Reviewer’s report

Title: What do patients with unmet medical needs want? A qualitative study of patients’ views and experiences with expanded access to unapproved, investigational treatments in the Netherlands

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Reviewer: Alison Bateman-House

Reviewer's report:

This was an enjoyable paper on a topic largely missing from the scientific literature. I appreciate that it would have been hard to identify individuals who had first-hand experience contemplating whether to receive an investigational product via expanded access, and I think you did as well as you could with that situation. I do wonder if maybe you would have been more able to identify, if not individuals with first-hand experiences, family members of these if you had looked to the rare disease community? You may have tried and just not found anyone... I also wonder how the answers of rare disease patient respondents would have compared with your respondents, among whom cancer was relatively common. I think that different patient groups might have different experiences/attitudes/perceptions should be noted in the discussion.

The references utilized are largely from the United States, but the interviews were conducted in the Netherlands, and different terms from around the world (named-patient programs, compassionate use, expanded access) are utilized throughout the paper. The paper would benefit from a short explanation of how access to investigational medicines is handled in the Netherlands and if there are country-specific issues that readers should know (for example, it is not until late in the paper that I saw mention that hospitals are typically not interested in patients paying out-of-pocket for items not covered by insurance, which obviously could have implications for why more doctors do not tell their patients about possible non-trial experimental options). The terms named-patient programs, compassionate use, expanded access are used more or less interchangeably, but this, from page 18, makes it sound as though there are differences, so please explain: "Respondents had very little personal experience with expanded access, neither with compassionate use programs nor with named-patient programs."

Regarding the funnel image, please explain: is this a visualization of what most Dutch patients experience? Couldn't a patient try a clinical trial earlier in the chronology, or is it just that such a thing wouldn't normally happen? Is there data to support this chronology as being the norm? I'd add some citations here or state that this diagram is constructed from the experience of your respondents or otherwise present some justification for this chronology. (Which I don't disagree with, but I'd like to know that it has some basis.)

Participants in F1-4 were considered to be lacking in health literacy; was there formal or informal assessment of this? It seems as though you were talking about their health literacy in general, not just awareness of expanded access, but on page 29 it says, "Respondents were well informed." Please clarify: maybe the respondents from page 29 weren't the folks from F1-4?
In general, throughout the paper, "respondents" appears to be used to describe both those in the focus groups and those with whom semi-structured interviews were conducted. However, it sounds like only the semi-structured interviewees had first-hand knowledge of expanded access. As such, I think it should be made more obvious whether the respondents being quoted are expanded-access naive or expanded-access familiar. For example, I assume the patient who took part in a Phase 1 trial (pages 21-22) was one of your semi-structured interviewees, not a focus group member, given her experience with expanded access, but on first read of this paper I took her to be a focus group member. Given the possible differences in attitudes and knowledge between those are who expanded access-naive and experienced, I think it is important to make it quite clear from which group a respondent is.

As mentioned above: do you think the expert patient focus group's discussion was colored by the fact that all the members had cancer, while it seems likely that F1, F2, F3, and F4 had one or more non-oncology patient? Same question about the individual interviews: do you think your takeaways from these were colored by the fact that the only disease involved was cancer (as opposed to say, a rare genetic disorder...) (Any reason to think the cancer experience is somehow unique?)

On page 9, under "interviews," there is a statement "through members of our valorization panel...." What is this valorization panel? Who was on it, and what did it do?

Were the patients who participated in semi-structured interviews (i.e, those who were thought to have had some experience with expanded access) all from the same nation/healthcare system (i.e., were they Dutch? Were they from the same areas of the country as the patients in the focus groups?)

The patients report having difficulty getting second opinions or being referred for specialty care. Please explain for the non-Dutch reader if there are systemic barriers at play in addition to what the patients report in your study (dr's pride, believe the problem is psychological). For example, do doctors get paid per patient, so referring a patient elsewhere will result in loss of income? Patients report expecting doctors to be up-to-date: is continuing education required of Dutch physicians? A few more details to help understand how the patients' exceptions meet or run afoul of national realities would be helpful.

In the United States, it is my perception that most patients understand there is a difference between a local (community) doctor and a research hospital doctor, in terms of awareness of new treatments. Would such a distinction be made by your respondents? If so, when they are talking about drs going to conferences and knowing what's coming down the pipeline, are they talking about all doctors, the doctors they see for second opinions, or whom?

The crowdfunding phenomenon is alive and well in the US: is it in the Netherlands? Or is it something of concern but hasn't really happened yet?

Did myTomorrows have input into what questions were asked or what patients were included?
I would like to see revisions made to address the above questions, but I do not see these as major revisions. Rather, I think the paper is in good shape once these fairly minor changes/additions are made. Also there were a handful of typos/misspellings that need to be corrected. I look forward to seeing this paper join the published literature on expanded access!

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

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

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