Patient involvement in rare disease trial design
Small populations making a big difference
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Chapter 5

Engaging patients in rare disease trial methodology development


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Submitted
Abstract

Background
Patient involvement in research projects has come a long way. In the European ‘ASTERIX’ project (Advanced Small Trial design for Regulatory Innovation and eXcellence) to develop methodology for clinical trials in small populations, we installed a Patient Think Tank (PTT) to include patients’ perspectives in new methodology for trials in rare diseases. In this paper we report on a qualitative evaluation of how both researchers and PTT members experienced this process. We focused on two main questions: 1. How did the participants of ASTERIX evaluate the collaboration between researchers and patient representatives? 2. What can be learned from the experience and to what recommendations for future projects does this lead?

Methods
We conducted interviews with 13 participants who were involved in the ASTERIX project, including junior and senior researchers and members of the PTT.

Results & Discussion
According to the participants, collaboration between researchers and patients has evolved throughout the project, and shaped the project positively. The main lessons are that patients should be involved as early as possible, preferably in the application writing stage, and that in the early stages a plan should be developed based on consensus about the patients’ role in the collaboration. Face to face meetings with interaction between the groups, where patients and researchers try to speak a language they both understand, are key to success of the collaboration.

Keywords: Patient engagement, Patient perspective, Rare Disease, Methodology
Introduction

Patient involvement in research is increasing (1-4), especially in the field of rare diseases (5). There are several advantages of patient involvement. For example, patient involvement in setting the clinical research agenda may increase clinical relevance of the research topics. There is also an impetus from medical journals and research funders that are introducing requirements for authors to account for the way they involved patients in a ‘Patient Partnership Strategy’(6, 7). Some guidelines for patient involvement in research projects exist (8-13). However, there is a need for practical guidance in research projects and accounts of best practices(14). In this paper, we attempt to draw lessons from a collaboration between researchers in the field of trial methodology for small populations and rare disease patient representatives, and formulate recommendations and best practices that may be used for collaboration between researchers and patient representatives in the future.

ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence) was a European funded project aimed to develop better statistical methodology for clinical trials in small populations (15), conducted between October 2013 and October 2017. One of the work packages (WP4) was about the use of patient level information and perspectives to enhance clinical trials in small populations. Specific goals were: ‘Optimize the use of patient registries to inform design’, ‘Deliver methodology to include patients’ preferences in the weighing of outcomes’, ‘Assessing the value of Goal Attainment Scaling to reflect the inherent heterogeneity in rare disease trials’, and ‘Establish methods to facilitate patient involvement in trial design’. The VSOP, the Dutch Alliance for Rare and Genetic Diseases selected and invited PTT members, in the first year of the project; members were chosen to represent a wide range of rare disease categories, including both acute and chronic diseases. All invited members, either patients or parents of patients with a rare disease, were selected because of their knowledge of clinical research methods, either because of their profession, by experience, or after training at EUPATI (http://www.eu-patient.eu/whatwedo/Projects/EUPATI/) or the Eurordis Summer School (https://www.eurordis.org/content/eurordis-open-academy). The patient representatives were involved with the aim of having ‘patient representatives collaborate with the researchers across the project to optimize the proposed research methods and ensure a process of constant feedback.’ (see also http://www.asterix-fp7.eu/patient-groups/).

