Patient involvement in rare disease trial design

Small populations making a big difference

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Chapter 4

The POWER-tool: recommendations for involving patient representatives in choosing relevant outcome measures during clinical trial design
Abstract

Background
In clinical trials, it is relevant to ask patients and/or their caregivers which aspects concerning their disease they consider important to measure when a new intervention is being investigated. Those aspects, useful as outcome measures in a trial, are of pivotal importance for the result of the trial and the subsequent decision-making. In rare diseases the choice of outcome measures may be even more important, due to the small numbers and heterogeneity of the patients that are included.

Methods
We have developed a tool to involve patients in the determination of outcome measures and the choice of measurement instruments. This tool was developed together with a patient think tank, consisting of a group of rare disease patient representatives, and by interviewing end users. We have road-tested our tool in an ongoing trial, and evaluated it during a focus group meeting.

Results
The tool consists of three steps: 1) Preparation, 2) Consultation of patients, 3) Follow-up during which the consultation results are implemented in the trial design.

Discussion
The tool provides guidelines for researchers to include the patient’s opinion in the choice of outcome measures in the trial design stage. We describe the development of the POWER-tool (Patient participation in Outcome measure WEighing for Rare diseases), and first experiences of the tool in an ongoing trial.

Keywords: Outcomes; Patient involvement; Rare diseases; Trial design
Introduction

Involvement of patients in the early stages of research is increasingly becoming a priority in the medical field (1, 2). The active involvement of service users, patients and patient representatives (for an overview of definitions that we use in this paper, see Used Definitions at the end of this paper) has become embedded in the medical research practice more and more (3-5). For example, models on how to involve patients in the early stages of health research on a more structural basis have been developed, such as the Dialogue model, that focuses on setting the research agenda (6, 7). In addition, on a European level, EURORDIS actively promotes the involvement of patients in research, for example by organizing a summer school for patient representatives including workshops to increase their knowledge of research processes (8).

There are several ways in which patient participation in medical research can be beneficial. Although there is no structural evidence that patient involvement actually improves the efficiency of medical research (9), examples exist of projects and research fields where the involvement of patients has made a difference (10-15). Patients may guide research into topics with more clinical relevance. Also, there is an ethical demand to involve patients in research on a more equal level (16, 17). A cultural shift is taking place, in which research in patients is replaced by research with patients, where patients are viewed as research collaborators instead of merely a source of data (18). One result of that trend is the growing appreciation of patient reported outcomes and attempts to quantitatively express subjective patient perspectives, which may enhance the direct patient voice in assessing the value of treatment and translate individual experience into evidence (19, 20). Finally, from an efficiency point of view, involving patients may potentially improve the usefulness of research, as it may help increase recruitment and retention rates.

An aspect of clinical research in which patients may play an important role is in the decisions about trial design aspects, and specifically the choice of outcome measures. The decision of what outcome measures are used in a trial is particularly important in randomized clinical trials to assess the efficacy of interventions. It is vital that the set of collected data is not only clinically meaningful but also captures, as much as possible, the total real-life impact of disease on an individual’s quality of life, which is only feasible when the patient’s perspective is included. Ultimately, such trials are aimed at improving patient care. Therefore, involving patients in the choice of when an intervention is considered efficacious seems not only logical, but also of pivotal importance for trial success. Also, when it comes to the conduct of outcome measurement in a trial, patients have the most hands-on experience in terms of invasiveness and burden to the patient. Some outcome measures, such as time-consuming questionnaires or outcomes based
on biopsies, can be used less often than non-invasive outcome measures, such as blood pressure measurements.

