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Engaging patients in identifying risk factors for ALS

Aviad E. Raz [a,*], Iris Schneid [a], Efrat Carmi [b], Ofir Kedem [c], Boaz Lerner [c]

[a] Dept. of Sociology and Anthropology, Ben-Gurion University of the Negev, Israel
[b] Israel ALS Association (IsrALS), Israel
[c] Dept. of Industrial Engineering and Management, Ben-Gurion University of the Negev, Israel

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ABSTRACT

While policy-driven discourses promote patient engagement in research, its practice is severely limited. Drawing on participant observations and interviews conducted in 2021, we describe a process of research collaboration with amyotrophic lateral sclerosis (ALS) patients and their relatives to modify an epidemiological questionnaire on ALS, engaging patients as experts in the process of adapting the questionnaire to be patient oriented. The two versions of the questionnaire (the original and modified) were administered in the Israeli ALS patient community to explore hidden mechanisms of risk factors for the disease. Our findings demonstrate the process, measures, and impact of patient engagement on questionnaire modification and use. Our qualitative findings illustrate the participants' suggestions for new questions, feedback on biases and gaps, and an unmet wish to present the patients' life story. Our quantitative data illustrate how the patient-oriented modified questionnaire had more questions answered more comprehensively, as well as more identification, measured by patients' willingness to identify themselves when filling out the modified questionnaire.

1. Introduction

Engaging patients as experts in research about their health is considered increasingly important (Hamilton et al., 2018). Policy-driven discourses state that patients' lived experiences and knowledge should be engaged to enrich the quality, relevance, and impact of health research (NHS, 2013). Engaging patients, it is argued, can lead to improved research priorities, study designs, study findings, as well as healthcare interventions, and knowledge translation strategies that align better with patient perspectives (Frank et al., 2015). However, there is much less practical advice available on the planning and delivery of meaningful patient engagement (Walker et al., 2021). Given the dominant paradigm of expert paternalism and objectification in Western medicine, the call for "patient centeredness" has been interpreted in varied ways. Despite reported successes in engaging patients, studies have highlighted challenges such as tokenism and limited scope in the role and function of patients on research teams (Baines et al., 2019; Hahn et al., 2017). There is, for example, increasing use of patient-reported outcome measures (PROMs) as a performance metric for evaluating the quality of care on health outcomes (McGrail et al., 2011). This is particularly promoted in areas where there is no consensus among the research community on what testing methods to include as outcome measures in treatment trials, such as retinal degeneration (Lacy et al., 2020). Through Cochrane, patients have primarily been engaged as referees for specific reviews and during translation of report findings to plain language summaries (Morley et al., 2016). However, calls for engaging patients in research can also reflect a broader emancipatory stance, for example in the way it is advocated by the neurodiversity movement. Following the motto "nothing about us without us," neurodiversity activists claim that no research on autism should be conducted without autistic researchers on the team (Fletcher-Watson et al., 2019). A major barrier is that there are currently no validated measures to test the effectiveness of patient engagement interventions (Domecq et al., 2014). This paper seeks to contribute to the body of work regarding patient-based research by engaging ALS patients in the process of improving epidemiological surveys developed by health experts (Parkin Kullmann et al., 2015; D'Ovidio et al., 2017). Our overall intention is to make an argument about the epistemology of patient expertise; however, this is combined with a more technical argument about how research participants can help to improve patient questionnaires.

There is a vast literature on community-based participatory research (CBPR), broadly defined as a collaborative, partnership approach to

* Corresponding author.
E-mail addresses: aviadraz@bgu.ac.il (A.E. Raz), iris.schneid@gmail.com (I. Schneid), efrat@israls.org.il (E. Carmi), ofirkedem1@gmail.com (O. Kedem), boaz@bgu.ac.il (B. Lerner).

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research that equitably involves community members, organizational representatives, and researchers in all aspects of the research process (Israel et al., 2001, 2005). Using this approach, community members contribute their expertise to increase understanding of various topics, including health, with the ideal goals of achieving co-learning, shared decision-making, and mutual ownership of the processes and products of the research enterprise (Minkler et al., 2003). In addition, CBPR has been successfully employed in problems of health-care disparities in a variety of racial and ethnic populations (Viswanathan et al., 2004; Wallerstein & Duran, 2006).