Patient involvement in research can take place in all phases of the research cycle, from identifying research priorities and designing studies before their performance, to disseminating results, implementing research findings (16) and reviewing research papers (6, 7, 17, 18). Also, patient involvement can take many forms, varying from
asking patients’ opinions to making decisions together (19, 20). For decisions about study design, e.g. whether to perform a cross-over or parallel group clinical trial for a new treatment, patients’ input may be less extensive than for other decisions, e.g. about outcome measures and frequency of measurements. However, especially in rare diseases, involvement of patients in all aspects of clinical study design is needed to enhance the acceptability of design issues, and the chance of success of small clinical trials of pivotal importance for the development of therapy. That is one of the reasons why the ASTERIX Project Team installed a Patient Think Tank (PTT) in the course of the ASTERIX project. The PTT and its collaboration with the researchers in this project differed from many other, more disease-specific collaborations. Since the remit of the ASTERIX project was to develop novel methodology, there were hardly any clinical researchers involved in the project, and the PTT members represented a variety of rare diseases. In their daily work the methodological researchers in the ASTERIX project, most of them statisticians, would hardly ever encounter patient representatives for whom the consequences of design choices might be of great influence. Therefore, this project posed a unique opportunity to learn about the pitfalls and advantages of generic collaboration between methodologists and patient representatives. We have interviewed both researchers and patient representatives who were involved in the ASTERIX project, to answer two main questions: 1. How did the participants of ASTERIX evaluate the collaboration between researchers and patient representatives? 2. What can be learned from the experience and to what recommendations for future projects does this lead?

**Methods**

The interviews were semi-structured around four topics: 1. How did the involvement of patients in ASTERIX evolve over time? 2. What were expectations of the project members? 3. How did they evaluate the project? 4. What would be their recommendations for involving a patient group in comparable future projects? We have followed the SRQR and COREQ guidelines for reporting qualitative research (21, 22).

**Participants and recruitment process**

We interviewed 13 participants who were all in some way involved in the ASTERIX project. The group of participants consisted of five members of the PTT including one person who had left the PTT early in the project, four senior researchers, three junior researchers, and one member of the ASTERIX Scientific Advisory Board. We chose to include one member who had left the PTT early, to increase the variability of opinions on the PTT. The selection of participants was a convenience sample: it was an opportunity to be able to speak to this variety of persons involved in rare disease research as they were all part of the ASTERIX project.
Data collection
During the last three months of the ASTERIX project, the study participants were approached by two researchers. They were asked to participate in an interview about their experience with the collaboration between patient representatives and researchers in the ASTERIX project. All persons who were approached agreed to participate and gave their oral consent. The interviews were held between July and October 2017, by videoconference. Each participant was interviewed once by either CG and EV, or by CG alone. All interviews were recorded, for which the participants also gave their oral consent. The median interview duration was 27 minutes, with a range of 16 to 34 minutes.

Data analysis
The verbatim transcript of every interview was sent to the concerned participant to give the participants the opportunity to remove quotes that they did not want to appear in the final manuscript. None of the participants asked for quotes to be removed or changed. For the analysis, the program MaxQda was used. A code tree was developed, based on the interview questions and the main topics that emerged, to structure the interview coding process. Transcripts were coded by EV and CG together, as a way to achieve reliable coding, where one half was coded by CG and checked by EV, and the other half was coded by EV and checked by CG. The researchers met twice to discuss the coding. Any discrepancies were resolved by discussing the codes, until consensus was reached. The results of the analysis were shared with all the members of the ASTERIX project, and all participants agreed with the outcomes and recommendations.

Results

1. Evolution over time
During the ASTERIX project various face to face meetings were organized. The PTT was invited in six of these meetings between October 2014 and September 2017, as is shown in Table 1. The first of these six meetings, in October 2014, was primarily aimed to discuss the scientific work plan of WP4 (patient involvement); therefore only a limited number of ASTERIX researchers was present. The second, third and fourth meetings were general ASTERIX meetings including all collaborators, the fifth meeting was a joint meeting with two other consortia funded under the same call, hosted by the EMA in March 2017, see also http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/02/event_detail_001393.jsp&mid=WCO0b01ac058004d5c3, and the sixth the final ASTERIX symposium, in September 2017 (http://www.asterix-fp7.eu/agenda/symposium/).
In the stage of writing the grant application for ASTERIX, there was discussion on the role of patient representatives in the project. The name Patient Think Tank was chosen, and the PTT would have a slightly different role than for example the Scientific or Ethics Advisory Board. The idea was to involve the patient representatives in the working meetings of the project and not as an Advisory Board which is less directly involved in the work (Quote 1). The first PTT meeting took place one year after the start of the project, and at this meeting not all ASTERIX researchers were present, since the goal of the meeting was primarily aimed at discussing WP4 (patient involvement). The other researchers in the project did not have any interaction with the PTT until the next meeting several months later in Amsterdam. This slow start of the PTT was mentioned in the interviews by several participants of this study, both patient representatives and researchers.