There have been many initiatives on involving patients in the choice of core outcome sets or the development of Patient Reported Outcomes (PROs), such as COMET (21), PCORI (22), OMERACT (13), COSMIN (23), ISOQOL (24), and ICHOM (25). Recently, a handbook was published on how to develop a core outcome set (26). In these initiatives usually there is a number of outcome measures to choose from. In rare or ultra-rare diseases, however, it may be the case that so little is known of the disease that very few or no outcome measures are known. For many rare diseases, no disease-specific measurement instrument exists, nor is it clear what could be a patient-relevant outcome measure. Generic measurement instruments are used but are often not very responsive, as they are often too broad in scope to be sensitive to the specific changes that an intervention may induce. Even disease-specific outcome measure tools may lack sensitivity when effects of an intervention show variation between individuals (27).

In this article we propose a method for collaboration with patient representatives during the design of phase II and III clinical trials: the POWER-tool (an acronym of Patient participation in Outcome measure WEighing for Rare diseases). During this collaboration, patient representatives together with other stakeholders can brainstorm on outcome measures and choose or prioritize them, when there are no standard sets of outcomes to choose from.

The model is intended for use in the research stage when a specific trial is in the design phase. We assume that the research agenda has already been set, preferably in collaboration with patients. The model could be used in the clinical phase of drug development, after preclinical testing, and when a phase I trial is in progress. However, preparations for the design of a phase II or III trial may already start earlier, and we recommend dialogue with patients as early as possible. Aspects of the POWER-tool may be used for this dialogue in an earlier stage. However, there are other models that may be more useful in the earlier stages, such as the Dialogue model for setting the research agenda (7), or the FIRST model (28). The use of outcome measures relevant for patients is particularly important in rare disease trials, not only for market approval or reimbursement decisions, but also to ensure that drugs are developed that really make a difference in the lives of patients with rare diseases.

We present the POWER-tool, and describe how we have developed it, including the evaluation of its first application in a focus group of patients with a rare disease.
Methods

The POWER-tool was developed in several stages. We started with a literature search, after which we made a few drafts that we discussed with a group of patient representatives (the Patient Think Tank). A later draft was evaluated with representatives of the EMA and a large pharmaceutical company. Finally, a draft was road-tested and evaluated during a focus group. Below, we will elaborate on each of these stages.

Literature search

First, we performed a scoping review relevant to our objective to develop a standard method to involve patients and their representatives in the choice and prioritization of outcome measures. Rather than being exhaustive, our literature search was aimed at finding research where an approach was used or tool was developed to involve patients in a structural way. We searched in PubMed under the terms ‘(“rare diseases”[MeSH Major Topic]) AND (( “Patient Participation/methods”[Mesh] OR “Patient Participation/organization and administration”[Mesh] OR “Patient Participation/trends”[Mesh] OR “Patient Participation/utilization”[Mesh] ))’.

Patient Think Tank

In three stages of the tool development we collaborated with the ASTERIX Patient Think Tank (PTT), consisting of ten patient representatives who have been educated about clinical research. Among its members are patient representatives in the area of (rare) cancers, Duchenne Muscular Dystrophy (DMD), Mucopolysaccharidoses (MPS), Alkaptonuria (AKU), Hemophilia, Primary Sclerosing Cholangitis (PSC), Cystic Fibrosis, and Fragile X syndrome, as well as a representative of EURORDIS. All patient representatives have experience in research, either or both as a patient and as a patient representative or researcher, and some of the representatives are fellows of EUPATI (29). The PTT is part of the research consortium ASTERIX (see also the website: www.asterix-fp7.eu).