In this paper we address the possibility of engaging patients in improving an epidemiological questionnaire that has already been developed by health professionals. In scientific survey terminology, this is part of the preliminary stages of survey validation, namely face and content validation. Face validation is the process of checking the questions in the questionnaire linguistically and analytically to find out what is supposed to be measured, where the researcher subjectively judges the operation of a construct used in the questionnaire. Face validity tests can also be conducted with selected respondents to know how easily and clearly they understand the items/questions in the questionnaire, including its feasibility, style formatting, readability, clarity in language, etc. (Carmines & Zeller, 1979). Content validation is a process of examining the contents of the items of the questionnaire to check whether they represent the entire theoretical construct of the designed model of the problem under consideration (Lawshe, 1975).

Focus groups and interviews with participants are often used as a strategy for survey item development, and the fundamental process for developing survey questions has always included qualitative approaches (Krause, 2002). Nevertheless, face and content validation of questionnaires, considered a golden standard of scientific research, are traditionally done by experts. Similarly, the currently accepted standard process for data mining methodology in medical machine learning represents an iterative process between experts: doctors and data scientists (Cabitza et al., 2017). This process includes understanding the database, preparation of the data, modeling, evaluation of the model, and deployment – without involving patients in any of these stages. To advance the science and practice of patient engagement, it is critical to develop measures to test the effectiveness of patient engagement interventions. Hence, this study reports on the process, measures, and outcomes of engaging ALS patients and their relatives in the validation of an ALS questionnaire.

2. Patient engagement in the context of ALS

ALS (Lou Gehrig's disease) is the most common adult-onset motor neuron disease. It is typically fatal within 2–5 years of symptom onset. The incidence of ALS is largely uniform (and relatively rare at about 1.9 per 100,000) across the world, but an increasing ALS incidence during the last decades has been suggested (Arthur et al., 2016). The cause of ALS is still unknown, but genetic, environmental, and lifestyle factors are all believed to play a role. It has been suggested that ALS may be associated with factors related to lifestyle choices, including smoking, intake of antioxidants, physical fitness, body mass index, and physical exercise, as well as co-morbidities and factors related to occupational and environmental exposures, including electromagnetic fields, metals, pesticides, and viral infections (Ingre et al., 2015).

Clinical research and trials in ALS are complicated by the heterogeneity of the ALS population characterized by patient variability in the disease progression rate, site of symptoms at onset, and survivability. Patient engagement is hence a particularly relevant challenge in ALS. This has been successfully demonstrated in the case of PatientsLikeMe, a virtual participatory platform collecting data from patient-members through self-tracking. In its early days, the platform hosted a community for only one condition, ALS, and allowed the tracking of a widely used, fixed list of 40 symptoms developed by clinical experts. The list captured the most common symptoms in the ALS patient experience as understood by the scientific community. However, drawing on the expertise of thousands of patients across the globe, it quickly became clear that many more symptoms, experiences, and circumstances characterize an individual ALS patient experience (Tempini, 2015). The PatientsLikeMe ALS study examined the impact of lithium carbonate in decreasing ALS progression and thanks to the high engagement of patients could be large and completed very fast over 9 months (Frost & Massagli 2009).