In general, most interviewees agreed that the PTT should have been involved in the project earlier on, preferably in the stage of writing the grant application (Quote 2). During the writing stage, an organization that supports rare disease patient groups was represented. However, there were no actual patient representatives involved in writing the grant application. Representation of future PTT members could have guided the project towards more patient relevant topics in a very early stage (Quote 3), and could have prevented later questions and discussions about the topics to be addressed by the researchers.

During the first PTT meeting in October 2014 the researchers of WP4 presented their plans to organize a survey for patient organizations, with several examples of trial designs for small populations, and a draft model to involve patients in the selection and weighing of outcome measures in clinical trials. The PTT advised not to pursue the idea of a survey, since the topics raised by the researchers were too abstract for patient organizations to be able to respond to them. They made it clear that they expected researchers to propose the most efficient trial designs possible, and explain the design in the Informed Consent material in a transparent and comprehensive way. With regard to the draft model for patient involvement, their main criticism was that in this version patients were involved too late. During this meeting, the PTT voiced a strong opinion, which changed the way some researchers thought about the role of the PTT (Quote 4). Only during the second meeting, the Amsterdam meeting in January 2015, 16 months after the start of the ASTERIX project, the members of the PTT met most of the researchers for the first time. Interaction was stimulated through formal and informal settings, for example a pub quiz during dinner where people were assigned to groups randomly. The third meeting, in Barcelona, was specifically organized in such a way that interaction between PTT members and (mainly junior) researchers was maximized. Junior researchers were asked to present their work in lay terms and their presentations
were followed by discussion in small groups consisting of researchers and PTT members. The combination of formal and informal discussion and collaboration between the PTT and the researchers in a language they both understood during these two meetings was evaluated positively by both the members of the PTT and the ASTERIX researchers. The Barcelona meeting was emphasized as a turning point in the collaboration between the PTT and the researchers, where the collaboration shifted towards a more equal level (Quotes 5 and 6).

During the fourth meeting, this collaboration was continued. The last two meetings were not regular meetings of the project, but aimed at dissemination of the results to a wider audience. Therefore they are less informative in terms of the process of patient engagement in ASTERIX. Apart from the face to face meetings, several teleconferences were organized during which particular topics were discussed, including a list of questions raised by the PTT about the planned research of ASTERIX and suggestions for additional topics, such as re-using information from placebo arms and the evaluation of type I and II errors in rare diseases. The questions partly had to do with topics that had not been included in the ASTERIX work plan. During the final year of the project the PTT members collaborated with researchers on translating ASTERIX results into lay language in 7 information leaflets (http://www.asterix-fp7.eu/patient-groups/leaflets/) during several teleconferences and individual writing sessions.

2. Expectations

Many participants of this study, both researchers and PTT members, mentioned that they did not have any clear expectations of the collaboration before the onset of the project.

Several researchers reported not knowing what to expect because they had not been involved in a project with a PTT before (Quotes 7,8,9). Some researchers expected an effect of patient involvement on the outcomes of the project, because the involvement of patients would mean that the statisticians would have to focus more on patient relevant topics (Quote 10). One researcher hoped that patients would also get a better idea of what statisticians are working on (Quote 11).

Some members of the PTT had doubts about the reason why there was a PTT installed, they were also unsure what to expect and were suspicious that it would be ‘tokenistic’, that the engagement would be a showpiece without real significance for the project (Quote 12).

Some researchers felt that throughout the project, the PTT seemed to always expect more of them. They had the impression that the PTT members wanted them to develop
treatments whereas being statisticians, they were not able to contribute to that (Quote 13). Participants stressed that there should have been more discussion and agreement about concepts from the beginning of the project, methodological concepts as ‘type I error’, ‘power’, and ‘risk’ (Quote 14).

