Author's response to reviews

Title: Patients' beliefs towards informed consent in low-risk pragmatic trials

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Author’s response to reviews:

Melissa Constantine, PhD
BMC Medical Research Methodology

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Dear Dr Constantine,

Please find attached the new revised version of our paper entitled "Patients’ beliefs regarding informed consent for low-risk pragmatic trials” (Ref No BMRM-D-17-00257).

We thank you for the opportunity to submit this revised version. Hope we have successfully addressed the reviewers’ comments. Below you will find our answers in red. In yellow are the sentences we have added/edited in the revised manuscript.

The manuscript has been reviewed and edited to ensure appropriate English.

We hope you will find this version suitable for publication in BMC Med Res Method.

Sincerely yours

Rafael Dal-Ré MD, PhD, MPH

Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or
requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Please also ensure that your revised manuscript conforms to the journal style, which can be found in the Instructions for Authors on the journal homepage.

Editor Comments:

Page 4, line 79-80 “…ethics committees could adapt….”, in this area “could” need to be qualified as it implies the ethics committees have the regulatory authority to make the adaptation. Need to clarify what ethics committees have this authority and if they do, what vehicle is is granted by i.e., US Federal Regulations? Is this interpretation per recently revised US federal regulations? Or is the authors intended meaning that ethics committees “should” adapt? Could and should have very different meaning.

We thank this editor’s comment. What we are conveying in this sentence is that RECs are entitled in both the US and the EU to consider the features of the trial under evaluation and to adapt the need to inform (or not) and the extent on all the 22 ICH Good Clinical Practice elements of informed consent. As it is well known, currently trial’s participant’s information sheet (PIS) are 15-page (or more) long; however, in van Staa et al (Ref No. 7) pragmatic low-risk trials, UK RECs accepted a 2-page PIS since they considered that a trial with two commonly prescribed medications need no extensive information on all elements. We think ‘could adapt’ is appropriate in this context.

Choppy writing. For example, page 4, line 83 had to be read multiple times to understand the idea that was intended by the authors.

To address this, we have divided the long sentence in two, that now read as follows (lines 90-97, marked-up version). “Although Research ethics committees (RECs) could adapt current informed consent requirements to the specific needs of the research, as was the case in two pRCT conducted in the UK with commonly prescribed medications where short (2-page) participant’s information sheets where used to inform potential participants [7]. However, research ethics committees with current regulations, RECs could never altered ( change to a verbal consent, for instance) or waived participant’s consent in the conduct of pRCT assessing the comparative effectiveness of commercially available medications.”

The main hypothesis of this work is stated on page 5, line 89-92, correct? If so, please replace “It was felt necessary…” with a statement such as “it is important to understand the difference in the views of patients with chronic health conditions as compared to non-patients…” (is non-patient considered the comparative group?).

We have edited the sentence as requested, that now reads as follows (line 102-5, marked-up version). “ It was felt necessary to assess It is important to understand whether having a chronic condition might influence individual views on written informed consent for low-risk
pRCTs, of special interest since this type of trial will be frequently conducted for the assessment of commonly prescribed drugs.”

No, non-patient was not the comparative group. This study has no comparative group.

Please explain how Netquest is a probability-based panel. With the abundance of on-line panels available, transparency in panel recruiting methods and selection as well as sample selection is critical information to allow review of data quality. To my knowledge, there are only 2 probability based on-line panels available for use, and I do not recall Netquest being one of them. Please note why this may or may not be important given the study design and primary hypothesis.

We thank this editor’s comment and suggestion. We have added the requested information. The paragraph now reads as follows (lines 110-8, marked-up version).” *"The Spanish survey was administered to individuals belonging to Netquest (GfK group) panel (https://www.netquest.com/es/home/encuestas-online-investigacion). This panel comprises almost 200,000 people. Adult Spaniards with internet access are invited to join (‘single-use’ invitation) with the goal of ensuring a representative sample of the non-institutionalized civilian Spanish population. This was a probability-based online panel –except for the oldest (≥75 years) age group which is less represented than in the general population. The design, conduct and results of the survey have been explained in detail elsewhere [9].”*

Please spell out what REC is before invoking the acronym.

