Author’s response to reviews

Title: Digital Pills: a scoping review of the empirical literature and analysis of the ethical aspects

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Author’s response to reviews:

Dear editor and dear reviewers,

We are very thankful to you and the reviewers for the effort and time put in the consideration of our manuscript. This has given us the chance to improve the manuscript. We have carefully considered all the insightful comments made by the reviewers and have made changes to the manuscript. In this process, we also involved another researcher that had already been previously contacted to support with data interpretation and the revision of the work. Given his additional contribution in the revision process, we believe he satisfies the requirements for authorship set out by your journal policies and have added him as a co-author. All authors have agreed to this decision and relevant document has been submitted as well. In the revision, we also changed the referencing in line with the modifications done according to the reviewers’ suggestions.

Please find a revised version attached to this submission as well as our detailed point-by-point response to the comments from both the reviewers. The line-numbers refer to the new version of the manuscript. We hope that these modifications satisfactorily address the reviewers’ comments.

Best regards,

Andrea Martani
On behalf of all the authors

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Reviewers’ comments and responses

Reviewer #1:

My initial reaction is that this is a paper that is ahead of its time. I also feel that this is a paper that misses the mark in what it could have been or done. It would have been more useful as a comparison between its "empirical" approach versus a more theoretical one (in the published literature), or in designing an empirical ethics study, or as a simple literature review. But as a scoping review, I find this work does not add much to the literature other than perhaps showing that scoping review methodology could be applied to looking at the ethics raised in clinical studies.

RESPONSE:

We thank the reviewer for this comment and the suggestions as to potential alternatives with respect to the design of this study, particularly that on comparing what is the difference between empirical and theoretical approaches. Since we did not begin with that aim, it cannot be included in our manuscript but is indeed a good “food for thought”. Although Digital Pills is a brand new technology and that a scoping review might have also been conducted in the future, our review at this moment does not preclude others from doing the same and in greater extent in the future. In fact, our work of presenting in a systematic way all the published literature concerning Digital Pills will contribute to an informed debate concerning the actual available evidence concerning this technology. It will stimulate further debate and larger reviews in the future on this topic.
Reviewer #1:

A scoping review is usually applied to looking at best practices in medicine or in aggregating findings to increase power across a number of studies. But given how new DP is and how few studies have been done on it, it seems like this particular study should be done several years in the future. This is also an ambitious project as very little in the ways of scoping reviews have been done in bioethics. It's an approach that could have been valuable if applied to areas where there is a lot of bioethics work such as on autonomy, or end of life issues.

RESPONSE:

We agree with the reviewer that scoping reviews are often used for different purposes than the one we had with this paper. We did not intend our review as a systematic one due to the broad nature of our study and because we did not have a very specific question such as whether digital pill improves efficacy. In terms of the few numbers of studies included in our review (N=18), this is uncommon, but not unheard of. For example, “Koskenvuori, J., Stolt, M., Suhonen, R., & Leino-Kilpi, H. (2019). Healthcare professionals’ ethical competence: A scoping review. Nursing open, 6(1), 5-17” had only 15 included papers. Or else, “Sundgren, S., Stolt, M., & Suhonen, R. (2019). Ethical issues related to the use of gerontechnology in older people care: A scoping review. Nursing ethics” had only 17. In our case, the low number of included papers is probably due – as the reviewer correctly points out in the next comments – to the fact that companies developing this type of technology do not often publish the studies they conduct. We thus made sure that we point this out in the limitations.

Lines [490-497] (copy-pasted below):

“Lastly, being our focus on published work of an empirical nature, we have not included all the literature of a theoretical nature, where many ethical issues concerning DP have been thoroughly discussed, and unpublished work. Companies developing DP might not publish some of the studies they have conducted in academic journals and the authors have no resources to contact companies and get such information. Yet, the purposes of this review were indeed to explore more empirical literature concerning DP and ground an ethical analysis in the elements emerging directly therefrom, in an attempt to bridge the gap between literature reporting on studies where DP were actually tested and the theoretical literature on this digital medicine.”

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Reviewer #1:

For a scoping review, this manuscript has a rather miniscule number of studies on which they rely. This paper made me think that perhaps it is too early in the study of DP to have a true scoping review. Much of this reads more like a literature review than a scoping review (even though scoping methods were used). At this stage in research, it strikes me that a lit review would be of greater applicability.

RESPONSE:

We acknowledge that the relatively number of included studies might seem atypical for a scoping review. As we pointed out above, several scoping reviews with an even smaller number of included studies exist. Moreover, we believe that underlining also the fact that there is little published literature concerning studies using DP is an interesting finding in itself, since it underlines that more published studies are needed to openly evaluate whether the promised benefits of Digital Pills can actually be put into practice. We have added this point in the limitations section.