A conclusion that can be drawn from the interviews was that there should have been more structure from the start. For example, aside from agreeing on methodological concepts, a generally agreed common ground from where to start with the PTT and concrete goals would have been helpful. (Quote 15).

3. Evaluation
All interviewed participants praised the initiative to include patients in ASTERIX and the way this was done (Quote 16). Although involving a PTT in the ASTERIX project was evaluated positively, there were also some basic recommendations that the participants mentioned. For example, the start could have been better organized, both timelier and more structured. Even though the process and the aims of the collaboration with the PTT was a topic of discussion within the Executive Board before the start of the project, this discussion was not recorded and no formal plan was proposed.

In the end, the PTT members appreciated that they were heard and their comments were valued and that they had influence on the topics that were addressed (Quote 16). Also researchers evaluated the input of the PTT positively. One researcher gave an example where lessons learned from the PTT during the ASTERIX project were extended into her daily work (Quote 17). Others concluded that the groups would always ‘be on different islands’ but that this is not necessarily a bad thing (Quotes 18 and 19).

A theme that was frequently mentioned during the interviews was whether the PTT-members were equal to the investigators. The position of the PTT evolved during the project, resulting in more contributions by the patients in later meetings, and the development of mutual respect. A researcher concluded that the PTT could have had a more active role in the meetings, and that they should have presented their perspectives and wishes more often (Quote 20). However, the conditions of participation in the project for PTT members were not equal to those of the researchers. The work plan had been fixed before they were invited. In general, most patients and patient representatives are not paid for their work as a patient representative or for their presence at meetings. Their knowledge was inadequate to follow some of the more advanced statistical discussions. Other elements also play a role. For patients and in particular parents of children with a rare or ultra-rare disease, privacy can be an issue when they participate (Quote 21).
The level of involvement of the PTT members is shown in the output of the ASTERIX project. PTT members were involved as participants in a qualitative study investigating rare disease trial design aspects that are important to patients (article under review). Some PTT members co-authored an article on involving patients in the selection and weighing of outcomes in clinical trials (23). All PTT members participated in the designing and writing of ‘Patient leaflets’ explaining methodological issues of trials in small populations in lay language. One of the researchers stated that PTT members should have been part of the investigator team because then the collaboration would be more equal, and their perspective could be best included in the project. More researchers and members of the PTT shared the opinion that more and closer collaboration would have been better (Quotes 22, 23, 24). One of the PTT members mentioned that every research project should have a PTT (Quote 25).

The recommendations following from the analysis of the results are summarized in Box 1 below.

**The process of the involvement**
- Consider to involve patient representatives in the writing of the project plan. Involving an organization that supports patient groups in such a process may not be enough; patient representatives are closer to the patient experience.
- Consider to define goals and methods in the project plan for patient involvement and to describe how this work needs to be done.
- Consider to define the formal position of the patient group. Possible options range from ‘advisory’ to ‘binding’, with the role of consultation in the middle.
- At the start of the collaboration, consider to dedicate a (part of a) meeting on agreeing on the interpretation of concepts that are central in the project. Part of this effort is an exploration of which concepts are central for different groups and which perspectives groups have on particular terms. In the Asterix project for example ‘risk-benefit’ estimations, power, and p-value.

**Meetings**
- Face to face meetings are important. Consider to have a mix of informal and formal meeting opportunities. A mix of small scale subgroups and larger scale (plenary) activities is recommended, as is a meeting where researchers and patients present their plans to each other in a language that both groups understand. Such a meeting may be planned as early as possible in the project, maybe even before or at the start of the project.