Done. Please see above

Table 1 and Figure 1 seem to present a different study samples. The demographics are provided in Table 1 for n=338, or n=85+85+85+85=340, while Figure 1 presents the recruitment for a study with 85+416+85+416+85+417+85+421=2010 completes

The study sample comprises 338 subjects (Table 1 figures)

In Figure 1 we depicted all subjects, both patients and non-patients. In the last line, boxes include both patients (HT patients = 85+85+85+83=338) and non-patients (Others: 416+417+421). We think readers should be informed on how we reached the final figure of all subjects that responded to the survey (n=2008) and how the HT patients we distributed by the 2 scenarios. Figure 1 helps to follow the information included in the first paragraph of Results.

What are the response values for the dependent variable, “recommend written or general notification/verbal consent”? The authors note the value of this dependent variable was dichotomized in the analysis, but if the response options used a 7-point scale that includes a midpoint value, the dichotomization of the response values needs further clarification.

It would be extremely helpful to include a table with the logistic regression results.
We thank this editor’s comment. Our text was confusing. To prevent any misunderstanding, we have added a sentence and separate the paragraph in two. Now it reads as follows (lines 127-33, marked-up version). : “In the hypothetical scenarios presented to respondents, the primary outcome measures were the respondent's recommendation to the REC (“If you were to give advice to the REC, would you recommend written consent or general notification/verbal consent?”) and the respondent's preference (“If you were a patient in this hospital, which would you personally prefer, written consent or general notification/verbal consent?”). Responses to both questions were ‘definitely’ or ‘probably’ for both written consent and the alternative option.”

Respondents were asked to evaluate the trial by indicating whether they agree, using a 7-point scale (1=strongly disagree, 7=strongly agree), with the following three statements: a) “It is valuable…”

Now it is clear that the dichotomization was with ‘definitely’+ ‘probably’ preferring or recommending written consent vs the alternative option as stated on “Statistical analysis” (first sentence)

A table with the logistic regression analysis has been added as Additional file-3. The following sentence has been added to the text ((lines 216-7, marked-up version).): “A table with the logistic regression analysis is shown in Additional file 3.”

Reviewer reports:

Maureen E. Smith (Reviewer 1): This is a theoretical study comparing the acceptability of written consent vs general notification and written consent vs verbal consent. The study in the general population (of participants in Netquest, an online closed panel of individuals) was previously published. This study focuses on a subset of participants from the original study with self-reported hypertension and two low-risk pRCT for anti-hypertensive medications. The study compared each 2 consent scenarios; the tested consent with written consent in a RCT for two low-risk medications and 2 consent scenarios; the tested consent with written consent in a RCT comparing medication use take at different time points during the day.

The study contributes an interesting analysis to the understanding and use of various consents in clinical trials. The focus of the study is to understand what consent method participants in Spain will agree to for a low risk RCT. Written consent is described as possibly delaying and sometimes prohibiting RCTs. Whereas other forms of consent or nonconsent, in the case of general notification, may more easily allow for RCTs to take place and reduce selection bias. The preamble about the different forms of consent may seem to bias the population against written consent, however, this did not prove to be true based on the results. In brief summary, this study's results in patients with a mild chronic condition, hypertension, were not different from the general study of all participants.

Specific comments by section:
Abstract

Line 40, 2008 should be written out. Done

Line 50, the first sentence may read better by saying: As in the general public survey, most patients……..

This sentence has been edited. Now reads as follows (lines 54-5, marked-up version). : “As was seen happened with in the survey of the general public, most more patients endorsed written consent than the alternative option.”

Background

While informed consent is one aspect of the problematic issues related to recruitment of participants to pRCT, it is not the only issue. The ethical issues associated with not informing study participants thoroughly of the issues related to the trial, must also be mentioned. There is good reason for making attempts for consent to occur.

We thank this reviewer’s comment and we have addressed it adding a sentence. The whole sentence now reads as follows (lines 77-9, marked-up version): “Acknowledging that appropriately informing potential trial participants is a key ethical principle, seeking written informed consent could jeopardize the conduct of clinical trials.”

