Patient involvement in rare disease trial design
Small populations making a big difference
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Chapter 1

General Introduction
General introduction

There are several definitions of rare diseases. In the European Union, a rare disease is defined as a life-threatening or chronically debilitating disease of which the prevalence is lower than one in 2,000 individuals. In the USA, a disease is defined as rare when it affects less than 200,000 inhabitants, equivalent to approximately 1 patient per 1,540 inhabitants (1). Only a few of the recognized rare diseases have a prevalence of around 1 in 2,000. Most of them are much rarer, such as Duchenne Muscular Dystrophy, with an estimated prevalence of 1 in 20,000 males (2), or Hemophilia, with an estimated prevalence that varies between 1 in 6,000 to 1 in 17,000 males (3). Other diseases are so uncommon that they are called ultra-rare, such as Progeria, of which the reported prevalence is one in eight million births. Worldwide there are an estimated 200 to 250 people living with this disease at any one time (4).

Although the number of patients with a particular rare disease is relatively small, all together, the total number of people suffering from any rare disease is large. It is estimated that between 5000 and 7000 rare diseases exist. The European Organization for Rare Diseases (EURORDIS), states that the proportion of individuals with a rare disease is estimated at 6 to 8% of the population in the EU (5). Most rare diseases are associated with a lack of available treatments and a relative lack of research to discover and develop such treatments. Also, rare diseases are associated with high socio-economic costs as well as considerable individual psychological burden (6).

In 2000, the European Union published the European regulation on Orphan Drugs, stating that ‘Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients’ (7). The goal of this regulation was to stimulate the development of drugs for rare, orphan diseases, which were mostly neglected by the pharmaceutical industry until then (8). The regulation followed similar acts in the US (1983), Japan (1993), and Australia (1998).

In the EU, research institutes or pharmaceutical companies may apply for orphan designation, which is often the first step towards marketing approval and clinical development. The benefits that come with orphan designation include reduction of regulatory fees, extra regulatory guidance and a marketing exclusivity period of ten years in the EU after market approval of the product (9). The number of orphan drugs that have entered the market since 2000 has largely increased; by August 2017, the EU has granted market authorization for 137 orphan medicines for the benefit of rare disease patients (http://ec.europa.eu/health/documents/community-register/html/orphreg.htm) (10). The decision of market approval, for
which in the European Union the EMA (European Medicines Agency) is responsible, may sometimes be a difficult or controversial one (11).

**The ASTERIX project**

The evaluation of the quality, efficacy and safety of a medical product is more challenging in small populations than in frequent diseases. In terms of quality, rare disease trials should meet the same standards as trials of more common diseases. However, due to the low prevalence, it is more difficult to recruit enough patients for a specific trial. To investigate the possibilities of increasing the efficiency of rare disease trials, the European Union launched a call in 2013 for scientific projects that addressed the methodology of clinical trials in small populations. Three projects were funded under this call: Ideal (Integrated DEsign and AnaLysis of small population group trials), Inspire (Innovative methodology for Small Populations REsearch), and ASTERIX (Advances in Small Trials dESign for Regulatory Innovation and eXcellence)(12). In the ASTERIX project, not only statisticians participated to improve rare disease methodology. Also a group of patient representatives (the Patient Think Tank) advised on research projects. Patient involvement in rare disease research was one of the main topics of the ASTERIX project. The Patient Think Tank, consisting of ten experienced patient representatives from a varying background and representing various diseases, gave advice on the course and the output of the project. The Patient Think Tank has played an essential role in the development of many of ASTERIX’ scientific products. The research presented in this thesis was funded by the ASTERIX project, and has a specific focus on the involvement of patients in clinical trials in rare diseases.

**What is the role of patients in research?**

Over the last decades, starting in the 1950s, there has been an emancipation movement of patients and organized patient groups (13). Patients have become more assertive, and more often involved in health care decisions (14, 15) and in research (16, 17). There is a political and ethical demand to involve patients in research on a more equal level, shifting away from the patronizing model and giving more autonomy to the patients. Involving patients in research may also improve research; it is assumed that patients guide research into topics with more clinical relevance. Over the years, involving an ‘expert patient’ or patient representative in research has gained popularity.