A first draft of the tool was presented to the PTT in a face-to-face meeting, where we had a discussion on the contents of the tool. The main feedback from the PTT was that the tool did not include patients on an equal level as the researchers, and that patients want to be involved as early as possible, in all stages of research, starting with setting the research agenda. We decided to put more emphasis on the specific focus of the tool, i.e. the choice and weighing of outcome measures, and added the recommendation that inclusion of patients in research should take place as early as possible, preferably before the discussion about outcome measures takes place. Subsequently, a second version of the tool was discussed with the PTT during a teleconference. During this teleconference we discussed the content of the tool and who would be the most important stakeholders and final end users of the tool. Based on this discussion we decided to include also the patient’s view on practical issues of trial design in the tool, allowing patients or patient representatives to give their input before and after a draft protocol is made.
Feedback of end users
We discussed our tool in its final stage with a representative from a large pharmaceutical company, from whom we learned about the delicate interaction between patients and the industry when there is a possible commercial interest from the side of the industry. We also discussed the tool with three representatives from the European Medicines Agency (EMA). In this discussion, we focused on the role of the regulators in the process of choosing outcome measures, the interaction between the industry and regulators and the vision of EMA on patient participation. Based on this discussion, we decided that the optimal timing of use of the POWER tool is before scientific advice from EMA is obtained. Both the pharmaceutical company and the representatives of the EMA made no commitments to use the POWER-tool; the discussions were entirely non-binding.

Focus group
In order to test its applicability and for further improvement, the POWER-tool was road-tested among a group of stakeholders. As a first step of the preliminary POWER-tool, twenty five patients with Spinal Muscular Atrophy (SMA) who had recently participated in an investigator-initiated randomized clinical cross-over trial were invited by letter through the trial investigators for a focus group discussion about outcome measures. The initiators and investigators of this trial were asked to be part of the consensus round of the POWER-tool and the focus group also. Three participants and one partner accepted the invitation and took part in the focus group, which was moderated by an independent person, and two observers were present. During the consensus round of the POWER-tool and the focus group, two trial researchers and a research nurse were present. The principles of the POWER-tool that was constructed based on the literature search and the feedback of the patient think tank were followed. The day started at 11.00 and ended at 15.00 and took place in the SMA expertise center of the University Medical Center Utrecht. The second step in the preliminary POWER-tool was to discuss the aspects of the disease which had most impact on the daily life of the patients. Then, a discussion was planned on how to measure these aspects. The outcome measures and measurement instruments that were used in the trial that they had recently taken part in were discussed. The two trial researchers and research nurse joined the focus group during the consensus round. After the consensus round, the POWER-tool was evaluated by both the patients and the researchers. After the focus group meeting, the patients received a summary of the results on the outcome measures, and a list of aspects of the POWER-tool that were adapted according to their feedback. The focus group was audiotaped, anonymized, and a verbatim report was made of the part where the POWER-tool was evaluated. The evaluation of the POWER-tool was then qualitatively analyzed. For the analysis, the program MaxQDA was used. The transcript was coded by the first author and checked by the second author. A code tree
The POWER-tool

was developed, after which adaptations were made in the POWER-tool. The quotes used as examples in this paper were translated from Dutch to English and then checked by a native English speaker.

Results

Results of the scoping review

The search yielded seven articles. In addition, two experts in the field of patient participation and policy (both working for the Dutch Genetic Alliance VSOP, the Dutch national umbrella organization for rare, genetic and congenital disorders) directed us towards specific research articles. Finally, 24 articles were found through this further search, by reference checking and by consultation of experts. Of these articles 13 were selected and used for the POWER-tool: Two articles described existing models for involving patients in research, that were used as a guideline for the POWER-tool: the Dialogue Model (7), and the FIRST model (28). The participation ladder was used as a theoretical model for equal involvement (30). The other 10 articles were on topics such as interview and focus group techniques, patient involvement in research, or handbooks on consultation. These articles are referred to where applicable in the POWER-tool.

FIRST model

The FIRST model gives a description of the circumstances under which structural and equal partnerships between patients and professionals in health research projects can exist. The model was developed by research steering groups at the Academic Rheumatology Unit of the Bristol Royal Infirmary, in workshops as part of the Outcome Measurement in Rheumatoid Arthritis Clinical Trials (OMERACT) conferences (28). OMERACT is an international network of professionals and patients organizing working groups that decide on outcome measures in rheumatology research. Every two years there is an OMERACT meeting, in which patients have played an important role since 2002 (13). The FIRST model consists of five aspects: 1. To facilitate the role of patients as partners in team meetings at an early stage; 2. To identify partners, projects and roles; 3. To reach mutual respect from both the side of academics/researchers and patients; 4. To support patient partners in their role, which can be all actions to help partners to work and communicate in a successful partnership; and 5. To train partners (both patients/patient representatives and academics/researchers) in such a way that they acquire all basic research knowledge necessary to collaborate. Steps 1, 2 and 3 of this model were used as a guideline for the POWER-tool. Our preliminary POWER-tool was partially based on these steps.
**Dialogue Model**

