Author's response to reviews

Title: Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness

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Author's response to reviews: see over
Dear Dr Weijer,

Re: MS: 1500430491178512: Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness

Thank you for your recent correspondence regarding this manuscript. We also thank the four reviewers who have made constructive comments about where and how this paper might be improved. Please find here our response to reviewers’ comments and amendments made to the manuscript. Amendments have been made in bold in the revised manuscript.

Editorial requests

1. Email addresses of all authors are now included on the title page.

2. Introduction has been renamed 'Background'.

3. A list of abbreviations is now included after the Conclusions section.

4. Conflict of Interest section has been renamed 'Competing Interests'.

5. Each author and their contribution has been mentioned individually.

6. Please include a figure title and legend section after the reference list.

7. Information about additional files is now provided.

Reviewer 1: Virginia Sharpe

Discretionary revision

Reviewer’s comment: I would recommend one Discretionary Revision which would be to emphasize in the abstract (which was missing from the manuscript) and in the conclusions the important point on page 15 that variance in the views
of different stakeholder groups makes diverse representation essential in the
development and regulatory evaluation of study proposals. Otherwise, narrow
representation will lead to skewed decisions.

Our response: We have added a statement to this effect to the conclusions
section, but not to the abstract as we are limited by word count and do not feel
that this is a more important conclusion than those that are currently described.

Reviewer 2: Neale Dickert

Major revisions
1. Reviewer’s comment: The range of clinical studies on pandemic disease and
the nature of the ethical and regulatory challenges that these studies might
raise is not made clear. For example, a vaccine study in the context of a
pandemic may raise challenges with regard to the rapidity with which review
has to occur, uncertainties about preliminary data, etc. However, the consent
process that would occur with individuals in that kind of study is not
complicated by severe symptoms or concrete time limitations in the way that
emergency care research is. As the authors state, there are certainly
pandemic situations where consent processes are complicated and barriers
do exist due to severe acute illness. However, there is no obvious reason to
think that one would treat the consent process in those circumstances (and
acceptability of alternative processes that are widely used in emergency care
research) any differently in the context of a pandemic than other emergency
care research settings. Rather, it seems more likely the case that what really
distinguishes pandemic research is not consent limitations but rather the
urgency to design, review, and launch a trial. Most emergency research, in
contrast, is very heavily scrutinized and very thoroughly reviewed, with
lengthy community consultation processes in many regions, for example.
There are also often very strict standards with regard to adequacy of
preliminary data, etc. The authors actually document the increased review
that seems to occur but don’t call attention to the fact that the available time
for such processes may be exceedingly limited in the context of pandemics.

Our response: We clarify that this work is intended to inform clinical
research in which potential research participants are likely to be ill with an
acute infection and that will most likely be conducted in hospital and/or ICU
settings. There are efforts at present to set up such research during inter-
pandemic “peacetimes” that can rapidly be activated. We aimed to produce a
paper that might broadly set out the available evidence on acceptability to all
stakeholders to inform protocol development. Our findings were largely from
emergency research conducted in a range of different clinical contexts and
we used this as a proxy for emergency research that might be conducted in a pandemic. The focus on pandemics reflects our research group’s recent clinical and current research experience of developing protocols for this kind of research.

**Amendments to the paper:** We have substantially revised the background to this paper to clarify our rationale and context.

2. **Reviewer’s comment:** Related to #1, the context of emergency care trials is essential to evaluating the appropriateness of different approaches to consent. In this respect, the findings from particular studies may be heavily specific to the condition or the study (TBI vs. MI vs. stroke for example). Almost no context is provided for pandemic research, making it very difficult to assess how the findings/studies reviewed really apply in the context of pandemic research.

**Our response:** We agree that our rationale for pandemic research in hospital settings was insufficiently explicit in our earlier draft and have substantially amended the background to set this stage more clearly. We have also added to the discussion the influence of context in judging the ethical acceptability of different consent model.

**Amendments to the paper:** We have substantially revised the background to clarify our context, added detail in our analysis to include study context, and added to our discussion this limitation to the generalizability of our findings – see in particular Discussion: “Application to a pandemic context”: first paragraph.

3. **Reviewer’s comment:** There is very little contextualization of the results of the review independent of the connection to pandemic research. The results read simply like a list of results in different categories with very little to explain how studies relate to each other or don’t, how contexts vary, etc. And it is not clear why some data (such as likelihood of attending a public meeting) are in any way relevant to this study that is intended to focus on pandemic research. Where contextualization or interpretation of results is offered, it seems at times quite arbitrary.