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Reviewer #1:

One of the challenges that these authors faced in this review but do not acknowledge is that the vast majority of empirical studies of DP are not found in the published literature. Most of the work has been done by Proteus and other pharmaceutical companies through human factors testing. They admit that they only found one published study on this. That's because for most of these companies, the human factors testing is (a) a form of market testing and (b) required for regulatory review but is not something they would publish. My guess is that there are many studies out there that are not in cataloged literature. This should be noted in the limitations.
RESPONSE

We thank the reviewer for this important observation. Indeed, we have added this as a limitation, to make sure that eventual readers are aware that the low number of included studies might be due to the absence of published literature and not to the absence of studies per se.

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Reviewer #1:

The authors state that the gap they serve to fill is "an ethical analysis with a more empirically oriented approach is lacking." One of the challenges in this paper, however, is that they never define what they mean by "ethical analysis" or "empirically oriented approach." An empirical ethics approach would be looking at the knowledge, skills, or beliefs, but this paper does not do that. Their "data" is looking at articles that are not focused on ethics to identify what ethical issues are raised. That should require reporting a list of ethical issues raised, and noting in how many of the papers those issues appear. Yet, even that might be misleading because if a paper did not mention an ethical issue, that does not mean it wasn't raised in the study, it just means it was not reported. Thus, this method applied to raising ethical issues in non-ethics papers contains a fatal flaw in approach.

RESPONSE

We are happy for this opportunity to better clarify the purpose of our study and to clarify terminology. In this review, our objective was – alongside that of mapping all the published empirical studies concerning DP – that of mapping and analysing all the “ethically relevant issues” therein mentioned. We have now clarified how we carried out our ethical analysis from these non-ethics papers. We did not mean to find directly in the text ethical issues – e.g., we did not mean to identify whether “Study x” was mentioning the issue of “autonomy”. On the contrary, our objective was to identify those issues mentioned in the text that have a (bio)ethical relevance, which we defined as having a connection with one of the principles of biomedical ethics. We have now attached a supplementary file that describes our ethical analysis process.
“Although the ethical issues that the use of DP might generate are extensively discussed, the literature providing ethical analysis of DP is predominantly theoretical in its nature, whereas an ethical reflection based directly on the data emerging from studies where DP have been tested is lacking. With the objective to complement the existing theoretical literature, the purpose of this scoping review is twofold. Firstly, it maps published empirical studies where DP have been tested with patients, in order to provide an overview of the available empirical evidence on this digital medicine. Secondly, it provides - in the context of those studies - a discussion on the ethics of this digital medicine based on the data from the studies where DP were tested.”

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Reviewer #1:

Some of the criticisms of the empirical studies seem to demonstrate a lack of understanding of the process of testing new devices and drugs. The lack of "clinical validation" and requiring "ethical supervision" (p. 3) raise these doubts. What is meant by ethical supervision (IRB?)? These are also not required by regulation for medical devices.

RESPONSE

We appreciate that you have pointed out this passage, which we agree needs to be clarified to avoid confusion. In this passage, we meant to say that medical devices require - just like drugs, although the process itself is much different – to undergo an approval process before accessing the market. We thus modified the text accordingly.

Lines [52-54] (copy-pasted below):

“These products share some features with traditional medications – such as the fact that they need approval from regulatory bodies before accessing the market – but they also differ from them.”

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Reviewer #1:

On page 5, the authors say the problem with the ethics literature on DP (none of which is part of the actual review but is included in the background discussions) is that the ethical analysis are "predominantly theoretical and speculative in its nature." What the authors do not state is why this is a problem? Ninety percent of the bioethics literature fits this description. Does this mean that all bioethics literature that is not empirical should be dismissed? At this point in the paper, usually raising a concern like this would be a suggestion to do the empirical study—to survey paper on their beliefs, attitudes, and knowledge of DP.

RESPONSE

This is a very prudent input and without it our words could have raised unnecessary misunderstandings for the field. Naturally, we do not mean that 90% of bioethics work should be dismissed. We have modified our text as to avoid potential misunderstanding (see lines 109-113).

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Reviewer #1:

On page 6, in the method, the authors exclude all theoretical papers, but do not explain why? If their goal is to show the identification of ethical issues but most of the papers that do so are theoretical, then without an explanation of why only empirical studies are valid for doing this work, it feels like they were simply throwing out a lot of the work.

