Author’s response to reviews

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

Authors:

Eline Bunnik (e.bunnik@erasmusmc.nl)
Nikkie Aarts (n.aarts@erasmusmc.nl)

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Response to the reviewers

We would like to thank all three reviewers for carefully assessing our manuscript, and the editor for giving us the opportunity to revise our manuscript in accordance with the reviewers’ thoughtful and helpful comments.

Reviewer 1: Alison Bateman-House, PhD, MPH, MA

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.

It would have been a good alternative to try to identify family members of individuals with first-hand experiences through rare disease patient networks. Instead we targeted our efforts at patient with severe diseases who may (at some point) consider expanded access, as we were mainly interested how patients would decide for themselves whether or not to try unapproved, investigational drugs.

In our focus groups, we had some patients who were knowledgeable about their condition (some of whom felt they were ‘more knowledgeable than their treating physicians’) and active in their patient communities, although we do not believe that these patients more often had rare rather than common diseases. We have underlined in our discussion that there may be differences in views and experiences between patient groups (see page 32).
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."

This is a good point. There are indeed differences between the programs in the Netherlands. However, as mentioned in the results: ‘respondents tended to speak interchangeably about newly approved drugs, off-label use of existing drugs, and investigational treatments within or outside of the context of a clinical trial.’ We therefore did not focus on the specific regulatory routes towards expanded access, but focused on specific elements (for example, level of evidence and setting of the treatment). We added a text box to explain how expanded access works in the Netherlands on page 7.

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.)

Before the interviews, we had already envisioned the circumstances (and the patient’s journey towards those circumstances) under which a demand for expanded access could arise. We added two citations on page 8 to papers in which second opinion and phase I clinical trial enrolment are discussed in the Dutch context, to support our visualization of the funnel.

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?

There was no formal assessment of health literacy. We changed the phrasing in the abstract and on page 29 (now page 32 and 33) for clarification.

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 who expanded access-naive and experienced, I think it is important to make it quite clear from which group a respondent is.

We appreciate the distinction made between respondents being expanded-access naïve or expanded-access familiar. Some of our respondents were more knowledgeable and experienced with regard to expanded access than others. The patient on pages 21-22 who took part in a phase 1 trial and is currently still using the investigational agent was a member of the expert patients focus group (FE). We made a change in the text to clarify that this respondent was a focus group participant (page 24), and another on page 36 to clarify that a respondent was an interviewee, and we explain on page 13 how first-hand experiences with expanded access were distributed among our respondents.

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?)

This is an interesting question. We are not sure whether the cancer experience is unique. When cancer is not (or no longer) effectively treated, it is progressive and life-threatening. We did notice differences between patients with life-threatening diseases and patients who had one or more serious, chronic diseases that were not life-threatening – notably, and understandably, a larger willingness to try unapproved agents (see page 34). But this may not be unique to cancer. For instance, we have had informal discussion with ALS patients, some of whom were part of our valorization panel (please see comment below), and noticed similarities between these patients and some of our respondents with cancer. We now note this as a topic for further research on page 37.

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?

A ‘valorization panel’ consists of stakeholders who offer feedback on the research questions, approach and results, and assist with the dissemination of the research results. Our valorization panel included representatives of patient organizations, physicians’ organizations, (hospital-based) pharmacists’ associations, trade associations for the pharmaceutical industry, and regulatory and health technology assessment authorities. The set-up of a valorization panel is a requirement of the Responsible Innovation program at the Netherlands Organisation for Scientific Research, which funded the research project (https://www.nwo-mvi.nl/showcase/value-valorisation-panel). The valorization panel serves as a counterweight to the collaboration with one or more private partners (in our case, myTomorrows), another central requirement of the Responsible Innovation program. We have added this information in a footnote on page 11.
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?)

Yes, they were Dutch and from the same areas as patients in the focus groups. We clarified this on page 11.