For example, one piece used to support the claim that deferred consent is acceptable to patients is reported to have found that 48% of patients indicated deferred consent is acceptable. I would argue that this does not support this claim.

Similarly, with regard to the impact of risk on acceptability, “92% willing to enroll on greater than minimal risk study, 97% for a less than minimal” is
taken to indicate significant effect of risk. These differences are in fact quite trivial from a “clinical” perspective.

Also, the following statement regarding third party consent is problematic in its failure to contextualize findings. “Fewer than half of patients (45% of 11) and clinician proxy decision makers (46% of 13) felt consent was necessary at all under emergency research conditions, while 71% of 17 spouses felt some form of consent was necessary [36].” This was a study evaluating perspectives on consent for a study of prehospital initiation of therapeutic hypothermia in the context of cardiac arrest. In addition to incredibly small numbers of participants, this is a highly specific context where decision making is exceedingly rapid, acuity extremely high, and the setting particularly problematic (out of hospital). Its applicability to many other acute care settings is likely limited.

**Our response:** We agree that context and clarity are important in the interpretation of the findings, and have added these where possible.

**Amendments to the paper:** Additional contextual detail given in the results section, including but not limited to the following queries raised by the reviewer:

- Deferred consent, potential research participants, paragraph 2: further context to explain the finding that 48% of 240 patients found deferred consent acceptable (37% were neutral, and 77% preferred deferred consent to waived consent)
- Waived consent, potential research participants, paragraph 2: The query raised about 92% being willing to enroll on a greater than minimal risk study, 97% on a less that minimal risk study” was in fact an error and should have read: 92% willing to enrol on a minimal risk study, 67% for a greater than minimal risk study. We have reworked this paragraph.
- Third-party consent, potential research participants, paragraph 2: Additional detail to contextualize the findings from a small post-study evaluation of a pre-hospital trial of therapeutic hypothermia following cardiac arrest.

4. **Reviewer’s comment:** While the full body of studies looking at attitudes across acute care research have not been put together, many “sections” of this review have been performed in large part before. It is thus not clear how novel the results are

**Our response:** Other systematic reviews have been conducted in this area. We identified three reviews in particular that were relevant to our study
question. Eltorki et al (2013) reviewed studies relevant to waived consent in pediatric resuscitation research. Lecourtier et al (2008) reviewed views of patients and the public about emergency research conducted under waived consent. Limkakeng et al (2014) reviewed attitudes towards research in emergency medical conditions, a remit that extended beyond a focus on informed consent processes. These reviews offer a detailed examination of some samples included in our review. However our review set out to map more broadly the range of evidence from multiple stakeholder perspectives and offers a steer for further research in some key areas not identified in these other works.

Amendments to the paper: Strengths and Limitations - we cite these reviews and clarify how our review differs.

Minor revisions

1. Reviewer's comment: The statement early on that informed consent is an essential “safeguard against unethical research practice” seems to misconstrue the role of consent. Unethical studies are not made OK by informed consent. Rather, consent is an essential element of most ethical research for a variety of reasons (opportunity to refuse, protection of one’s own interests, etc.). This is likely simply loose wording, but being clear about the role of consent is important if one is examining ethical aspects of doing research without it. Similarly, the following statement – “in addition, pandemic research frequently offers access to novel treatments and may confer a benefit not only to the participants but also to the wider population”- seems to misconstrue research outside of the context of pandemics, most of which is precisely designed to benefit the population rather than individual participants.

Amendment to the paper: We clarify that informed consent is one aspect of ethical research conduct and define the elements of informed consent more precisely in background paragraph 2 and 3.

2. Reviewer's comment: A bit more discussion of the variation in practices and approaches within Europe and in other regions could be helpful.

Our response: There is considerable variation in practice both across Europe and internationally. In Europe, new legislation has recently approved by the European Parliament to replace Directive 2001/20/EC with a Regulation that will be legally binding across all EU countries. This is a complex and detailed area beyond the scope of our paper, however we have
Amendment to the paper:
- Results, Waived consent: We highlight the legislative context guiding research conducted under waived consent in the USA.
- Discussion: “Application to a pandemic context”, paragraph 2, we describe the legislative changes that should contribute to a more harmonized approach across the EU, and the importance of this in a pandemic context.