In the Dialogue Model (7), four steps are described to realize patient participation, in particular for the setting of a health research agenda. These four steps can be used as a structure in the process of collaboration between groups from different backgrounds, such as patients and academics: 1. Exploration, a phase in which partners are identified, contacted and interviewed to assess their willingness to participate; 2. Consultation and prioritization, where partners (both patients/patient representatives and academics/researchers) are consulted in focus groups; 3. Integration, in which the input of the partners is analyzed; and 4. Follow-up, when the usefulness of the process and the input of partners is evaluated. Phase 2, the consultation phase, was used as a guideline for the POWER-tool. We have used this phase in our preliminary POWER-tool.

**Participation ladder**

Participation of patient representatives can be addressed on different levels. Only asking for the opinion of patient representatives can be considered participation, but this is not the level of participation intended by the POWER-tool. The participation ladder (Figure 1), originally developed for citizen participation in decisions by local authorities, can be used as a typology of levels on which patient representatives can be involved (30).

The participation ladder describes eight levels of involvement in three categories, where the lowest level 1 represents minimal involvement, and higher levels represent more equal involvement:

![Participation ladder diagram](Figure 1: The visual representation of the participation ladder)

The two bottom steps on the ladder are considered non-participation, where people, in this case patients or their representatives, are not enabled to participate. It is considered
that patients need education or ‘cure’, and patients are passive instead of active. The three middle steps, categorized as ‘tokenism’, indicate situations in which patients are involved, but not on an equal level. They can be asked for their opinion or be informed, but the final decision is made by (in this case) the researchers. In the levels depicted by the top three steps patients are on at least the same level as the researchers. In the highest step, the patients have more influence on the final decisions than the researchers.

Based on this model, we conclude that patients and researchers should work together on at least a partnership level, so that patients are not just consulted, but their opinion is considered to be of equal value as the opinion of the researchers (31). We have set up the POWER-tool to achieve such a level of collaboration.

Results of the focus group
The evaluation was attended by the three focus group participants (SMA patients), two personal care providers, two trial researchers and one research nurse. The relevant quotes are shown in Table 1.

Table 1. Relevant quotes of the focus group

<table>
<thead>
<tr>
<th>Results of the focus group</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quote 1</td>
<td>H: Because what did you think about being invited? P2: I already really liked that. And I think it.. it shows commitment that they ask us, to think about it with them. And that they are open to that. So the collaboration.. collaboration is maybe a bit too strong.. P1: So that they want to learn from us. P2: Yes, I really appreciate that. It does feel as if we are truly heard.</td>
</tr>
<tr>
<td>Quote 2</td>
<td>H: Well, if we were to talk, just as we do now, about how would the trial.. how would a new trial potentially be designed. What kind of things should we measure then.. P2: I think I would not do that with 20 people. H: Not with twenty people. P3: No, definitely not with twenty. I would consider six, max, or eight. But a bit more [than today] would have been nice. But just to hear more experiences. H: And not one-on-one? P3: No, but I think more people is better. Unless the topic is very private.</td>
</tr>
<tr>
<td>Quote 3</td>
<td>P2: I am sure, on a topic as that of today, I would [choose] a mixed group, because then you come to an average. P1: […] Because if you have SMA, but could still walk? That would be completely different.</td>
</tr>
<tr>
<td>Quote 4</td>
<td>M: And when the topic is thinking about aspects that are important to you, right, the limitations where you would want to see change, what we discussed this morning.. does the same apply? Or would you like to have more background information on that? Or is that slightly easier? P3: I think that is easier.. P1: I believe that is easier. Yes, that is very near, that is something that you deal with constantly. P3: Those are things that you know anyway, that you carry around anyway.</td>
</tr>
<tr>
<td>Quote 5</td>
<td>P: I think these are quite complex questions. It is not like.. it is blue or black, no, I think it is a question that you have to think about for some time. I cannot in a couple of days answer these questions just like that.</td>
</tr>
</tbody>
</table>
During the focus group, the evaluation of the POWER-tool was discussed. The evaluation of the POWER-tool was generally positive. The participants appreciated being invited (see Quote 1).