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 Netherlands, clinical guidelines specify when patients should be referred by their general practitioners to (hospital-based) medical specialists. For a range of rare medical conditions, patients may be referred on by medical specialists to centers of expertise for diagnosis, second opinion and possibly state-of-the-art treatment or clinical trials. Dutch medical specialists working in university medical centers are salaried employees and are thus not paid per patient. Salaries are capped. Medical specialists who are self-employed, either independently established/working in private practices (usually for elective procedures only) or working in peripheral hospitals (offering care that is covered by health insurance), may earn per patient or procedure. We have no indications to believe that loss of income is a reason for specialists not to refer on/refer for second opinion to any great extent in the Netherlands. Patients are generally well aware that they have the right to a second opinion. We added some of these details on page 18. Also, we added that continuing education is required of Dutch physicians (see page 26).

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?

Many of our respondents were aware of a distinction between large (teaching) and/or academic hospitals on the one end of the spectrum and small, so-called ‘peripheral’ or community-based hospitals. When they talked about doctors going to conferences, they talked about medical specialists in large hospitals/university medical centers. We thank the reviewer for pointing this out and explicated this on page 26.

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?

There is some anecdotal evidence of patients seeking treatment abroad using crowdfunding (i.a. in the US, Germany, Belgium, Georgia), mostly through newspaper reports or other media. The
UK Charlie Gard case was discussed in the Dutch media. The phenomenon has not yet been studied in detail in the Dutch context.

Dutch hospitals generally do not accept private/privately collected funds, and will provide services only when these are covered by health insurers. Health insurers are generally unwilling to cover treatments beyond standard of care. This limits Dutch patients’ ability to get treatments in their own country based on crowdfunding. We clarified this on page 34-35.

Did myTomorrows have input into what questions were asked or what patients were included?

The leadership of myTomorrows felt that it was not lawful to share personal/contact details of their patients with us, and consequently we did not speak to any of the patients who used their medications. myTomorrows thus did not have input into what patients were included, nor in what questions were asked. We did have individual discussions with many of their employees, some of whom did have first-hand experiences with investigational treatments, which was largely of the reason why they decided to apply for a job at the company. We did not include our notes from these informal interviews as we felt they may not have been representative of a larger group and were held in a different setting. On page 40 we now note that myTomorrows has not been involved in the design or conduct of the study, the recruitment of respondents or the writing or publication of this manuscript.

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!

Thank you for this recommendation.

Reviewer 2: Kasper Raus:

I think this is an excellent paper on an interesting topic. It is an interesting qualitative study that provides insight into the reasoning and attitudes of patients with unmet needs.

Thank you for the compliment.

My only remark would be that the paper is almost entirely descriptive and might perhaps benefit more from some ethical discussion. The discussion section of the paper is also particularly descriptive.

The purpose of this paper is to report the results of our qualitative study. In another paper we offer ethical discussion of recent developments in the area of expanded access. We now provide a reference to this paper in the introduction. Also, on page 36, we draw out the ethical implications of our findings.
My second remark is that I was somewhat surprised with the conclusion of the paper. On page 34 the authors remark that "this study does suggest that raising awareness of those opportunities would not give rise to a significant increase in high expectations or 'false hope'". However, the paper describes the example of a respondent who sold her house in search of a cure. On page 27, the authors describe respondents who are willing to go a long way to buy investigational drugs. On page 33 that authors state that in the face of life threatening illness patients would be willing to take more risks, even at small change of medical benefit. To me this does seem to suggest that there might be high expectations and perhaps even false hope... They claim not to have high expectations, but their actions seem to suggest otherwise. I am curious what the authors would respond.

Reviewer 3 has highlighted this inconsistency, as well. We would like to explain the origin of this inconsistency. In our individual interviews with patients who had first-hand experiences, we did find that respondents had been willing to go a long way (and were still alive). We had been studying the literature on developments in the area of expanded access, and much of the criticism had focused on the concern of false hope. When we held our focus groups with patients suffering from a range of serious, chronic, progressive, rare and life-threatening diseases, we found – to our surprise – that respondents, even when they did not understand the medical-technical details of investigational treatments, deliberated very carefully about the many conditions under which they would be willing to try or pursue investigational treatments. They were not particularly willing to risk the precarious equilibrium that they were able to maintain at the time (between pain and pain management, exhaustion and the energy to get through the day) by trying unapproved drugs. This may have been different for respondents who were facing death, who were often more willing to try treatments in light of small chances at medical benefit. However, there is a fine line between hope (in light of a small chance) and false hope (zero chance). We are not sure whether ‘false hope’ exists. This would be an interesting topic for further normative research. We note this on page 38.