In addition, in the Background we referred to written consent in a number of occasions, since the regulations of both the EU and the US asked for it in almost all types of trials.

Line 75, trial should be plural

Done

Line 76, sentence after the comma should read, …written informed consent is asked from all participants.

The sentence has been edited, and now reads as follows (lines 85-7, marked-up version): “Currently, This fact, however, is not considered in both the US and EU clinical trials regulations, and for all types of trials, except for cluster-randomized trials, ask for written informed consent is asked from all participants.”

Lines 79-81, the sentence is difficult to understand. Needs to be revised, particularly starting at line 83.

To address this, we have divided the long sentence in two, that now read as follows (lines 90-97, marked-up version): “Although Research ethics committees (RECs) could adapt current informed consent requirements to the specific needs of the research, as was the case in two pRCT conducted in the UK with commonly prescribed medications where short (2-page)
participants information sheets where used to inform potential participants [7]. However, research ethics committees with current regulations, RECs could never altered (change to a verbal consent, for instance) or waived participant’s consent in the conduct of pRCT assessing the comparative effectiveness of commercially available medications.”

Methods

The methods were described elsewhere in a previously published study. The methods were appropriate for this study.

The netquest panel should be referenced with the website for readers of this article.

Done. Please see above

Line 95, 2008 should be written out (two thousand and eight) Done.

Statistical analysis is well described and refers to the previous article in which the full analysis is described. It would have been interesting to see if the primary outcome correlated with any of the demographic characteristics.

We thank this reviewer’s comment. We did not perform the possible correlation of the primary outcome with demographic characteristics due to the limited number of respondents (n=338; 83-85 respondents per group). This analysis was performed in the published article that comprises all the whole sample (n=2008)

Results

Line 151, the word any should be substituted for none Done

Paragraph lines 165-169, should reference the specific table. I don't see where these numbers are coming from.

These numbers do not refer to any table. They are placed here since they were not included in any table.

Line 194-196, should mention that this is not statistically significant

We thank this reviewer’s suggestion and have edited and now reads as follows (lines 219-21, marked-up version): “A large majority of respondents agreed that the described trial was it is valuable to conduct the study, with no statistically significant differences between the two scenarios: 90.6% in drug pRCT, 93.5% in dose-timing pRCT (Table 3).”

Line 197, the word pose should be replaced with face. Done
Discussion

Line 204, should read: …suggests that being affected with a chronic -but easily….. The paragraph has been edited.

The suggestion that the age distribution had something to do with inaccurate beliefs about participating in a RCT (lines 213-220) could have been tested with the data rather than hypothesized. This should also be mentioned as a later study.

We have added a sentence to address this suggestion (lines 255-7, marked-up version): “Perhaps The different age distribution (hypertensive patients sample being much older) could might help to explain these two differences; this could be object of a future study."

Line 221, the word do is not needed at the end of the line The word ‘do’ have been deleted.

I would have liked to see more discussion about why this population might prefer general notification as opposed to verbal consent. Is there something about the Spanish medical system that would make it more difficult to interact with a physician about the RCT? Other attitudes and beliefs must play a role in this finding.

We thank the reviewer’s comment, but the design of the survey cannot allow us to know what beliefs play a role on HT patients responses. In addition, and as we mentioned “the study design did not allow us to assess directly which alternative method (verbal consent or general notification) respondents would prefer or recommend.” [Remember that any respondent was asked to respond to 1 scenario: written IC vs verbal IC OR written IC vs general notification]

However, we have added the following sentence to address the first comment (lines 263-7, marked-up version): “The relatively high percentage of respondents in our survey supporting general notification (43%) versus written consent may be explained, in part, by the high trust the Spanish population has in physicians (95%) and in the universal public National Health Service (75%) [12], where the hypothetical scenarios were placed.”

The discussion about framing having an effect on responses, is significant, in my opinion. The description of the negative aspects of written consent was biased against written consent.

