisions (which the author can choose to ignore)

Comment

The tables can be reduced – for example table 4 is not needed as it can be described in text. The language and headings used in the table can also be improved.

Response

We agree table 4 was omitted

Reviewer's report

Reviewer: Carol Stocking

Reviewer's report:

General

The manuscript could be edited (by the authors) for clarity. The question explored -- are persons participating as subjects in medical research (in this case in Sri Lanka) being protected by appropriate ERC review -- is important. The method (seeking evidence about human subject protection in publications) has been used in several articles in US journals (e.g. those by Weil, Karlawish and others -- probably not worth citing but it could be done to support their method). The authors sought evidence from two sources (three if we count the CMJ separately from Medline) and report their discoveries from each.

Minor Essential Revisions

Is preparation of a thesis often the predecessor of to future conduct of research? Are these the scientists who will be publishing in the future? May we imagine that being required to get consent or an ethics review when preparing a thesis will lead to a career in which consent and ERC review is part of all research? Or are the two samples just two independent resources? [I have simply assumed that only theses involving human subjects were included in the study. Right?]

Probably the articles on Medline with no human subjects could be excluded from the discussion.

Response

We have clarified that these are three independent sources of publications arising from human subject research carried out in Sri Lanka

Comments on the tables:

Table 1 would be more interesting to me if it were percentaged to compare those with approval and those without (e.g. in the first line, 55%, 45% so that one could quickly see how the various depts. are doing. I'd probably put them in descending order and probably report only the percentage reporting ethical approval. Tables 2 & 3 -- since 5 year trends are being reported the bottom line slightly confuses matters.

Response

Revised as suggested

Comment

Table 4 --could be omitted

Response

Omitted

This paper would be much easier to read if the manuscript were carefully re-read by the authors and tightened. The authors correctly point out that failure to mention ERC or

consent in a published document doesn't mean that review was not obtained. This is an important point, make sure it doesn't get lost. You might want to include a mention of risk level in the discussion of different levels of ethical review. I read the International Committee of Medical Journal Editors as already complying with your suggestion.

"When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. When reporting experiments on animals, authors should be asked to indicate whether the institutional and national guide for the care and use of laboratory animals was followed."

Reviewer's report

Reviewer: Lisa S. S Parker

Reviewer's report:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Comment

Page 6, Methodology, Protocol development process -- I recommend relabeling this section and adding a paragraph that actually describes the protocol that is developed. Some of that description seems to follow in the "Data collection" section on page 8 and might be moved here. The reason for this recommended change is that the sentence "During these meetings, it was agreed that a proxy indicator reporting ..." does not make sense when the following information has not been provided:

* what is the research question that the study sought to answer?

* what was the initial protocol that underwent subsequent discussion, review, and revision?

The use of a proxy indicator should be explained more fully; what is the proxy a proxy for?

Moreover, the second line in this current paragraphs ("A consultation meeting ...") is a mere sentence fragment, and the following sentence ("Revised protocol") should begin "The revised protocol"

Response

We have revised accordingly. We have omitted the title 'protocol development'. Therefore, we have not described the original protocol and the changes as it will carry too much detailed. We have also omitted the proxy issue and instead have described what we did. Research question is also clarified as 'to what extent ERC approval and informed consent procedures are documented in three independent sources of publications arising from human subject research carried out in Sri Lanka'.

Comment

page 10 -- Here the authors claim "recent candidates are more conscious of the informed consent process as indicated in table 3," however, they lack evidence for this claim. (a) They cannot justifiably make a claim about the state of mind of candidates (their conscious awareness of informed consent). (b) They cannot extrapolate from evidence that consent was taken to any claim about the process, including the candidates' awareness of the IC process. As will be suggested below, the authors ought to recognize, explicitly, the limitations of self-reported data or evidence of having obtained consent. At the very least, they ought not comment on the _process_ of consent taking, as they report no data on the process (es) pursued by candidates.

Response

We have deleted this part

Comment

Page 11 -- The authors comment: "In research that was not related to human subjects, only one study gave evidence of obtaining ethical approval." Given the focus on human subjects protection regulations and guidelines and the Institutional Review Board system in the US, the question will arise, at least for US readers, "what sort of ethical approval is required for research not involving human subjects?" The authors should explain the nature of ethical approval with nonhuman animals, as some (perhaps many) readers would not be familiar with that process. Indeed, there might be confusion that an IRB-like body was mistakenly asked to give ethical approval for a study not involving human subjects.