Three main topics came up, which led to the adaptation of the final version of the POWER-tool: 1. Number of participants and stage of the disease; 2. Individual interviews versus a group session; 3. Difficulty of talking about outcomes. Based on the first topic, on the number of participants and the stage of the disease, we adapted the preliminary version of the POWER-tool. We added in the protocol, in paragraph 2.c ‘Consultation methods for both days - Focus groups/brainstorm sessions’ that an ideal focus group should consist of six to eight people (see Quote 2). We also added, in paragraph 1.a ‘Who to invite?’ that patients in several stages of their disease should be asked to participate in the POWER-tool (see Quote 3).

For the second topic, a preference was stated for a focus group instead of interviews, which we have incorporated in the POWER-tool in paragraph 2.c ‘Consultation methods for both days – Interviews’ (see also Quote 2).

The third topic that was discussed during the focus group was the difficulty of talking about outcomes. We experienced that the patients were very comfortable in talking about the practical aspects and constraints of their disease (Quote 4), but it was more difficult for them to answer the question of how to measure these aspects. The participants reported that these were complex questions to them (Quote 5). Based on these remarks, we have chosen to split the POWER-tool into two sessions, as is described in the protocol in paragraph 2.a ‘Meeting 1: Outcome measures’ and 2.b ‘Meeting 2: Measurement instruments & practicalities’. We decided that the best results would be achieved when researchers translate the patient’s preferences in outcomes, that are formulated in the first meeting, into measurement instruments and a trial protocol, which can then be evaluated again with patient representatives during the second meeting.

The POWER-tool
The POWER tool consists of three consecutive steps, which are described below: 1) Preparation, 2) Consultation, 3) Follow-up. We advise that the consultation step takes place during two meetings, which can be held either online or face-to-face.
STEP 1: Preparation

1.a Who to invite?
We advise to aim for representation of all groups within a patient community, such as different generations of patients or parents, and patients in different stages of a disease, depending on the focus of the planned research (7), (32). Patients who have some experience with trials may be preferred, because these patients have more experience with measurement instruments and practical issues of a trial.

1.b Training
Before the consultation starts, patients/patient representatives can be given some background information on the planned research. This is mainly applicable to Meeting 2: Measurement instruments & practicalities in the consultation step (step 2). Researchers can send the patient representatives some research articles, or (preferably) a document that explains the background and the planned research in lay language. Patient representatives may also be stimulated to inform themselves through programs such as EUPATI. The researchers should keep in mind that not all patient representatives may be familiar with the performance and rationale of particular design topics, such as randomization (31, 33).
When researchers have never been in a cooperative project with patient representatives, they may need to be trained before the meeting, for example in communication and education skills.