Line 261, should begin with the word it: Done

Line 268, belief should be believes Done

Stephanie A. Kraft, JD (Reviewer 2): The goal of this manuscript, i.e. to understand how patients with a chronic condition view various approaches to informed consent for low-risk pragmatic trials, is an important one. However, I have a number of concerns about the framing and interpretation of this manuscript, primarily related to the focus on the hypertension population. First, it is not clear whether this population was looked at because of the potential implications of having any chronic condition vs. having hypertension and therefore being familiar with the
specific medications described in the scenario. The authors give the first explanation in the background and the second in the methods, but they do not discuss whether/how the hypertension diagnosis could influence people's responses. A bigger concern is in the differences that the authors report as compared to the general Spanish population. They describe differences of up to 5 percentage points, but none of these seem to be meaningful even if they might be statistically significant. Overall, it's not clear to me that this manuscript adds anything meaningful beyond the results that are already reported from the authors' general survey of the Spanish population.

We thank this reviewer's comment. The sample of this study belongs to a large sample (n=2008) of Spanish citizens. The results of the 2008 respondents have been published as stated in the manuscript (Ref. No. 9). In the survey, respondents were asked to report if they were hypertensive and if they were being treated with antihypertensive medications. This report refers to those 338 subjects that acknowledged to be hypertensive and being treated.

This is relevant since the survey was designed describing two hypothetical pragmatic RCTs (pRCTs) on hypertension. One could hypothesize that being diagnosed and treated on a disorder that is the object of the hypothetical pRCTs could help respondents to understand the scenarios better than people that do not report this condition. This was the first reason to conduct this analysis in HT patients. The second one is that, as we mentioned in the Discussion, limited data (120 respondents of an online survey) (Ref No. 11) showed that only a minority of patients (38%) supported written consent vis a vis the alternatives (verbal consent, broad notification or no notification), when a survey in US citizens showed that a majority (77%) supported written consent (Ref no. 8). We felt it was important to know what were the beliefs of Spanish chronic patients on this topic, once we knew the attitudes of the general population.

As the reviewer stated, there were no differences between general population and HT patients believes…but this can only be stated once this analysis on HT patients was conducted.

Another major question is regarding the differences between these results and the results on the Nayak et al. survey, particularly regarding relatively low levels of endorsement for verbal consent. Do the authors have any hypotheses to explain this difference? Why would the support for verbal consent be so much lower than general notification?

The differences found between US and Spain responses were addressed on the published article (Ref. No. 9) in which we compared the results of both surveys. This study refers only to what HT patients believe regarding the need of obtaining informed consent in low-risk pRCTs. In addition, and as we mentioned “the study design did not allow us to assess directly which alternative method (verbal consent or general notification) respondents would prefer or recommend.” [Remember that any respondent was asked to respond to 1 scenario: written IC vs verbal IC OR written IC vs general notification]

With regards to general notification comment, we have included the following sentence to address it (lines 263-7, marked-up version): “The relatively high percentage of respondents in
our survey supporting general notification (43%) versus written consent may be explained, in part, by the high trust the Spanish population has in physicians (95%) and in the universal public National Health Service (75%) [12], where the hypothetical scenarios were placed.”

Some other specific concerns, which are likely addressable, include:

- The background section focuses on concerns about recruitment, which are of course important, but there is no mention of the ethical arguments for/against written consent. Some limited discussion of these arguments may be relevant.

To keep the extension of the Background to a reasonable limit and to focus readers attention to the objective of the study, we postponed the discussion of this to the Discussion. However, in the Background we have added a short sentence that mention it (lines 77-9, marked-up version): “Acknowledging that appropriately informing potential trial participants is a key ethical principle, seeking written informed consent could jeopardize the conduct of clinical trials.”

In addition, in the Background we referred to written consent in a number of occasions, since the regulations of both the EU and the US asked for it in almost all types of trials.

-Line 73 refers to "only 76% of participants," which is not a fair characterization ("only" almost never means "76").

