Patient involvement in rare disease trial design
Small populations making a big difference
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General Discussion

The ASTERIX project, the European project supporting the research described in this thesis, has resulted in many publications in international peer-reviewed journals and presentations at international conferences. These papers cover a wide range of topics concerned with rare disease trial methodology, specifically the topics of co-primary endpoints (1), sequential designs (2, 3), randomization (4), patient involvement (5) and GAS (6). Also, on many topics, patient information leaflets have been developed in lay language (see also on the ASTERIX website: http://www.asterix-fp7.eu/patient-groups/leaflets/). In this manner, the results of the ASTERIX project are made accessible to a wider audience. In March 2017, members of the ASTERIX project, together with the two other FP-7 programs IDEAL and INSPIRE, presented their results during a meeting at the European Medicines Agency (EMA). The consensus of the meeting was that the three projects have been very valuable in adding more knowledge on rare disease trial methodology.

Several members of the Patient Think Tank that was part of the ASTERIX project, were present during the meeting at the EMA. On the second day of the meeting, on specific invitation of the researchers of the ASTERIX team, the patient representatives started to take part in the discussion, especially on the topic of Goal Attainment Scaling. This lively discussion is representative for how patients have been part of the scientific discussions during the ASTERIX project. However, it has taken some time and effort to bring together scientists and patient representatives in this manner, as is also shown in chapter 5 of this thesis.

The discussions that have taken place within the ASTERIX consortium show that statisticians and patient representatives may sometimes ‘live on separate islands’. For example, patient representatives and statisticians have discussed the quality and amount of evidence that is needed in rare disease research. In the words of Prof. Koch, ‘There is no such thing as a free lunch’. This means that when less evidence exists or when only a small number of patients are willing or able to participate in a certain trial, there will also be less knowledge on the risk-benefit ratio of a new drug. Should patients with a rare disease settle for a drug of which the possible side effects or downsides have been investigated less extensively? This contrast also emerged in the discussions on randomization and the use of placebo in drug trials. Where statisticians see a Randomized Controlled Trial as the best way to gather evidence, patients prefer a potentially efficacious drug over the certainty of their disease symptoms, which may be severe and may even lead to early death. For many patients, a trial is a source of hope, and often the only source of hope. When it comes to progressive diseases, patient representatives feel that more risks should
be taken. In the words of patient representative Elizabeth Vroom: ‘Would a Cessna airplane need as many safety precautions as a Boeing 747?’

Although the ASTERIX project has made significant steps in developing new methods for rare disease trials, it has been difficult to really look beyond the beaten track. The European Medicines Agency has strict rules when it comes to granting market authorization for new drugs, to warrant that new drugs are safe and that no ineffective drugs appear on the market. However, in some cases, these rules may appear too strict in the perception of patients, for example for ultra-rare diseases or for diseases of which very little is known. ASTERIX has contributed a little for these special cases. An example is the recommendation to use registry data as a historical control group in special cases, such as when a disease is very serious and degenerative, and the experimental treatment has high expected gain. In such cases, randomization would be considered unethical. Using registry data as a historical control group would decrease the necessary number of participants in a trial, and can minimize the number of trial participants receiving a placebo, or even replace the placebo arm. Rare disease patients often have strong opinions on the use of a placebo arm, since a new treatment may be a source of hope for them. They often prefer to minimize the placebo arm as much as possible. Methods such as using registry data reduce the quality of evidence, but in extraordinary cases, such as ultra-rare diseases, lower quality of evidence may be better than no evidence at all.

Patient involvement in trial design

As is shown in part 1 of this thesis, and in many other publications elsewhere (7-9), rare disease patient groups often form strong communities. They share information, support research, and help patients and their families to obtain services they need. In many instances these groups initiate fund-raising and sometimes they are even involved in the setup of clinical trials. Several patient advocacy groups have also assisted academic researchers in the development and maintenance of biobanks and patient registries. Rare disease patient groups have played an important role in the history of orphan drug development and they provide substantial support to rare disease researchers today (10).

In the ASTERIX project, we have asked the Patient Think Tank to provide their input on a topic that is even more abstract than drug development. Trial methodology in rare disease research is a topic that is usually only discussed between researchers, statisticians and sometimes policy makers. Although it was a challenge to bring together the ideas of the patient representatives and the researchers in this project, the input of the patient representatives has been very valuable. For instance, the POWER-tool was devised in strong collaboration with the Patient Think Tank.
The collaboration between the researchers and the Patient Think Tank has evolved throughout the project. One year after the start of ASTERIX, the group of patient representatives was formed and the first meetings between researchers and the Patient Think Tank took place. It took some time for the group to get acquainted with each other, and to understand the needs they had and roles they expected. After two years, the entire research group met with the Patient Think Tank, and it was only then, during smaller sessions with in-depth discussions on the research questions of ASTERIX and the relevance of these topics to patients, when first steps towards each other were taken. One of the lessons learned in ASTERIX is that this collaboration could have started earlier in the project. As patient representatives have mentioned often, they wanted to be more involved in the direction of research topics that ASTERIX was taking. It would have been best if there had been more patient representatives present earlier in the project, possibly even during the process of applying for funding.