1.c Expressing confidentiality and acknowledgement of the contribution
If any of the participants in the process does not feel recognized as an individual providing a valuable source of knowledge, he/she may experience a lack of respect (34). This could be discussed before step 2 (the consultation phase); in such a setting, patient representatives and researchers can state their expectations, and discuss whether these expectations can be met. One way of avoiding feelings of inexperience or inadequate knowledge from the patient’s side is to be conscious of the use of medical terminology. The use of jargon should be minimal, clear communication is most important.
Also, confidentiality is important for both parties. Patients or patient representatives may share personal details about their health, and researchers may share confidential information on the research and early results. When researchers are industry-based, it is important to make sure that they do not advertise their potential product. In the case of rare diseases, it is not unlikely that clinicians and patients know each other. Therefore, patients may prefer to use a method that ensures their anonymity, such as a Delphi method (35) or an anonymous online meeting. Such methods may be used instead of face-to-face meetings.
To attain an atmosphere of confidence and trust, the moderator of the focus group should be neutral to the topic, and have experience in stimulating all participants, and in particular patients and patient representatives into taking part in the discussion.

1.d Planning
We suggest planning and finalizing both sessions of the consultation phase before the intended submission of the clinical trial protocol to the IRB or ethics committee, or submission of the protocol for scientific advice from regulators (31). There should also be appropriate time between the two sessions, as it may be a very large investment for patients to come to a research site twice. In the invitation letter everyone should be informed of the goal of the meeting, so that they can prepare for the meeting and know what to expect.

1.e Budget
Before the consultation phase with patient representatives and the researchers is organized, one of the factors to consider is the budget that is available for such meetings. Depending on the available budget, one can decide whether face-to-face meetings are feasible, or if an online meeting is a better option. Travel reimbursement, the costs of a venue and possibly catering need to be taken into account.

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STEP 2: Consultation

Meeting 1: Outcome measures
During the first meeting of the POWER-tool, patients (and patient representatives) can have a discussion on which aspects of their disease are most important to them, and which aspects they would hope to see changed after an intervention. Questions that can be asked during this round, are: What is the influence of your disease on your day-to-day life? Where would you like to see improvements when it comes to your disease? Which aspects do you think are most important to be measured in a trial? After the discussion, we advise that the group makes a prioritization of the mentioned outcomes, after which a consensus round can take place on this prioritization.

This meeting should be planned before a protocol is written, so that the outcomes of the discussion and the consensus round can be used to write the protocol. The researchers can then decide on measurement instruments to complement the outcomes that are proposed by the participants in the POWER-tool, which are discussed in the next meeting.
Meeting 2: Measurement instruments & practicalities

The goal of the second meeting is to reflect on the protocol that the researchers have written. The choice of measurement instruments can be evaluated with the patients (and patient representatives). Also, patients can reflect on the feasibility of the measurement instruments, and on other practical issues of the trial, such as the number of measurements, the accessibility of the research site, etc.

In order for patient representatives to prepare for this meeting, they should be given the protocol beforehand.

Consultation methods for both days:

Intervews

When there are not many patient representatives for a particular condition, individual interviews may be the most information-rich method of consultation. There are several interview techniques that can be applied. The most common is the face-to-face interview, where the interviewee and interviewer meet in person. However, there is also the possibility of online or telephone interviews. In face-to-face interviews, the interviewer can make more use of social clues, whereas in online or telephone interviews, the interviewer has the advantage of being able to interview people who cannot be reached as easily otherwise, for example who live far away or who, due to their condition, are homebound (36). When enough participants can be found, however, a focus group may be preferred (see also BOX 2).

Focus groups/brainstorm sessions

A focus group may be a good option when several patients or representatives are available, and researchers are also interested in the interaction that can take place during a focus group. For example, people in a focus group communicate with each other, which may give researchers more insight in issues that are part of their everyday life than when patients are interviewed one-on-one (37). To succeed, one of the prerequisites for a focus group is that participants do not feel intimidated or patronized. It is of vital importance that all voices in a focus group are heard and taken equally seriously. Also, before inviting health care professionals along with patients in a focus group, the patients’ potential dependence should be considered carefully. A situation where a patient is not willing to speak up because his or her treating physician is also present should be avoided (31).