3. Methodology

3.1. Study design

This article reports on semi-structured interviews conducted in 2021 with ALS community members (patients and their relatives) in Israel, who participated in testing and modifying an epidemiological ALS questionnaire that has been developed by ALS researchers and clinicians internationally (Parkin Kullmann et al., 2015; D'Ovidio et al., 2017). The original questionnaires were themselves the product of a process of modification led by researchers, in which a questionnaire was compared to other relevant questionnaires, such as the Stanford University ALS Consortium of Epidemiologic Studies (ACES) questionnaire (ACES, 2015). In this process, questions were added or modified on topics such as alcohol and tobacco use, medical history, hobbies and pastimes, and pesticide and chemical exposures (Parkin Kullmann et al., 2015; D'Ovidio et al., 2017). Our attempt at engaging ALS patients and their relatives was a preliminary part of a broader project in which the modified ALS questionnaire was distributed in the ALS community and analyzed to discover latent variable models, which may shed light on potential ALS risk factors (namely factors associated with ALS). The fifth author and his group have already developed and implemented algorithms that have been successful in analyzing demographic and clinical data of ALS patients, leading to personalized health care predictions (Gordon & Lerner, 2019; Halbersberg & Lerner, 2019). As clinical and epidemiological data are added for patients, the algorithms, and thus the disease progression prediction, improve.

Following the interviews conducted with patients and their relatives, which are described below, we used the participants' input to modify the original version of the questionnaire (V1). We then used an internet platform to randomly direct participants to the modified (V2) and original (V1) questionnaires which were put online, and 66 respondents filled out questionnaires (see Table 2). We begin by describing the patient engagement stage of the project, and then move to discuss how we comparatively analyzed data from the two questionnaire versions, after their administration, in order to examine the impact of patient engagement.

3.2. Recruitment and sample

Following ethics approval, we contacted ALS community members through the Israeli ALS Association (IsrALS) network. The second author (a female PhD student in sociology with training in qualitative methodology and an interest in the research topic) conducted all the interviews. Nine out of ten interviews were conducted in Zoom and one interview with a patient was conducted through the WhatsApp smartphone application at her request, during which the questions were typed to the app

Table 1
Socio-demographics of pilot participants.

	Gender	N participants	Age range, (M)
Patients	Men	5	32-73 (63)
	Women	3	61-73 (68)
Relatives	Men	1	34 (34)
	Women	1	42 (42)
	Total	10	32-73 (65)

and were followed by the answers. This particular interview lasted 7 h, not including several breaks. The rest of the interviews lasted about 2 h each, and given the Covid-19 pandemic circumstances were conducted via Zoom, and recorded with the participants' permission. All the participants agreed to the recording as part of their informed consent. No one else was present in the interviews besides the participants and the researcher. Several shorter exchanges were conducted following requests from participants for clarifying parts of the questionnaire. Where needed, the interviewer made field notes after the interview, elaborating for example on the interview data, setting, and circumstances.

3.3. Procedures

Based on relevant literature, the research team (composed of three male researchers and two female researchers) prepared the interview guide for the semi-structured interviews. At the beginning of the interview, participants received an explanation regarding the purpose of the study to examine how joint completion of the ALS questionnaire can improve it. Then, the interviewer watched the interviewees fill out the online questionnaire, which was put online by the fourth author (a male M.Sc. student in data science who is undertaking a broader project to study risk factor for ALS) using the Jotform(https://www.jotform.com/) platform. The interviewer explained the questionnaire when prompted by the participants and took notes regarding their feedback. After filling out the questionnaires, participants were asked the following questions:

1. Do the questions we ask really help to focus on possible causes of the disease?
2. Do you think other, more specific questions are needed?
3. Did the questionnaire teach you something you had not thought of before about the disease?
4. Do you have anything else to say that might improve the questionnaire?

The questions were developed by the authors based on the literature review. Participants were also asked if they wanted to add anything else that they thought could contribute to the research. Each participant was offered 100 NIS (about 30 USD) as compensation for their time and effort.

3.4. Data analysis

The interviews were analyzed thematically to uncover discursive themes and categories of themes recurring within and across groups of respondents (Charmaz & Belgrave, 2012). We followed an exploratory, qualitative methodology, which is aimed at using unstructured, open-ended data, and is thus particularly appropriate for the current investigation. Our approach was to develop themes by constantly making comparisons and noting relationships among initially identified themes, inductively specifying and refining them, and then putting them in thematic categories or families. This iterative, reflective practice enabled us to extend existing theory on issues that have been largely understudied (Charmaz & Belgrave, 2012).