Response

Taking into consideration the comments by other reviewers we have confined this paper to human subject research. There fore the above part was omitted. Hence we have not discussed ethics relevant to non-human research as it will be beyond the scope of the paper.

Comment

Page 12 -- Speaking of the need for debate about the appropriate levels of ethical approval, the authors comment "this is especially applicable to countries where ethics review capacity is limited." By this comment the authors seem to imply that it is permissible for research capacity to outstrip or exceed the capacity for ethical review. This is very troubling. It would seem that if the capacity to review research protocols for their ethical permissibility is limited, then the number (or nature) of protocols should be similarly limited. It is true that in the presence of scarce resources, including scarce ethics resources, review of protocols that present only minimal risk might be expedited. But the general sentiment expressed in the quoted comment is probably not what the authors intend to express.

Response

We have deleted this paragraph

Comment

Page 13 -- Why do the authors consider "unintentional exploitation" as the only concern that may arise due to lack of local ethical review? First, this focus on the risk of exploitation seems to buy into the view of those in the developing world as primarily subject to exploitation, as likely/potential victims, as perhaps less susceptible to ethical concerns that affect subjects in developed world (e.g., research burden and risk, psychological disruption, undue pressure to participate). Second, while ethical review may be suitable to guard against exploitation, the process of informed consent is a particularly poor means of avoiding exploitation. Whether the ethical review adequately guards against exploitation will depend on whether the review is primarily focused on review of the informed consent protocol/process or whether it evaluates the ethics of the study design itself.

Response

We have deleted this section

Comment

Page 13 -- Contrary to the authors' commentary, the ICMJE already incorporates the issue of ethical approval and informed consent into the requirements. See: "II.F. Protection of Human Subjects and Animals in Research When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

When reporting experiments on animals, authors should be asked to indicate whether the institutional and national guide for the care and use of laboratory animals was followed." It is troubling that the authors are not aware or do not acknowledge this inclusion.

Response

We apologize for this omission and have now included this in the introduction with reference. Discussions are centered around the adherence to this requirement.

Comment

Page 14 -- The authors claim "Similarly research that has not been subjected to ethical review or fails to meet accepted ethical standards should be considered as unacceptable science." Why? I agree with the claim, but then I am already persuaded by others' arguments. The authors need to offer an argument in support of this claim, especially for publication in a medical ethics journal. Their presentation of data alone does not constitute such an argument. Moreover, it is not clear that something that is _unethical_ is necessarily unacceptable qua science. For "unacceptable as science" to follow immediately as a conclusion from "unacceptable on ethical grounds" would imply or rely upon a view of science that is at best controversial. Again, the authors would need to supply an argument for this view.

Response

In this light of this comment and comments from other reviewer we have taken this off and tone down the discussion

Comment

Page 14, final line -- Again, I question why the authors choose to raise the risk of exploitation as the only risk mentioned.

Comment

Final recommendation -- I would suggest that the authors include a brief paragraph in which they summarize the limitations of their study. These include

(a) the limitations of self-reported data (although the authors suggest that more degree candidates and published researchers may have sought ethical approval than report it, it is also possible that some are reporting having sought such approval but, in fact, did not); (b) the inability to review all of the articles for which abstracts were found (given space limitations, it is reasonable to anticipate that ethical review would not always be stated in the abstract); and (c) lack of study of the actual content of ethical review, the actual process of informed consent, and the actual level of understanding of research subjects both of the research, the consent process, and the meaning of informed consent. Although the authors mention several of these factors (a-c) in their text, it would be helpful to summarize them briefly as limitations of the study.

Response

We have done this in full as suggested

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

p. 5, "The other is looking" -- delete s from end of 'provides' **Done**

p. 10, insert a comma after '1989' **Done**

p. 12 -- in the abbreviation for versus -- vs -- the v should not be capitalized **Done**

p. 13, line 4 -- delete the comma after 'mandatory' **Done**

p. 13, par 2 -- the verb 'occur' should be 'occurs' -- add an s **Done**

Table 1 -- I recommend changing the headings as follows:

Not mentioned about ethical approval --> Ethical approval not mentioned **Done**

Mentioned about ethical approval --> Ethical approval mentioned **Done**

Table e -- here and in the text, the term 'verbal' is misused. Instead the authors probably mean 'oral' (i.e., spoken not written). 'Verbal' means "expressed in words, written or spoken." **Done**