During Meeting 2: Measurement instruments & practicalities, researchers and patients or representatives together evaluate the feasibility of the protocol that researchers have written. To preclude feelings of intimidation and enhance confidence to speak their minds, patients and patient representatives should have an equal voice in this focus group. Patients are asked to give their personal view and experiences on outcomes and
on the feasibility of the chosen measurement instruments, and their input should be considered as valuable as the input of all others in the focus group. Ideally, a focus group should consist of six to eight people, as was recommended during our evaluation of the POWER-tool.

Delphi procedure
One of the key advantages of the Delphi procedure is that the participants are not directly confronted with each other. This can be helpful when patients or patient representatives prefer anonymity. Another advantage of the Delphi method is that, due to the lack of direct confrontation, people are more likely to think independently. In direct confrontations, there is less time to let arguments sink in, and the social interaction may cause people to be persuaded more easily (31).

In the Delphi procedure, questions are sent to the participants online (for example, through e-mail). Ten to 18 participants are recommended in a Delphi procedure. In the procedure, there are usually several rounds. The first round is the brainstorm phase. In this round, the participants can list all outcomes that they see as relevant. In the second round, these relevant outcomes can be narrowed down to the most important ones by all participants. In the final round, the most important outcomes will be ranked according to importance.

Consensus round
After the consultation of patients in Meeting 1: Outcome measures the group has not necessarily reached consensus on the most important outcome measures. Also, the choice of outcomes can have a substantial impact on critical trial design characteristics such as sample size, duration of follow-up and recruitment. The choice of outcome is thus related with the feasibility of the trial as a whole and the time it will take until results of the trial become available. Considerations of this kind may change the preference of different stakeholders. Therefore, as a next step, we advise to do a consensus round after Meeting 1. The aim of the consensus round is to reach consensus on a collective prioritization of outcome measures, with discussion or voting. There are several consensus round methods, such as the final round of the Delphi procedure or a nominal group process, where ideas of all participants are collected, discussed and then decided upon in writing (35).
STEP 3: Follow-up

3.a. Evaluation
After the final consensus round, all participants should get a chance to state how they have perceived the process, and evaluate the final outcome. Evaluation of the process can also be done in between rounds (31). If participants feel that they have not been heard, or disagree with how the process has been executed, the moderator may decide to repeat one of the steps of the POWER-tool.

3.b. Report: Keeping participants informed
Before, during and after the trial, participants of the process should to be informed on how their input is incorporated in the final protocol (32, 34). This can for instance be done through a newsletter (38). Also, participants may be interested in the scientific advice that has been obtained from a regulator after the process of the POWER-tool, and on the progress and results of the trial.

3.c. Transparency of the process
The outcome of the POWER-tool can be shared with a wider audience. For instance, when the trial protocol is described according to the SPIRIT guidelines (39), the process with which the choice of outcomes has been established can be described under Section 3a: Methods—participants, interventions, and outcomes.
Discussion

In this paper, we propose a tool in which patients and researchers together decide on, and prioritize, outcome measures in the design stage of phase II/phase III trials.

This tool is based on existing literature and input from patient experts. It is a proposal of how patient and researcher interaction could take place in the situation when there is no standard outcome measure available, or used outcome measures are not sufficient or not relevant to patients. This sets the POWER-tool apart from models where patients are included in the choice of outcomes or outcome sets where measurement instruments already exist, such as COMET (21), PCORI (22), OMERACT (13), COSMIN (23), ISOQOL (24), and ICHOM (25). It is also different from models where research agendas are developed, such as the FIRST model and the Dialogue model (7, 28). With this tool we hope to give tools to researchers who wish to include patients in the choice or prioritization of outcome measures. However, aspects of this protocol may also be used in an earlier stage, as we advise that patients and patient representatives are involved in the setup of clinical trials as early as possible. When the POWER-tool is applied in an early stage, it may change and/or improve the setup and outcome measures of a trial, and therefore improve the usefulness of that trial and reduce research waste. It could be an answer to the increasingly widespread need for patients to have an equal say in research that they, in the end, benefit most from.