The research team discussed the initial interviews and agreed on themes emanating from them, which were then analyzed further inductively. Then in the next rounds of the analysis and discussions, some of the themes were refined. The research team did this together on the first few interview transcripts, discussing the relevance of the themes and agreeing on needed modifications and reclassifications. The second author completed the analysis of the remaining transcripts. In this manner, we collected data and analyzed them simultaneously, starting with the initial interviews and their analysis and following with an additional round of interviews and their analysis. Following the analysis of the first round of the interviews we made some mild changes to some of the questions, adjusting the phrasing for clarity and simplicity. We did not use a specific software for qualitative analysis. Participants were able to receive their interview transcripts for comment and/or correction, yet only one participant requested this.

We discussed new findings as they appeared and their relationships to the themes in team meetings, where agreements were reached to prevent the potential bias of a single rater. The iterations stopped after the first five interviews, when the authors agreed on all the themes and no new themes were identified, suggesting that theoretical saturation of the sample was achieved (Corbin & Strauss, 2008). Each of the themes is described below and illustrated with quotes from respondents, who are given pseudonyms. These quotes were translated by the first author from Hebrew to English. Quotes were selected because they were noted by at least two of the authors as examples that best captured the identified themes. We focus here on views presented concerning the contribution of patient engagement.

4. Findings

Of the 29 ALS community members who responded following the first recruitment ad (for patient engagement in questionnaire validation) we posted in the IsrALS online network, 19 ultimately refused to be interviewed or were unavailable, and 10 participated in the pilot (Table 1). This was the maximum number of participants that could be recruited. Two interviews were conducted with family members and eight interviews with patients. In four of the latter, the patient's relatives also participated in supporting the patient.

The following findings are organized according to the four major themes that emanated from the interviews: 1. Technicalities, 2. Biases due to proxies, 3. Misunderstandings regarding questions, and 4. New questions. Patient and their family members voiced similar opinions and these groups are therefore discussed together.

1. Technicalities

This was the most common form of feedback voiced by participants: technical comments that arose during the completion of the original ALS questionnaire (V1). What follows are typical examples. Participants mentioned that when answering the question "What is your age?" they do not see the numbers when writing the answer, and it takes a long time for the field to update. For the "income" field, all interviewees said they did not pay attention to the guidelines, initially recorded a monthly amount, and then had to change it into the required annual amount. Two interviewees were members of a kibbutz and did not know what their income was. Most interviewees asked why income was relevant at all to the pursuit of ALS risk factors. In the "Military Service" field, participants asked how to fill in positions they changed while in the military:

> "If let's say half of the service I was a fighter, and half of the service I was not a fighter, does that have any meaning?" (Z., relative)

In filling out the place where you were born and raised, interviewees who moved between places of residence had difficulty deciding which of the places to associate the answer with, the place where they were born, the place where they grew up as children, or the place where they lived the most years. The list of places of residence, which was important for potential associations to environmental risk factor, raised concerns for interviewees who had more than the allotted five places during their lives. As one of the respondents said: "Just in Israel it was 14 places" (N., patient). Also, not all localities were listed in the pull-down menu.

Another field dealing with the first symptom of the disease presented a difficulty for some of the interviewees because they had two separate symptoms at once. For example, one of the respondents (a patient) had both weakness and convulsions, and some hesitated and said it was just hard for them because it was a collection of symptoms. Other respondents mentioned a number of technical glitches regarding saving the questionnaire and returning to it at a later stage.

2. Biases due to proxies

Biases caused by filling out the questionnaire on behalf of the patient were indicated by our respondents. For example, in questions about the degree of stress in the workplace, several patients said that 'degree of stress' is a selective measure and may be misleading. If a proxy answers for the patient, without consulting the patient, based on how the patient is perceived, that might be a problem. One of the respondents said: "I worry a lot, but never show it, you know, everything is closed inside" (I., patient).

Another concern was inaccuracy in the information transmitted: "My father was exposed to lead when he swam in a river near Chernobyl. He cannot answer the questions anymore, but what if I didn't know that? Then the information would be missed" (Z., relative). Another respondent, who filled the questionnaire for her husband, said: "I do not have accurate information, so I figured, let's just write down something there and continue..." (I., relative).