In rare diseases in many instances, these patient representatives have considerably more knowledge about the particular (rare) disease than many physicians, even specialists. Patient representatives may also gain knowledge on research practice through specific patient expert courses, such as the European Patients Academy (EUPATI, see https://www.eupati.eu/) and the Summer School that is organized yearly by EURORDIS
(see https://openacademy.eurordis.org/summerschool/). The practical experience of these patient representatives combined with research knowledge makes them excellent partners in rare disease research.

The inclusion of the patients’ view in the research process is relevant in several stages of the empirical cycle. For instance, when patients are involved in the setting of the research agenda, they can guide the proposed research topics towards a more patient relevant direction. A striking example where patients have made a difference in the research agenda is that of the Dutch Burns Foundation (Nederlandse Brandwonden Stichting). In order to establish a national research agenda for burn research in the Netherlands, the Dutch Burns Foundation and researchers from the Athena Institute, VU University Amsterdam, invited burn survivors and professionals in prevention, care and research for a participatory trajectory entitled the BhURN project (‘Brandwondenonderzoek heeft Uw Reactie Nodig’— burns research needs your response). During these discussions, a discrepancy was found between the ideas of the researchers and the burn victims. Burn victims preferred more research on itching and edema, whereas researchers had always focused on wound healing, infection prevention and the prevention and treatment of invalidating scarring. After the project, the results were translated into a research program proposal, and a funding program was established for the relevant research areas that had received little attention before the project (18).

Patient involvement can go a step further when patient organizations take the lead and become research initiators themselves. For example, several research initiatives in the field of bleeding disorders were patient-led and the results were published in peer-reviewed journals (19, 20). Another example is the disease Alkaptonuria (AKU) for which a very active patient community has collaborated with research professionals in trials to evaluate a potential new drug (21). Duchenne Muscular Dystrophy also has a very active (international) patient community, called the Duchenne Parent Project. Fundraising events are organized regularly, where money is collected to support fundamental and clinical research (22).

**Rare Disease Registries**

Patients and parents can already play a role in the development of treatments for rare diseases, long before a clinical trial is contemplated. Very often little is known about the course of a rare disease, and for many rare diseases there is no clue about a possible (drug) treatment, let alone a trial being planned. In such an early phase a rare disease registry can be a way of gathering crucial information on the disease course and the variability of the patient population. We define a rare disease registry as a standardized data collection including information about patients with a particular rare disease. A rare disease registry could also be useful at a later stage when a clinical trial is being set up.
It can provide important information that improves the efficiency of clinical trial design and open doors to possible alternative approaches of rare disease trial design. However, it is important to know that to make such a registry useful for informing a clinical trial, specific information, for example on relevant outcome measures, should be collected from the very start. Patients can play an important role here, either as informants of relevant variables to include, or by being the lead initiators of such a registry.

**Outcomes**

At the trial design stage, the decision of what outcomes are used in a trial is particularly important in randomized clinical trials to assess the efficacy of (drug) interventions. Outcome domains can be considered as a continuum, of which physical measures, or biomarkers, such as blood pressure are on one side, and more complex, integrated measures such as quality of life are on the other side (23). According to the EMA HRQL Reflection Paper (24), subjective outcomes such as Health Related Patient Reported Outcomes (HR-PROs) can also be used as primary or key secondary outcomes in drug studies, provided that the instruments measuring these outcomes (measurement instruments) have been validated and the trial is controlled and well-designed. In drug research, biomarkers or surrogate outcomes are usually included as primary outcomes. Surrogate outcomes are used as a substitute for a direct measure of how a patient feels, functions, or survives (25). However, it is vital that the set of collected data also captures, as much as possible, the total real-life impact of a disease on an individual, which is only feasible when the patient’s perspective is included. Ultimately, trials are aimed at improving patient care. Therefore, involving patients in the decision how to measure the efficacy of an intervention seems not only logical, but also of pivotal importance for trial success.

An example of patients making a difference in the choice of outcomes is the OMERACT (Outcome Measures in Rheumatology) initiative. In 2002 it was decided to include patient representatives in these conferences. The patient representatives highlighted fatigue as a very important factor, which had never been considered important by physicians before. Since then, fatigue was put on the agenda as a relevant outcome, but more importantly, patient involvement became a standard in development of core outcome sets (26, 27).