3. **Reviewer’s comment:** It is important to recognize that “deferred consent” and “waived consent” are really not discrete practices. In the US, for example, studies conducted under the exception from informed consent (called waiver in the paper) almost always require consent for continued data collection and sometimes use. Deferred consent has been pointed out on numerous occasions to be a bit of a misnomer because it is just an absence of prospective consent with later consent for data collection and/or use (you can’t consent later to something that has already happened). I recognize that the term deferred consent is used in many countries’ regulatory structure, but I would hope that this study would clarify that it is really not a discrete approach in general. This is not to dismiss it as an approach, just to say it is the same approach as waived consent in almost all cases.

**Our response:** We distinguished between waived and deferred consent to classify papers and agree that the difference in these models lies more in different use of terminology embedded in different regulatory frameworks.

Amendment to the paper: Results, waived consent: We clarify that deferred consent and consent waiver are similar in practice and highlight that there are differences linked with regulatory frameworks.

4. **Reviewer’s comment:** the introduction is very difficult to follow. Most importantly, it does not address the nature of consent challenges in pandemic illness, and the connection to situations like comparative effectiveness research on standards of care is particularly unclear.

**Amendments to the paper:**
- We have revised the background to better contextualize this work and, as advised, included here detail about the nature of consent challenges in pandemics.
- Discussion, “Application to pandemic context”: paragraph 3: we clarify the link with comparative effectiveness research in our discussion of different study designs that are considered of potential use in pandemic research planning.
5. **Reviewer’s comment:** The basis for inclusion of pediatric studies but not neonatal studies is not clear

Our response: We excluded neonatal research due to the ethical questions that arise in this work due to the acute vulnerability of these parents. Third-party consent is usually obtained for inclusion of neonates in research and others have raised questions about the validity of such consent. Alternatives such as obtaining antenatal consent have been proposed however questions arise here about the legality of such consent. Given the heterogeneity of included studies and the overall purpose of this review we felt it would not be possible to cover these issues in the depth and scope they required.

**Amendments to the paper:** We have now included reference to a paper discussing these issues for interested readers.

6. **Reviewer’s comment:** It would be helpful to provide the full search strategy in an appendix.

**Amendment to the paper:** We have included the full search strategy in appendix A

7. **Reviewer’s comment:** Commonly some method of checking reliability or ensuring quality of data extraction is employed.

**Our response:** We followed the rapid review methodology that allows the step of double-checking to ensure quality of data collection to be omitted. Potential for bias due to human error does arise here and we have commented on this in our limitations section.

8. **Reviewer’s comment:** Box 1 is poorly organized. Additionally, waiver of consent under the US exception from informed consent for emergency research does not require that a study be considered minimal risk, though there are other provisions that must be met. The minimal risk requirement in order for waiver or alteration to be allowable is for studies that do not fall under this exception for emergency settings.

**Amendments to the paper:** Box 1 (key concepts and terms) has been reorganized to start with general definitions of terms and then to describe the four consent models. We have also amended our description of waived consent.

9. **Reviewer’s comment:** Table 1 is also poorly organized (alphabetical rather than by consent model, for example) and provides little helpful data from
each study (such as a key finding or rate of acceptance).

**Our response:** We have revised table 1 to present descriptive information about each paper by consent model. Some papers address more than one consent model and there is therefore some repetition across tables.

**Amendments to the paper:** Revised table 1

**Reviewer 3: Mihaela Matei**

**Major revisions**

1. **Reviewer’s comment:** Regarding the scope of the paper, it is not clear whether the intention of the authors is to focus their analysis on pandemic research or, more broadly, on acute illness research.

   If their objective is the epi/pandemic research rather than acute illness research, the literature review conducted by the authors are not relevant for consent issues in epi/pandemic research since only one paper out of 52 initially selected by the authors is related.

   This point needs further clarification and new developments. For instance, following Ebola outbreak, several publications have recently appeared dealing with research ethics in infectious diseases outbreaks.

   Having considered the above, I see two possibilities: one possibility would be to concentrate the paper on “acute illness” research with no mention of pandemics. One paragraph in the discussion section could mention and discuss the relevance of the study to pandemic research. Another possibility would be to remain in the field of pandemics and to update their review by extending the search to recent publications on Ebola.