**General**
- Consider to acknowledge the patient input by reimbursing the patient representatives.

**BOX 1. Recommendations following from evaluation of the PTT in the ASTERIX project**
Discussion

In this paper we evaluate the involvement of a group of patient representatives in a European project (the ASTERIX project) to develop novel methodology for clinical trials in small populations. We investigated two main topics: 1. How did the participants of ASTERIX evaluate the collaboration between researchers and patient representatives? 2. What can be learned from the experience and to what recommendations for future projects does this lead? Our main conclusions are that the collaboration between researchers and patients has evolved throughout the project, and shaped the project positively. The main lessons learned are that patient representatives should be involved as early as possible, preferably in the writing stage of such a project, and that in the early stages a plan should be developed about the patients’ role in the collaboration. Also, face to face meetings with interaction between the groups, where patients and researchers try to speak a language they both understand, are key to success of the collaboration. The recommendations in the Box give a translation of the findings from the interviews.

The recommendations are based on experiences of the ASTERIX project, which lasted for four years, while the patient engagement process lasted less than three years. A shorter project may demand even more attention for the process of collaboration. Discussion of, and agreement on, goals and tasks at the beginning of the project, and involvement of patients at an earlier stage is advised.

In general, the collaboration between the PTT and the researchers of the ASTERIX project was evaluated positively. There has been a clear evolution in the meetings. During the first meeting patients and researchers did not communicate on the same level and in the same language, which made patients feel that they were not heard very much, and researchers did not have clear expectations of the input of the PTT. After several meetings where the PTT and researchers collaborated and discussion was stimulated, they started to value each other’s input more. In the end, both groups acknowledged that early involvement and more equal collaboration from the start would have been better. Other research has also shown this ‘learning process’ among researchers as an outcome of impact of patient involvement (24, 25).

The ASTERIX project is an example of patient involvement in a project aimed at developing trial methodology, which is a step beyond patient involvement in research for a particular disease. Over time there has been a change of attitudes of researchers and the knowledge of patient representatives has increased. Moreover, the collaboration has led to more mutual respect and understanding, and the building of relations for future opportunities. The amount of time spent with each other has been an important
factor to make this come about, as well as the patience to listen to each other. The Barcelona meeting where researchers presented their work in short lay-language talks to the members of the PTT has been a key factor in the ASTERIX project.

To involve a PTT in ASTERIX, was an ‘out of the box’ approach, since ASTERIX was a methodology project in which highly trained methodologists developed innovative methodologies for research of rare diseases. The contribution of the PTT changed the way topics were discussed and the culture of the meetings, but it did not change the work on all of the topics. The PTT members gave their opinions and sometimes clearly had a different view, or suggested topics that had not been included in the description of work. Sometimes, those opinions were hard to integrate in the planned work. For some topics, they changed the approach of the researchers, as is shown in co-authored articles on for example patient involvement in the choice of outcome measures (23).

This study has several limitations. The evaluation is based on interviews with a selection of people involved in the ASTERIX project. Although the interviewed participants were not selected for specific reasons, the experiences of others may differ. Two of the authors participated in all meetings (CG, HL). Although we tried to use meeting minutes for this evaluation, they proved not to be very useful, since they had not been written with the aim of this paper in mind. This makes our accounts on the meetings less detailed and mainly based on memory. This paper was sent to and approved by all ASTERIX participants.

Patient engagement can make a difference but it needs to be carefully planned in order to maximize outcome and minimize effort by all concerned. We advise patient representatives to be involved starting from the drafting of the project plan until all papers are delivered. Then, patient involvement can truly make a difference.
References


Appendix I: Patient quotes

**Quote 1** R1: ‘Well, I remember when we were developing the project, which I was involved in, we were discussing on what would be the powers of the PTT. We were also discussing the name of the PTT. PTT is a word that sounds kind of neutral, in the sense that, you don’t necessarily recognize that the PTT should be taken as seriously as the scientific board of advice, and this was a strong request of some participant in the consortium at that time, who were developing the project. This was mainly due to their lack of experience with such patient committees. And it is quite nice to see that during the project they realized that the advice of the PTT was so valuable that they should be given an, well, equal status as that of the scientific board of advice.’

**Quote 2** PR1: ‘I think some of the things that I would have done different is maybe being involved in an earlier.. at an earlier stage. So looking at when.. You know, now we will always push within our.. within our rare disease field, we will always push to be involved in the grant application stage, and consulted at that point. So I think that maybe that’s the only thing that maybe we could have been involved in. in the design.’