3. Misunderstandings regarding questions

Some of the respondents commented on questions in a way that demonstrated substantial gaps between the original meaning of the question and the way it was understood. Many interviewees said they did not have a clear sense of purpose regarding most of the questions and therefore did not invest much thought in answering them even though it was very important for them to participate in the research and contribute to risk factor identification for future generations. For example, one interviewee – a patient whose wife filled out his questionnaire – said he disregarded the questions whether he came in contact with metals (such as lead) but told the interviewer that had he given it more thought, there might be instances of such contact, including "A tip of a pencil that got stuck in my hand and remains there to this day." Another respondent likewise commented that:

> "Questions need to be more focused so that we understand what you want to know … when I realize why you are asking this question and what it examines, I invest more in the answer and know better how to answer it … Let's say you are examining the connection between ALS and other diseases, if I knew about this then I would gladly take the time to give the background of all my diseases "(S., daughter of an ALS patient, speaking on his behalf).

Some of the interviewees asked the interviewer what the purpose behind some of the questions was. For example, N. (patient) described that as part of her work as a freelancer, she had jobs in many different cities, more than the five allotted fields where one was asked to provide details of where one has worked. She said: "I worked in many cities, it's enough, it's okay, and I moved to the next question. But maybe the real secret is in the sixth place I worked in? I would have liked to know what part of the data I should emphasize, the place where I did the job, or the job itself." Similarly in relation to the question of exposure to hazardous chemicals, one of the respondents mentioned:

> "It's about a lot of technical details, there could be relevant answers, but it needed a lot of double-checking, but I didn't give it serious consideration, I just thought about what I remembered easily. I guess it can't be one hundred percent accurate, and it didn't seem to me so important to do whole research about it. What you eventually write down in the questionnaire does not have to be exactly what happened throughout one' s life" (Z., relative).

The question about hazardous material exposure elicited various concerns from respondents. Some respondents asked for less details, while some asked for more. Respondents who worked in agriculture said there was not enough options concerning agri-chemicals. Respondents who were city dwellers working in a white-collar job said they did not pay much attention to that question, although they should have. Some mentioned options that were not part of the list, such as using aluminum utensils. Respondents suggested that adding an open field would be a good solution for such a problem.

Similar concerns were mentioned in the context of questions regarding personality traits. For example, one respondent commented:

> "In the personality questions, I thought more items should be related to stress, such as people who take on lots of responsibility. Or whether people are more introverted or extroverted. That could actually be related to stress and therefore to risk factors. There should have been questions about optimism or humor, although I'm not sure which is more suitable" (S., relative)

Respondents also had concerns regarding questions about the period before and after diagnosis. They asked why it was relevant to answer questions in relation to the period after the diagnosis: "Wait a minute, are we talking about the period before the disease or now?" For example, when asked about smoking, one of the interviewees did not know whether to record that he started smoking cannabis as a result of the disease. One of the interviewees said that she had a number of injuries close to the time of diagnosis and those served as warning signs for her that something was wrong. In her view, these injuries may be more relevant to disease progression than as risk factors for the disease. Another respondent said:

> "Two years ago, my father fell and got a strong blow, we do not know if … in retrospect it was the first sign of illness but then we did not know, he had dizziness and we linked it to the vertigo that came a few years ago" (S., relative).

Another example that was mentioned by respondents was diet. When a dietary change was made, after the onset of symptoms but before diagnosis, and the patient began to "eat extreme amounts of walnuts" – should it be regarded as a potential cause, an outcome, or something else? Many of the patients interviewed also mentioned that the questions about sports activities and hobbies were too general. The problem for many respondents was that the answers changed over the years, but the questionnaire did not have a relevant field to report this.

4. Suggestions for new questions

Respondents suggested adding questions with an emphasis on family and community life that address, for example, community and family support, and whether family relationships are regarded as a source of strength or tension. Another suggestion concerned adding questions about hereditary risk factors:

> "Focus a little more on the hereditary part, ask what types of diseases father and mother had, brothers and children, not just the patient. Maybe you can find a connection? Grandma died of a stroke but she also had diabetes all her life" (S., relative).