   **Our response:** Our intention was to focus on clinical pandemic research that might be conducted in hospital and ICU settings. We agree that our rationale for this focus was insufficiently clear in the previous draft of our manuscript and have redeveloped sections of the manuscript to clarify this.

   Our focus for this work was on countries with an infrastructure to conduct emergency research and, in part, to inform protocol development for influenza pandemic research in Europe, and our search excluded non-OECD countries. We have not therefore re-focused the review on findings from the recent Ebola outbreak, which took place in a very different context. Efforts at research and treatment during the Ebola outbreak were significantly affected by the lack of medical and research infrastructure, as well as logistical
challenges. While there are certainly lessons to be learned from efforts to conduct research during this time, we feel it is beyond the scope of our paper to do justice to a full discussion of these.

**Amendment to the paper:**

- **Background:** substantial re-write of the background including in the final paragraph clarification of our use of alternative consent models used in emergency research as a proxy for those that might be used in developing pandemic research protocols.
- **Discussion, “Application to a pandemic context”:** We address the limited generalizability to pandemic context.

2. **Reviewer’s comment:** In addition, it is not clear why the authors decided to focus their review only on consent models used in emergency research. They seem to imply that the practical and ethical issues raised by the informed consent process in epi/pandemics or acute illness research are similar to the issues encountered in emergency research. Some authors have already pointed out the specificities of epi/pandemic research and argue that the two situations are not “ethically” equivalent. For instance, Ruth Macklin et al. argue that “procedures for obtaining consent from individuals in an outbreak situation could depart from those typically used in other investigations and still be ethically acceptable” (Conducting Research in Disease Outbreaks, PLOS, April 2009, e333) This option is not considered and not even discussed in this paper.

For instance, pandemic disease research in developing countries (e.g. Ebola virus epidemic) raises specific consent issues related to cultural characteristics. In addition, cluster research methods are frequently used in this context raising distinct ethical issues. Therefore it might be relevant and useful to consider and discuss in this paper alternative consent models, such as consent in cluster-randomized trials.

**Our response:** We hope that the revised version of the manuscript clarifies our context. We agree that the proposed use of alternative consent models is based on the level of capacity of the patients not of the urgency of the pandemic context.

We have now also included discussions on study designs, however, we have focused these on comparative effectiveness research and adaptive clinical trials. Detailed discussion of the ethical debates surrounding these trials is beyond the scope of our paper. However it does warrant further consideration, particularly as these designs are of interest to those developing pandemic research protocols. In the context of Ebola, there is
currently a debate about the best design for research conducted in the heat of an outbreak crisis.

**Amendments to the paper:**
- Background: final paragraph clarifying the basis on which we considered emergency research as a proxy for pandemic research.
- Discussion: see “Application to a pandemic context” subsection, paragraph 3 for discussion about different study designs that might be used.

3. **Reviewer’s comment:** Regarding the discussion, this section is mainly dedicated to recommendations. The specific ethical questions raised by this type of research are not addressed, in particular the ethical issues in relation to informed consent in pandemic/acute illness research.

In addition, if potentially important issues are mentioned in the first paragraph of the Discussion, like the discrepancy between participants’ and regulators’ views, comments on this point are rather scarce.

Another interesting finding of the study, which could be developed, is the importance of a direct experience of the third party consent model versus hypothetical scenarios.

**Our response:** We have added to our discussion in line with the above feedback.

**Amendments to the paper:**
- Discussion: see paragraphs 2 and 4 for additions to the discussion of ethical issues related to pandemic research
- Discussion: see paragraph 3 for additions to the discussion regarding discrepancy between acceptability of hypothetical scenarios and direct experience.
- Discussion: see paragraph 7 for additions to discussion of the discrepancy between potential research participant, clinical and regulator perspectives.

**Minor revisions**
1. **Reviewer’s comment:** (p.5, line 10) - The “rapid review” methodology is not necessarily known from every one. Even if corresponding and pertinent references are given (ref 12-14), it could be further explained in a few sentence

**Amendments to the paper:** We have added brief explanation of rapid review methodology in the first two sentences of the “Methods” section.
2. **Reviewer’s comment:** p. 12, line 6) Another interesting finding of the study not discussed is the negative correlation between the rate of acceptability of enrolment using deferred consent and the level of risk.