An example where the input of the patients’ view has changed outcome measures in the research field is in the field of Duchenne Muscular Dystrophy (DMD). Until recently the most commonly used outcome measure in trials for DMD was walking ability, as measured by the 6-Minute Walk Test (6MWT) and the North Start Ambulatory Assessment (NSAA) (40). These measurement instruments are, among other instruments, recommended by the FDA and EMA guidelines (41, 42). However, these instruments can only be applied in ambulant patients, whereas most DMD patients lose their ability to walk by late childhood. Upper limb weakness usually occurs in a later stage of DMD. When patients were interviewed, the use of the upper limbs turned out to be considered a more important outcome measure by patients than walking ability. This inspired patient advocacy groups to develop a measurement instrument on upper limb functionality which eventually might increase the number of patients eligible for a trial (43). With the POWER-tool, these changes from less relevant to more relevant outcome measures for patients could happen more often and at an earlier stage in the field of rare disease research.
We have road tested our tool during a focus group with three patients who had already participated in a trial. Initially this was not the optimal timeframe to execute the tool; the actual trial had already ended and refinement/adaptation of the protocol was no longer possible. Nevertheless, for the testing of our tool this was no problem, as the discussion on relevant outcome measures and appropriate measurement instruments and the prioritization could still be held and evaluated. Participants of the focus group were generally very positive about the POWER-tool, although this may also be partly due to the setting of the focus group. The focus group was the first opportunity for patients to discuss among each other their experiences of participating in a trial, which they did enthusiastically. Also, they were generally very positive about being invited and the fact that they could provide feedback on the trial that they had taken part in. This may be causing some bias in favour of the POWER-tool, although being asked to provide feedback and think along with the researchers is also part of the POWER-tool. It is difficult to separate these aspects: maybe participants would also be very enthusiastic about a different method that involves them. Replication of this study and comparison with potential other tools is therefore needed in order to finalize the tool.

When it comes to the use of the POWER-tool, it would be best if end-users such as pharmaceutical companies and/or agencies such as EMA would endorse a protocol such as the POWER-tool. However, the interaction between the pharmaceutical industry and patients is very delicate, especially when large commercial interests are at stake. Regulations on collaboration between these two groups may differ from country to country, making the POWER-tool possibly more suitable in some countries compared with others.

The tool can be further developed in future trials, where it is used before the trial is performed, and preferably before the trial protocol is finalized. It can provide a valuable tool to use in clinical research, especially in rare diseases, to include patients in the design stage of trials in a more structural way. The tool could then be a useful tool for participation, changing the direction from research in patients towards research with patients.

**Used definitions**

**Patient representatives:** Persons with a relevant disease or close relatives of persons with a relevant disease who operate as active research team members on an equal basis with professional researchers, adding the benefit of their experiential knowledge to any phase of the project (definition adapted from the EULAR taskforce (36)).
**Patient’s organizations:** Not-for profit organizations which are patient focused, and whereby patients and/or carers (the latter when patients are unable to represent themselves) represent a majority of members in governing bodies. These could be either general umbrella organizations (e.g. representing either (European) specific disease organizations and/or national umbrella organizations) or (European) disease specific organizations (i.e. representing national organizations or individual patients on acute and/or chronic diseases) (44).

**Patient caregiver:** A person who is the primary caregiver of a patient, such as a parent, partner, child or other family member.

**Researcher:** A person or group designing a trial. These may either be academic or industry based researchers and clinicians.

**Outcome measure:** The measurable characteristic (clinical outcome assessment, biomarker) that is influenced or affected by an individuals’ baseline state or an intervention as in a clinical trial or other exposure (45).

**Measurement instrument (test, tool):** An assessment system comprising three essential components: 1) materials for measurement; 2) an assay for obtaining the measurement; and 3) method and/or criteria for interpreting those measurements (45).
References


44. EMA. Criteria to be fulfilled by Patients’ and Consumers’ Organisations involved in EMEA Activities. London, UK: EMA; 2005.