RESPONSE

As the reviewer correctly points out, it is appropriate to justify our choice not to include theoretical literature. For this reason, we have added clarification in the “methodology” section and in the “limitations”. In brief, the reason why we excluded theoretical studies is that the objective of our review, was indeed to identify all the studies where Digital Pills had been tested and ground an ethical analysis directly on them, rather than mapping out the ethical issues from the theoretical literature concerning DP.
See lines [132-135] and [490-497] (already copy-pasted above):

“We were aware that much literature of a theoretical nature had been published concerning ethical issues related to DP [28]. However, we decided to focus our research question only on empirical literature since our objective was to ground an ethical analysis on the published empirical studies where DPs were tested.”

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Reviewer #1:

Page 7, the authors do not explain what they do when there is disagreement on interpretation. The response of "debate" on page 8 is not an adequate answer to how disagreement was handled. Debate does not mean coming to consensus, or voting, or having a third person break the tie.

RESPONSE

The reviewer is correct in pointing out that we lacked to explain in the text how we solved disagreement. We changed the text accordingly explaining what we did in this part of the study in greater details.

Lines [184-193] (copy-pasted below):

“After two authors examined each paper independently, they coded all the information that they individually considered of ethical relevance. The authors then met another time to crosscheck the data they coded, they organised it according to themes and justified why they considered the different themes of ethical relevance based on a connection with one of the principle of biomedical ethics [31]. When disagreement emerged, this was solved through debate until consensus was reached. A summary of the reasoning behind the choice of themes and the justification why they were considered of ethical relevance is provided in the supplementary material [Additional File 3]. The authors then refined the specific themes and sub-themes to organise, collate and then report the ethically relevant aspects retrieved from the analysed records. These were then ordered in the categories defined by Klugman et al. [6].”

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Reviewer #1:

The list of "ethical issues" identified in here (Additional file 2) seem not to be evidently ethically relevant issues. Usability and need for training may be ethical in the sense of thinking about what is expected of users, but without an explanation (none of which is provided), it is not clearly relevant.

RESPONSE

We added as a supplementary file [Additional File 3] a document where we explicitly clarify why we considered all of the mentioned issues of ethical relevance. Our reasoning was based on Principlism.

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Reviewer #1:

I do appreciate the authors' comments that there simply is not enough evidence that DP approaches to medication adherence are more effective than other methods or that there truly are social benefits to this approach (pp. 17-18).

RESPONSE

We thank the reviewer for this comment. Indeed we believe that this is one of the most important findings of this review, which shows that there is a need of multiple-arm clinical studies where DP are compared with other tools to improve medication adherence and of cost-effectiveness studies, to see if they are cost-effective in monetary terms.

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Reviewer #1:

The authors note of the studies they review that they all suffer from small sample size (it would have been useful to have a count of total number of participants in all of the studies). However, it is ironic that they do not see the same criticism in their own work—this is a small sample size in terms of number of studies and in terms of number of aggregate subjects involved. On p. 17, the authors say, "…comprehensive evidence to thoroughly assess DP from an ethical perspective is lacking." This strikes me as saying two things: (1) There's not enough data or studies to do the sort of review they have attempted here and (2) the authors are not sure what an "ethical perspective" is. After all, that term is never defined in this paper and the benefits of an ethical perspective are not discussed. Do they mean ethics of research design? Identifying the ethical issues that affect patients, providers, and society? (I have doubts because in each of these sections they seem to focus on challenges presented by these devices and their implementation. In fact, the only ethical issues they really discuss are those of privacy). I wonder if part of the problem is that the research team does not consist of established bioethics scholars and only one has established expertise in qualitative research.

RESPONSE

We thank the reviewer for this comment. We have added the sum of the total number of participants in all the studies. As recommended in previous comment, we acknowledge that the included number of studies was limited, also due to the fact – as the reviewer also pointed out above – that the producers of the pills would not publish some of the studies they do. This has been added as a limitation. Similarly, we have also now added what we mean by “ethical perspective” and have incorporated a supplementary material that walks the readers through how and why we considering an issue to be ethical.

This also gave us the chance to change the sentence previously on p.17, which we made more concrete to avoid potential misunderstandings.

Lines [459-461] (copy-pasted below):

“This indicates that comprehensive evidence to thoroughly assess, for example, if the extensive use of DP can improve the cost-effectiveness of certain treatments in a given healthcare context, is lacking.”
Reviewer #1:

One things that is not made clear is why empirical studies are better at identifying ethical challenges than more theoretical papers. Given the results presented in this paper, it strikes this reviewer that theoretical papers may do the better job here because the published studies were (a) not focused on the ethical issues and (b) did not address many of them.

RESPONSE

The reviewer is right in pointing out our imprecise wording, which sometimes could cause misunderstandings. We did not aim at mapping the ethical issues already raised in the normative/theoretical papers concerning DP. We were aware that many ethical issues that are present in the theoretical papers would have not been present in the empirical ones. However, our objective was exactly that of having an ethical analysis based on the elements that emerge directly from empirical literature. This has allowed us, for example, to point out at one discrepancy emerging from the empirical literature: although “societal benefits” of the use of the pills are constantly mentioned, these are rarely substantiated either by the data of the single study or by any other thorough explanation.