**Quote 3** R2: ‘I think, if really in the first phase of the project, when it was assigned.. I think it would have been good if.. if already then we would have some sessions with at least the executive board and the patient representatives, or for example also with the advisory board involved, to more concretely fill in.. or, to actually find out what our implicit expectations were.’

**Quote 4** R3: “The plan was swept from the table and I thought “Well, we are doing our best here, give us some credit”. That was a difference of opinion there. It was also because of the way some patient representatives communicate. But when the project developed….(...) I think that we should have involved them instead of think for them. We thought “they will consider this important”, or “they will have an opinion about this”. But we should have asked them, in the project plan, “is this a good idea according to you?”’

**Quote 5** R2: ‘Well, I think we have really grown in the project, because when you look at those meetings, ASTERIX meeting in Amsterdam.. there it was starting to take off a bit more. I am thinking.. yes.. I.. in my opinion that meeting.. the communication with the clinical researchers.. started to take shape there. And in Barcelona I think was that meeting where the collaboration with the patient representatives really started to take shape. Because.. That ASTERIX meeting in Amsterdam.. there is no strong image in my head like oh finally the patients got.. a large platform to.. to say what they had to say. That was.. the case there, but not in a way that we wanted. And in Barcelona actually
all of us were partners on equal terms, and I thought that was really beautiful when that happened.’

**Quote 6** PR2: ‘I thought in Barcelona, there I noticed for the first time, that, particularly the younger people, were open to [us].. no matter how hard they thought it was.’

**Quote 7** R1: ‘So actually I thought it was kind of daring to install such an advisory board or a think tank or whatever you call it. I was very curious to what it would bring and I think, yes, because of the technical nature of the project, that my expectations were not even that high.’

**Quote 8** R3: ‘So before [the project] I thought it was good, that the patients would be happy with the idea of installing a PTT. I felt positive about it. I thought the group would feel the same way, because other projects did not have this, and we did. It was a little bit ‘look how well we are doing this’. That was my initial feeling.’

**Quote 9** R4: ‘At the beginning.. It was interesting, a little bit thought provoking set up. I found it a great idea, I was curious how it would come out. I liked it. But if you would have asked three years ago I would not have been able to say what I would have expected.

**Quote 10** R5: ‘I hoped that the ASTERIX researchers would be able to focus more on the topics relevant to the patients because often we as statisticians or mathematicians live in our own world, our ivory tower so to speak and then the mathematical elegance of an approach seems more relevant to us than the consequences have for the patients.’

**Quote 11** R5: 'And on the other hand, I could not imagine that patients or patient representatives have anything against needing less patients in a clinical trial or having shorter trial durations and less biased results. So I hoped that the patient representatives would involve themselves more in the statistical design features, make suggestions to us what we could improve or what we could statistically analyze.'

**Quote 12** PR1: ‘My concern with any project that involves patients is that it could be quite tokenistic, and a tick-box exercise really. I think that people are recognizing the importance now of involving patients in particular research projects, but I think there’s very.. you know, people have different ideas about how that should be done.’

**Quote 13** R5: ‘...something more of us. Something more than just lowering the sample size and getting more valid results and of course the trial duration which is often long in the case of rare diseases… I always had the feeling that they saw the need for that
but they always wanted something more from us. I had the feeling they expected us to develop a treatment for … we are just statisticians; we cannot cure anybody or… we can improve the design methodology.’

**Quote 14** PR3: ‘It would be good if all participants agree on the definitions of concepts. For example type 2 error and power. You should have a sort of general lecture before the start, so that everyone understands what the meaning of these concepts is.’

**Quote 15** PR3: ‘At the first meeting, there was too little structure. I had expected more specific questions that we could answer from different perspectives. But that was not the case. (…) I would rather have had specific goals that we could work on.’