There were interviewees who highlighted additional risk factors based on personal experience. For example, one of the respondents mentioned that she had "a lot of X-rays … maybe that had an impact", an interviewee who was injured a lot in the past suggested asking about physical injury as a risk factor. Two interviewees noted that there was a connection to changing dietary habits. Everyone would have liked to see more questions about the symptoms of the disease, as well as the rate of progression:

> "Maybe you can include a question about the first symptoms of the disease, it's something I would expect … what the patient felt in the early stages, how quickly the diagnosis is given from the moment the symptoms appear" (B., relative).

Respondents suggested to extend the search for risk factors to examining disease progression, since questions about ALS progression can help in

"finding a connection between environmental factors in past and present occupations, in terms of activity, nutrition, and work … perhaps you will find there a link to the rate of disease progression, even if not to the onset of the disease" (L., patient).

Some respondents commented that they have already accepted ALS as a given, and it would be more interesting to find ways to improve the quality of life with the disease. When asked about the genetic test for ALS, most said they did not take the test. In contrast, relatives were (perhaps not surprisingly) interested in the genetic test and S., a relative, even argued that "All patients should have a DNA test done automatically."

At the end of the interview, all participants asked for information about the results of the study and said that it was very important in their opinion. One interviewee stated that answering the questions led her to the conclusion that a universal database of answers open to patients should be worked on so that they can compare their information and knowledge.

5. Administrating the original and modified questionnaire versions

Following the feedback from patients and their relatives, the research team deliberated about possible modifications, and created a modified questionnaire (V2) based on the input of participants. All the technical issues were addressed, and all the suggested questions were incorporated, resulting in more than 100 modifications. For example, questions about the disease, its symptoms and rate of progress were moved to the beginning of the questionnaire in order to better engage patients with the questionnaire. These questions were then repeated at the end, with the instruction "After filling out the questionnaire, do you want to add and/or refine any risk factors". Then, we published a second invitation through the IsrALS network to all patients (about 700 in Israel) and their relatives to fill out the questionnaire through a link we provided. The objective of inviting a spouse/partner to complete the questionnaire was to enable paired statistics to be performed on people who are likely to have similar environmental exposures; these statistics are used for comparisons with nonmatched controls, in line with the strategy of the original questionnaire (Parkin Kullmann et al., 2015). We used an internet platform to randomly direct participants to the modified (V2) and original (V1) questionnaires which were put online, and 66 respondents filled out questionnaires (see Table 2). At the beginning of the questionnaire, respondents signed an informed consent and could select the option of identification for future contact.

6. Aftermath

We now turn to describe both the qualitative data related to participants' perspectives on the process as well as the quantitative data we collected as performance indicators regarding how research participants can help to improve patient questionnaires. Participants commonly stressed the importance of having an accessible database: "Data based on the questions you asked might lead people to think of new directions" (M., male patient). In addition to illustrating the epistemology of patient expertise concerning ALS, participants' feedback stressed another common theme – narrating an ascribed positive identity for patients. Many of the participants (family members and patients) made spontaneous comments (often after finishing the questionnaire) referring to what they felt was lacking in the process in terms of addressing the real/authentic identity of patients: "I was frustrated that there were no actual questions about Dad" (F., daughter). In another interview (#4), with a male patient whose wife filled out the questionnaire for him, she provided more information on him to the interviewer: "[filling out the question about employment] When he was in the army, he was responsible for aircraft ammunition, he was giving commands but also helping others, giving an example to others, it was very important for him to be a role model for his soldiers." Similar conversation was used to fill out what participants felt was omitted from the schematic questionnaire; for example, "[choosing the level of work-related stress in the questionnaire] Level of stress … well … I can tell you it was really, really high. Once he got home and asked me: when did the kids grow up so much? […] it was stressful for him, being away from the family, but he never talked about it, he didn't want me to worry, always kept up appearances." Both comments focus on positive pre-ALS social traits which for the participant depicted the authentic social identity of the patient. In another interview with a female patient (age 73) who communicated through texting using a smartphone, the interviewee texted: "I want to tell my story, I am less happy with these kinds of questions [referring to the questionnaire]." To illustrate her point, the patient said: "[answering the question: "do you engage in sports (yes/no)] everyone said I was a good swimmer, I loved swimming … now I am too lousy. But I do hydrotherapy – does that count as sports? [interviewer: So, the next question here is would you define this as a hobby or an organized sport?] … This is to keep my organs from deteriorating … I hope for a long time to come … so let's say it's a hobby … " (R., patient, field diary and interview). This quote also depicts a wishful linking of pre-ALS and present behavioral patterns.