**Amendments to the paper:** Please see discussion paragraph 2 where we discuss risk perception and decreased acceptability.

**Reviewer 4: Don Willison**

**Major revisions**

1. **Reviewer’s comment:** The authors set out to identify literature that could inform research in the context of a pandemic. Only one paper was found that was specifically in the context of a pandemic. The remaining were settings like cardiac arrest, stroke, ICU, etc., involving emergency medical situations for individuals. While some lessons can be drawn from these cases to that of pandemic, the larger context of a public emergency involving mass casualties is very different. Under circumstances of pandemic or mass emergency, the regular norms around consent will likely be very different, as will be the capacity to invoke the usual protocols for development and implementation of the consent. Research during a pandemic may also involve individuals not immediately acutely ill but also at risk. In addition, research in a pandemic may involve interventions on a population-wide basis and not just on select individuals within the population. These concerns about generalizability of findings to a pandemic context are not given sufficient attention. While the authors touch briefly on this in the Conclusion section of the paper, there is a need to address this more completely and directly in the Discussion, Limitations, and Conclusion sections of the paper.

**Our response:** Our intention with this work was to scope the literature on acceptability of consent models that might inform the development of clinical pandemic research conducted in hospitals and ICUs. We accept this was insufficiently clear in the previous iteration of the paper and have now reworked the background of the paper to set this stage more clearly. There is none-the-less a question, as raised by this reviewer, about the generalizability of our findings to that of a pandemic context and we have included discussion of this in our revised manuscript.

**Amendment to the paper:**

- Background: we have substantially re-worked the background section to better set the context for this work.
- **Discussion:** see subheading “Application to a pandemic context”, paragraph 1 for discussion on the limitations regarding generalizability of
our findings

2. **Reviewer's comment:** The authors identified 52 papers they considered relevant. The papers are quite varied. Thirty-eight of these are quantitative papers, 13 are qualitative, and 1 used mixed methods. The settings vary across studies. Some address hypothetical cases while others address actual patient experiences. This heterogeneity represents a challenge to summarize the findings. However, within the manuscript, there was very little description of these papers. While Table 1 summarizes each of the papers, an additional table that summarized common features across the papers would be helpful. Granted, the authors have made some statements about certain factors such as: actual cases vs. hypotheticals and the impact of risk of the research on responses, but it would be helpful to have a richer discussion around the papers themselves.

**Our response:** We have substantially amended the reporting of our findings in response to feedback on the need for additional contextual detail.

**Amendments to the paper:**
- Results: we have re-visited the results section providing greater contextual detail
- Table 1: we have substantially amended this to present additional study detail and to present these by consent model.

3. **Reviewer's comment:** In addition to the setting, how a question is framed can strongly influence how a survey participant responds to the question. This is particularly the case in the context of questions around third party, deferred, and waived consent for research. Therefore, before one can compare findings across papers, it is important to establish that the study contexts and framing of questions were sufficiently similar to be able to draw direct comparisons. Unfortunately, there is insufficient information provided to ascertain whether there is sufficient homogeneity in the framing of the questions across studies to draw comparisons.

**Our response:** We concur that the framing of a question and the context of a study can influence the way in which participants are likely to answer questions. This is in addition to other factors such as whether the survey was self-administered or interviewer led, and whether participants had direct experience of the study context. In determining the validity of individual study findings, we conducted a quality assessment that included evaluating study aims and methods in relation to their findings. Nevertheless the variability in design as well as reporting was a challenge in working with our sample and limited the kind of analysis we could do.
Amendments to the paper:

- Strengths and limitations: we discuss and highlight the heterogeneity in our sample and limitations of this.

4. **Reviewer’s comment:** Currently, the paper is framed as a quantitative statistically focused summary of the extant literature. Comments 2 and 3 above call for the addition of substantially more qualitative analysis of the data. For example, on page 13, under “waived consent”, in the paragraph titled “potential research participants”, the authors state: “Some studies suggest greater number of participants would be willing to take part [49, 53, 56], while others showed fewer numbers being willing to participate [55, 61]”. However, there is no further analysis of those five papers to examine what may be the cause of those differences.

Amendments to the paper: Results: we have re-visited the results section providing great contextual detail including, but not limited to, the point raised above – see Waived consent, potential research participants: paragraph 1.

Please don’t hesitate to contact us if anything should remain unclear.

Yours sincerely,

Nina Gobat, PhD