When relevant, throughout the manuscript, we explained what findings are attributed what group of respondents (page 17, 18, 19, 21, 22, 25) and we nuanced the phrasing of our conclusions (pages 38-39).

Reviewer 3: Ghislaine Van Thiel:

This manuscript addresses the relevant topic of patients' experiences with and views on expanded access and other non-standard treatment options. The authors set out to address a relevant knowledge gap. The qualitative research methods are suitable and well executed.

Thank you.

I have three areas of comment: (1) definitions (2) presentation of results and (3) justification of the conclusion.

(1) Throughout the manuscript a variety of situations is discussed: the use of unapproved drugs, access to and participation in trials, the use of approved but not (yet) reimbursed drugs,
complementary therapies and non-standard treatment options. The results show that patients' knowledge does not allow them to make clear distinctions between these situations. However, the authors can, but they chose not to structure the results in such a way that would elucidate the patients views on each of these situations. This is in my view important because a patients' willingness to use an approved, yet not reimbursed drug is essentially different from participating in a phase 1 trial, which in turn is very different from a phase 3 trial. The confusion about the exact topic of the paper is therefore very present and makes the paper difficult to read.

- In the background section, the authors state that the use of investigational drugs is an 'entirely different option' than complementary and alternative medicine. However throughout the manuscript, these treatments resurface and it seems that patients do not think or know that these are so different. What does this mean for the main research question?

With this comment, the reviewer has touched upon a central problem with our interview and focus group study. While we were specifically interested in patients’ views and experiences regarding the use of unapproved, investigational drugs within expanded access programs, many of our respondents did not have first-hand experiences with expanded access, and had little knowledge of expanded access and of the differences between various types of ‘non-standard’ treatments. We explain this on page 8-9.

When we asked patients under what conditions they would be willing to try an unapproved, investigational drug, we tried to explain very clearly that we were not talking about participation in a clinical trial or about trying treatments for which a scientific rationale was lacking altogether (such as alternative and complementary medicine or treatments offered by quacks), but about using as a therapy a new drug that was under investigation, for which there was some but insufficient evidence of its safety and efficacy and which has not been approved for marketing. We made changes to explain this on page 9-10 and 21. Also in our discussion, we discuss this problem of lack of knowledge (see page 32).

In general, we chose not to focus on specific regulatory routes towards access to investigational drugs, but instead to focus mainly on patients’ considerations for wanting or not wanting to access investigational drugs, such as the available level of evidence, the setting in which the treatment is offered, and whether data is collected.

(2) The presentation of the results starts with the theme of patients experiences with standard of care. The paper is already quite long and the relation between this theme and the main topic is not well addressed. I suggest the authors provide a link between the theme and the paper's topic or omit this section.

This is a well-observed point. We discussed amongst ourselves whether or not to include this section in the manuscript. We felt that the section explains some aspects of the Dutch healthcare system that may be relevant to the reader (e.g. the hesitance (as of yet) towards malpractice litigation) and of the context from within which patients in the Netherlands start on a trajectory towards investigational treatments, the limitations they confront when offered standard of care,
which cause them to turn and seek alternatives, including expanded access. We made changes on pages 13 and 16 to explain this, and provide the link.

(3) The conclusion starts with reclaiming that patient understanding is low. I was really surprised to read the conclusion that 'The findings strengthen the notion that patient may be capable of making well-considered choices with regard to the use of unapproved, investigational drugs'. Of course, in theory every competent person may be capable to decide, but that is not what this conclusion refers to. In my view this conclusion cannot be supported by the results (minimum conditions for informed choice are not met). If the conclusion leans on the 'suggestion' that significant increase of high expectations or false hope will not occur: I do not see how this is supported by the results, or any other studies. The patients views seem to me to be all about hope and expectation. I would be interested in the authors’ motivation to draw this conclusion.

The other reviewers have also rightfully highlighted this tension in our manuscript. In our response to the third comment from reviewer 2, we explain the origin of this inconsistency. We changed the phrasing in our conclusion (page 38) to address this.