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Reviewer #1:

The writers seem to be generous in their use of the term "ethical issue." For example, they suggest on page 16 that quality of life and evaluating effect of DP on that is an ethical issue. I would disagree on that categorization. I think the authors were expecting to find more ethics discussion in studies that were not designed to look at ethical issues. In fact, most of their "findings" seem to be about what these studies did not report than what they did.

RESPONSE

We thank the reviewer for this comment, which prompted us to add more detailed explanation. We added a document in the supplementary material with a justification why we consider the different themes as “ethically relevant”. Moreover, we improved the clarity of our process at the end of the methodological section of the manuscript.
Reviewer #1:

I think one valuable outcome of this paper that could have been useful is to compare the ethical issues raised in these papers against the issues raised in the theoretical papers. This analysis would have shown if there is a greater need for ethics to be part of empirical approaches to evaluating DP, or what an empirical ethics study of these issues should address. It would also provide some evidence for the claim that an empirical approach to ethical issues is necessary. However, I am not sold on the idea that finding the ethical issues raised in use studies is a valuable contribution to the literature and understanding. In fact, it appears that not a single identified ethical issue in this review was not previously identified in a theoretical paper, most of which refer heavily to published studies.

RESPONSE

We thank the reviewer for suggesting different ways our suggested approach could be of use in the future. We will definitely consider this suggestion for potential other studies on the topic of digital pills. For the moment, we agree that some of the points we cover in our paper had been identified in previous theoretical articles published on this subject. However, we also think that our contribution adds a different perspective. For example, at page 17 we point out how our scoping review permits to uncover a contradiction concerning the use of Digital Pills. In the studies, it is argued – at the same time – that patients will be free to decide whether to share their data or not (i.e. preserving privacy), but also that the benefits of having Digital pills (i.e. promoting beneficence) depends, to a great extent, on the fact that patients need to share their data. To our knowledge, issues like the latter had not been discussed in previous theoretical literature and thus represent an addition to the interesting and growing debate concerning the ethical implications of Digital Pills.
Reviewer #2:

The authors of this paper used a scoping review methodology of published trials of digital pills to examine the ethical issues discussed in these trials. This is a very well written and robust paper. I have very few suggestions and believe that it makes an important contribution to the examination of the ethical issues raised by digital pills. The authors provide a very thoughtful and critical examination of the ethical claims raised in these trials. The paper will make a very important and transparent addition to the field. I have identified a few minor corrections.

Background

* Line 83: should be "chooses"
* Line 131: should be studies

RESPONSE

We are grateful to the reviewer for identifying these typos, which we made sure to amend as suggested.

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Reviewer #2:

Methods:

* What was the concordance rate between the assessors at each stage?

RESPONSE

We thank the reviewer for pointing out this factor that we failed to report in the methodology. We added the concordance rate in the different phases of the study selection. Moreover, this prompted us to notice that we had made a slip up concerning the number of duplicates, which we also amended.
Reviewer #2:

Results:
* Line 196: studies
* Line 204: patients
* Line 206: define TB

RESPONSE
We are thankful to the reviewer for spotting these further mistakes, which we also corrected as it was recommended.

Reviewer #2:

Discussion:
* Many papers did not discuss challenges to the claims that privacy was protected through encryption. It would be worth discussing the limitations of encryption and informed consent in situations involving a complex technology in situations where there may be real or perceived coercion.

RESPONSE
Your thoughtful comment motivated us to reflect more on this issue. Here below we copied the new lines we added.
“On the contrary, the moral dimension of privacy, which is particularly relevant in the field of health data management [56], remains underappreciated. DP allow to monitor delicate aspects of people’s lives – such as the fact that they are taking medications for mental disorders – thus requiring that also other aspects of privacy other than data-security are considered – such as potential loss of control over the intimate sphere and disempowerment. This is particularly important to decide about the potential future use of DP in the regular clinical context. In the latter case, privacy might not be adequately protected only by encrypting the data, but it would require also making sure that patients do not feel indirectly coerced to use DP – for example because health insurances might require them as a condition to cover treatment costs or employers as a guarantee that workers are preserving their health [57]. Furthermore, the emphasis on the fact that privacy is protected at the technical level through encryption or the use of secure servers cannot overshadow the fact that personal aspects of private life are nevertheless monitored and thus potentially accessible to other parties. In this respect, it must be underlined that DP also collects lifestyle data, thus potentially exposing personal behaviour.”