**Quote 16** PR1: ‘So I think, you know, looking back on the first meeting that we had, you know I think. I got the impression that the researchers are quite surprised at how vocal and opinionated some of the group were. What I really liked about that meeting [the first meeting in Utrecht] is that you [the respondent now addresses the interviewer who was part of WP4] really did take that on board, and went away and changed things, and then came back to the group. So I think that, you know, within that first meeting, none of us really knew what to expect from that, but it was a fact that you did think about it, that particularly impressed.. impressed me. To a point where we’ve all been able to, from that first meeting, we have all been able to move forward to the end of the project, and carry on working like that throughout. And I think that’s been a real positive outcome for this project.’

**Quote 17** R6: and it was really interesting because it was something that I never thought about. I always thought, ok, maybe in rare diseases it is the way to go, so to say, to have only a few centers, and then you have better statistical properties and so on, but it’s really hard for them [the patients] if they have to travel, for a long time, and it’s not really worth for them, so to say. […] And this is something that we can really apply directly. We don’t have to research a lot about it, we just can apply it directly to the next trial. So.. so it’s really important.

**Quote 18** R7: ‘I think we have developed things that are useful and widely applicable from the perspective of research. But we still have, focusing on the very technical aspects that have been developed from the mathematical, attained an expert level that has been not very much shared from the patient point of view. So this is the gap between the statistical and mathematical development and the usefulness of the things that we have been developing.’
**Quote 19** PR4: “The division between researchers and patients (…) that is not a negative judgement, it is just a conclusion. You are on different islands. I am on the ‘patient island’. It is not better or worse, but the division is there. ASTERIX was great for that. We were at a meeting and I had a comment and they said ‘we never considered that’. They really listened. (…) that made it a success. For example at the EMA meeting (the fifth meeting) one of the researchers said: ‘why do not we not ask the patients in the room?’”. Very good!’

**Quote 20** R5: ‘And also I think the patients, the PTT, could have taken a more active role because often we present to them and they comment but maybe they should also present what they want. But that is for the next project probably. More an interaction instead of we presenting and they listening. It would be more equal then maybe.’

**Quote 21** PR3: ‘It’s all just very complicated. Because when I look at my personal point of view.. In the past in a relatively simple manner.. or in a relatively naively manner I have shared with the world that my son has a disease. That was also shared on the internet. Later, when my son got older, I realized that, you know, that may actually stick to him. And then I started retracting all the information back from the internet. These are very tricky things. It makes a difference if you are talking about a patient group that consists of mainly parents or a patient group that consists of mainly patients. I think that patients can handle this more easily because they know what they want, while when you are dealing with patient groups that consist of parents.. I think a lot of parents do not realize at all that at a later stage their child may not at all like what has been shared about him or her.’

**Quote 22** R7: “they should be part of the investigative team, so that they touch vividly the questions and they get really involved, because they have to deliver, and only by delivering is when you realize the actual problem because you have to make it tangible in writing and you have to be very specific. (…) So my advice would be to involve them as researchers... And to write down and make it very explicit. (…) So everyone will have more clear ideas on the interaction and the value and the contributions. We all will be forced to work differently.”

**Quote 23** R3: ‘Make them part of your group. Maybe now the PTT remained an appendix; “we have the PTT and we can consult them when necessary”. And they may be at conferences but they are not member of the group so to say. We really had a ‘scientific meeting” where they were not invited. They could have been there so that they could see what it was all about.’
Quote 24 PR1: ‘So now that we are almost at the end, I thought that maybe we could have more direct contact, or more close collaboration, and it also took us some time to really understand that we are... on some terms or on some topics that we are talking about the same stuff in different words and that we don’t understand each other so...’

Quote 25 PR2: ‘Every project should have a PTT, simply ALWAYS. The EMA should also promote this, I think. How this should be organized? That is hard to say. Time is important. You have to get to know each other. That can be done faster than in ASTERIX. But you need meetings like in Barcelona, where researchers and PTT members met. My dream is that the PTT and the research team are ‘equivalent’, not ‘equal’, that they sit at one table equally. It takes time to create that cultural change.’