We compared the performance of V2 (the modified questionnaire) to V1 (the original questionnaire that was also administered in the pilot) by looking at identification and missing cases. Identification was measured according to the number of participants who agreed to identify themselves for future contact in case it was needed. Since respondents were randomly directed to the two versions of the questionnaire, with choice of identification presented at the beginning of the questionnaire, we assume that identification did not directly measure the effect of questionnaire modification. Indeed, identification rates in V1 and V2 were overall similar (60 and 66%, respectively), with slightly more identification in V2. There was considerably more identification amongst patients in V2, perhaps as a result of patients being more interested in or committed to the goals of the study (see Table 2). The missing cases ratio was measured according to the number of elective questions appearing in both V1 and V2 that were not answered or answered in a way that could

Table 2
Socio-demographics of participants in the original and modified questionnaires, and comparative measures.

Stage	Total	Relatives	Patients	Age (Mean)	Gender (F, M)	Identified participants (N of relatives, patients, overall %)	missing cases (all participants)	Missing cases per category of questions, for all participants
Pilot	**10**	2	8	59	4,6	2,8, 100%	0%	N/A
V1	**20**	12	8	51	14,6	7,5, 60%	26%	Symptoms and causes 15% Weight 45% Work 40% Place of residence 47% Sports 58%
V2	**36**	17	19	54	20,16	9,15, 66%	25%	Symptoms and causes 6% Weight 37% Work 30% Place of residence 25% Sports 47%
Total	**66**	31	35	N/A	38,28	18,28, 69%	N/A	N/A

not be used. The missing cases ratio was overall similar in both versions (Table 2). There were no missing cases in the pilot because the facilitator took care that participants fill out all the questions.

When we compared the missing cases ratio between V1 and V2 in specific groups of questions, in 5 (see Table 2) out of 14 categories the differences demonstrated a considerable improvement (measured by less missing cases) in V2. In addition, complex multi-choice questions on residence, work, and sports had a higher response rate in V2 than in V1.

7. Discussion

Our study demonstrated that patients and their relatives have a lot to contribute to the validation and modification of an epidemiological questionnaire, including feedback that focused on technicalities, biases due to proxies, understanding gaps, and offering new questions. We believe that the engagement of patients and their relatives was substantive even though they did not co-develop the research design and could not participate in the data analysis. Our assessment of the improvement is based on comparing performance indicators of V2 (the modified questionnaire) and V1 (the original questionnaire) by looking at identification and missing cases. As detailed in the previous section, there was slightly more identification in V2, with considerably more identification amongst patients. In 5 out of 14 categories of questions, there were fewer missing cases in V2. Importantly, complex multi-choice questions on residence, occupational history, and sports had a higher response rate in V2 than in V1. Evidently, a lot of the technical issues as well as the gaps in understanding could have been resolved by providing open fields in the questionnaire. However, this was not an option as the pursued analysis required standardized input based on pre-defined multiple-choice questions that can be coded and quantified. Although in principle this could have been done with an open text, it would have taken much more time and effort. In addition, replacing the standardized questionnaire with open fields was apparently too drastic for the quantitative researchers in the team, who were responsible for the data processing. Our qualitative findings illustrate how the formalities of the questionnaire contrasted the participants' motivation to give an authentic voice to patients (Strohminger & Nichols, 2015). While ALS is a progressive neurodegenerative disease, its effects are largely on motor functions, rather than on memory or other cognitive skills. Many of the participants' oral accounts elaborated on motor skills that had characterized the patient's life before ALS, but were lost because of the disease, like swimming or working. ALS patients and their caregivers, due to the nature of a condition that advances inexorably, are "left free to contemplate at leisure and in minimal discomfort the catastrophic progress of one's own deterioration. In effect, ALS constitutes progressive imprisonment without parole" (Judt, 2010, p. 15). The narratives we heard from participants were perhaps part of a reaction to this predicament, scrolling through the patient's pre-ALS life to remember them as they were.