In the beginning, as is also mentioned in chapter 5, some patient representatives were sceptical on the reason why they were invited to be part of the ASTERIX project. When patient involvement becomes a more mainstream practice, the potential danger of tokenism may occur: patient representatives feared that patient participation in the ASTERIX project would be a ‘tick box exercise’, where involvement of patients is only performed on paper. Patient involvement takes time and effort, which is not always available (11). However, in the ASTERIX project, patient representatives have had a true influence on the road that ASTERIX has taken. The Patient Think Tank had very strong opinions on some issues, and for some research topics, such as how to involve patients in the choice of outcomes, they have changed the setup and execution of the research plans. However, it might have improved the results and implementation of results of the ASTERIX project had the PTT been more involved in other ASTERIX research topics as well.

In chapter 4, the participation ladder is mentioned as theoretical background for the POWER tool. 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 (12).

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:
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.

In the ASTERIX project, there has been some discussion on which level of collaboration there should be between the Patient Think Tank and the researchers. For future projects, it is suggested that patients and researchers 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 (13). It can also be argued that in different stages of research, different levels of participation are needed (14). In some cases, for example, it may only be feasible for a collaboration to be at the level of informing, when all involved parties agree with this. However, apart from the chosen level of participation, a main conclusion from this thesis is that where relevant, participation of relevant stakeholders should be considered as early as possible and throughout the entire process of research.
Future directions
There is an ethical demand to involve patients in research on a more equal level (15, 16). 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 as a source of data (17). The ASTERIX project may serve as an example where patients were involved in issues on trial methodology in rare diseases. Although many aspects of this collaboration could be improved, such as the timing of the involvement and the amount of interaction between the researchers and the patient representatives, patient representatives felt that they were heard and their input was truly considered valuable. Examples where patients can be involved in the research process are the choice of outcomes, the setup, content and use of a rare disease registry, the use of measurement instruments and practical aspects of a trial.

Goal Attainment Scaling
Goal Attainment Scaling is a very concrete and direct way of involving patients in research, as patients are asked to formulate which aspects of their lives they expect to improve with a certain intervention. It may also provide a solution in cases where other measurement instruments are not responsive enough, such as diseases that are rare and also heterogeneous. However, the use of GAS as an outcome measure in trials is still under debate. In this thesis, we have made the first steps towards further validation of GAS for this purpose.

For the use of GAS we have made some recommendations on the number of goals that can be chosen, on the aspect of weighing different goals and on what type of scale can be used best. GAS is applicable for RCTs when there are no other measurement instruments that are responsive for a specific group, for instance, in small heterogeneous groups such as Duchenne Muscular Dystrophy. It may also be useful to use GAS in haemophilia to measure improvement in daily living when higher trough levels are reached with a specific medication. For the example of haemophilia, which is not an ultra-rare disease, measurement instruments can be developed that are more suitable than GAS. When no such measurement instruments exist yet, however, GAS may be the best possible solution.

In this thesis, we have concluded that more validation research on GAS is needed. Validation studies can be performed when GAS is added as an extra outcome measure in ongoing trials. The validity of GAS should be evaluated in several diseases areas, similar to other measurement instruments. GAS is a very special case among measurement instruments, since it does not measure one construct at a specific moment in time, but a change in individual constructs over time. Therefore, the measurement instrument asks for a more flexible approach of evaluating validity. Other than regular instruments,
GAS can only be validated on trial level. The content and the attainment of the goals that patients have chosen can only be interpreted per individual, but when GAS is used in trials to test a potential new drug these individual scores are less relevant. In such trials the group scores are more interesting. The group scores cannot be interpreted by content, only the difference between groups is relevant in such cases. Therefore, validating GAS for Randomized Controlled Trials (RCTs) needs a different approach than is generally taken for instruments that measure a clear construct. The classical way of executing validity studies does not comply with the special needs of this instrument.

**Future directions**

GAS is an example where ASTERIX has looked beyond the beaten tracks. It may be a very valuable addition to the range of possible methods to evaluate interventions when a disease is very rare, heterogeneous and when no other measurement instruments are available that are responsive enough. However, there are some methodological constraints and the validity has not yet been studied as extensively as should be. We have made a first step towards investigating the validity of GAS by proposing a validation blueprint and giving recommendations based on a simulated GAS dataset, and we are planning to further validate GAS in ongoing studies.
References