In line 73 (83 in the marked-up version) we wrote: “…only 39% and 76% of potential participants wanted to be told about voluntariness and the purpose of the study, respectively [5].” We would have expected to have almost 100% of potential participants wanting to know the ‘purpose of the study’ they were invited to participate. That’s why, from our perspective, it is correctly written ‘only […] 79% of potential participants wanted to be told about […] the purpose of the study”

We disagree with the reviewer when stating that “"only" almost never means "76%"”. In fact, in many circumstances one could correctly write ‘only 76%’. For instance, when referring to infant vaccination, public health officials aim to achieve 90-95% of vaccination rates (that will ensure 100% effectiveness through vaccination + herd immunity); if in a community 76% of infants are actually vaccinated, one could appropriately write ‘only 76% of infants are …’

Similarly, the description of the Kraft et al. study in lines 221-225 is written in a way that it mischaracterizes the results of that study. These examples raise a more general concern that other literature may not be cited carefully

Kraft et al study refers to two populations (537 IRB professionals and 120 patients) and two scenarios (Medical record review and randomization). In our manuscript, we mentioned the results of those subjects (120 patients) relevant to the topic of our work (randomization) and what we try to convey to readers.

Our text includes the results of the third column (from the left) of Kraft et al Figure 2:
which clearly shows that among 'patients' 37.5%, 41.7%, 15.8% and 5.0% preferred discussion and written permission, discussion and verbal permission, broad notification and no notification, respectively

‘Randomization’ in Kraft et al study refers to: "A health system will compare the relative effectiveness of two commonly used FDA-approved drugs (Drug A and Drug B) meant to treat hypertension. Data are lacking on the relative effectiveness of Drugs A and Drug B in reducing the incidence of heart disease. Drug A and Drug B cause mild side effects that are similar in frequency."

We believe we have correctly understood Kraft et al findings on what patients responded when considering the ‘randomization’ hypothetical scenario. The edited text in our manuscript reads as follows (lines 258-63, marked-up version):: “These present results are somewhat surprising. Since the Limited available data on what do patients (120 respondents of an online survey) believed regarding consent to participate in a hypertension drug low-risk pRCT, showed found that only 38% of respondents endorsed written consent and 42% asked for endorsed verbal consent. In contrast, with 21% believing indicated that broad notification was sufficient (16%) or no notification (5%) was enough needed [11].”

-While this manuscript focuses on a EU population, the authors discuss a fair amount of US-based data and refer to US trials, but they do not discuss or even mention the US regulations. It would help to provide a bit of regulatory background early on.

We thank for this reviewer’s suggestion. We discussed on US data because, to the best of our knowledge, it is the only available. We do not believe there is the need to mention US regulations because a) it is already mentioned in the US papers cited in our manuscript, and b) our interest is the EU -where no data are available regarding the topic addressed in our work.

-The methods could benefit from some additional detail in this manuscript, rather than just citing to the other papers. Specifically, I would find it helpful to clarify how the scenarios were presented to participants - it is not clear, except for in one small line in the middle of the table that is easy to miss, that this was a hypothetical debate on a REC.

We tried not to include information in this manuscript that was included in the already published article (Ref No. 9). However, the Box and the whole survey (provided as Additional file 1) help readers to know how scenarios were presented.

In addition, and to specifically address the reviewer’s concern, we have added a second ‘hypothetical’ in Methods that now reads as follows (lines 120-6, marked-up version): “The survey started by explaining a hypothetical hospital in which all patients were informed through letters, brochures and posters on the simultaneous provision of care and the conduct of research (Additional file-1). Two hypothetical scenarios were assessed: two low-risk pRCT in hypertension, comparison of 2 drugs with similar risk/benefit ratio or taking the same drug in the morning or at night. Each scenario had two routes: written consent vs verbal consent; written consent vs general notification. Each respondent was randomized to one of the 4 routes”
Furthermore, a third ‘hypothetical’ has been added in the next paragraph (lines 127-32, marked-up version): “In the hypothetical scenarios presented to respondents, the primary outcome measures were the respondent's recommendation to the REC (“If you were to give advice to the REC, would you recommend written consent or general notification/verbal consent?”) and the respondent's preference (“If you were a patient in this hospital, which would you personally prefer, written consent or general notification/verbal consent?”).”

Finally, there were a number of places throughout the manuscript where the writing was quite unclear. The manuscript would benefit from thorough English grammatical review.

We thank for this and have followed the reviewer’s suggestion.