There was widespread agreement that stress should be considered in terms of risk factors and might have a significant effect on the onset of the disease. While we separated the major themes for the sake of analysis, they were evidently inter-connected for the respondents. For example, many respondents mentioned difficulties to fill out the questions about hazardous material exposure (concerns which were coded under 'technicalities'). These respondents were also concerned about understanding this question's purpose. Some respondents asked for less details in the question, while some asked for more details. Clearly, the cognitive challenge of understating the question's purpose was inter-connected for respondents with the challenge of technically finding the proper way of filling out the question.

Participants also contributed significant new angles going beyond validation. For example, respondents suggested to extend the search for risk factors to examining disease progression. From the respondents' point of view, particular emphasis should be placed on the comparison between things that happened in the past and what happens *after* the discovery of the disease. For example, a change in dietary habits shortly before the disease was discovered could be arguably linked to attenuated disease progression. Additional new questions added by the participants touched on "family relations – whether they are a source of support or stress" (male patient). Based on participants' feedback, we added questions about relationships with parents, spouses, and children, as well as relationships at work.

While our study elicited relevant and important views from patients and their relatives, it has limitations. We tried to limit biases by presenting questions in a neutral format, having someone external to the ALS community conduct the interviews, and implementing systematic and transparent coding processes. Our sample size was relatively small and not everyone responded to our interview invitation request. Finally, as with all qualitative studies, the results presented here should be interpreted cautiously as they only reflect one group of patients and their relatives.

Our findings support the claim that people affected by a health condition, including associations of patients as well as associations for patients founded and led by relatives-cum-caretakers, can become valuable collaborators in research by tapping the experiential accounts of peers to make sense of their own experiences, and to evaluate and challenge medical claims (Frigeri & Montali, 2016; Whelan, 2007). The patient contributions described in this study regarding the validation and modification of the core clinical ALS questionnaire included feedback on content, length, relevance, and importance of questions, as well as suggested changes in scope and format. These contributions join a growing list of other potential contributions described in the literature, including assisting with topic prioritization, translating findings for lay audiences, and identifying clinically important outcomes relevant to patients (Gierisch et al., 2019).

8. Conclusion

There are many perceived and actual barriers to seeking robust patient engagement in research. Our study provides information on emerging practices that other research projects need to consider when approaching how to foster patient engagement. All parties should collaboratively outline goals, roles, and expectations. Members of the research team who are designated as facilitators of patient engagement should receive suitable training. Ongoing evaluation of engagement efforts is needed to assess the value this brings to both science and patient collaborators. Hopefully, this report on the process and outcomes of engaging ALS patients and their relatives in the validation of an ALS questionnaire will pave the way for more attempts to engage patients as experts. In the context of AI, this can also be implemented by engaging patients as trainers of supervised algorithms such as neural networks (Gulshan et al., 2016). With more implementation and mutual learning, we hope to see patient engagement becoming a staple of good science.

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Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

N/A.

Ethics approval

This study has been performed in accordance with the Declaration of

Helsinki and has been approved by the Departmental Ethics Committee at Ben-Gurion University of the Negev, # M-102-011120.

Consent to participate

Informed consent to participate in the study has been obtained from participants.

Consent for publication

N/A: This MS does not include identifying details, images, or videos relating to an individual person.

Author contributions

AR: Conceptualization; Methodology; Formal analysis; Funding acquisition; Writing - original draft; Writing - review & editing. IS: Data curation; Formal analysis; Investigation. EC: Data curation; Project administration. OK: Formal analysis. BL: Formal analysis; Funding acquisition; Project administration; Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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