Reviewer’s report

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

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Reviewer: Craig Klugman

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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.

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.

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.

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.
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.

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.

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.

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.

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.
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.

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).

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.

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.

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.
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.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
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I have been a consultant for a pharmaceutical company that works in the DP space. However that has been a fee for service arrangement and ended 6 months ago.

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