**Measurement instruments**

In rare diseases the choice of outcomes is often more problematic than in more common diseases, due to the small number of patients and the heterogeneity of these populations. Moreover, there are often no disease-specific measurement instruments available for outcomes specific to rare diseases. Generic measurement instruments are sometimes 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. They may also show threshold or
ceiling effects in heterogeneous populations, which limits the - already small - number
of patients who are eligible for trial participation.

Patients often have the most hands-on experience when it comes to measurement
instruments in terms of invasiveness and burden to the patient. Some instruments, such
as time-consuming questionnaires or biopsies, can be used less often than non-invasive
instruments, such as measuring the blood pressure. An example where patients have
used their experiences to improve research is the field of Duchenne Muscular Dystrophy
(DMD). Until recently, the most commonly used outcome in clinical trials of DMD
was walking ability, as measured by the 6-Minute Walk Test (6MWT) and the North
Start Ambulatory Assessment (NSAA) (28). 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. Therefore,
the use of the upper limbs is considered a more important outcome measure by patients
themselves than walking ability. This inspired patient advocacy groups to develop a
disease-specific measurement instrument on upper limb function, which eventually
might increase the number of patients eligible for a trial (29).

Goal Attainment Scaling
Another way of increasing the repertoire of outcome measurement instruments in
rare disease research could be the use of Goal Attainment Scaling (GAS). GAS is a
measurement instrument that is intended for individual evaluation of an intervention. It
was developed and described in the late 1960s for use in the field of mental health (30).
It allows patients to set individual goals, together with their treating professional. The
number of goals and the content of these goals may differ per patient, but the attainment
of the goals is measured in a standardized way. This makes a standardized evaluation of
an intervention possible, even when the patient group is very heterogeneous. GAS could
for instance be used as a measurement instrument in trials for DMD, so that inclusion
criteria for a trial could be much broader than only including patients who can walk.

Main questions addressed in this thesis
Involving patients in rare disease research faces many issues that still need to be tackled.
It is a field with many stakeholders, of which the patients are, or should be, the most
important. One of the ways of improving the efficiency of clinical (drug) trials, is
involving patient representatives from the start. Patient representatives can play a role
in all parts of the scientific cycle, from setting up a registry, through choosing relevant
outcome measures, to recruitment of trial participants and dissemination of results. In
this thesis, four main questions are addressed:
1. When and how should patients be involved in the process of clinical trials in rare diseases?
2. How can rare disease registries be used to improve clinical trial design?
3. How can patients be involved in the choice of outcomes in clinical trials for rare diseases?
4. Could Goal Attainment Scaling provide a solution to the problem of insufficiently responsive measurement instruments in rare disease trials?

Outline of the thesis
This thesis is divided in two parts. **Part one** (Chapters 2 to 5) focuses on the involvement of patients before and during the design stage of rare disease trials. **Chapter 2** describes a qualitative study in which a group of patient representatives was interviewed to find out what aspects of clinical trial design are most important to them. **Chapter 3** focuses on how rare disease registries can be set up in such a way that they might be used for clinical trials in a later stage. In **Chapter 4** a tool is proposed to involve patients in the choice of outcomes for clinical trials. **Chapter 5** describes an evaluation of the process of collaboration between – mainly statistical – researchers and the PTT in the ASTERIX project. **Part two** of this thesis focuses on a specific measurement instrument that might be useful in rare disease trials in heterogeneous populations: Goal Attainment Scaling. In **Chapter 6** a systematic review is described investigating whether GAS has been used in drug trials and if so, whether this measurement instrument has been validated in this setting. **Chapter 7** deals with the statistical aspects of GAS, namely which statistical tests should be used, how many goals are optimal and how weights can be assigned to goals. In **Chapter 8** we propose a blueprint to validate GAS as an add-on study in a clinical trial. Finally, in **Chapter 9** the results of all investigations presented in this thesis are discussed and recommendations are given for the conduct of rare disease clinical research and involvement of patients, as well as next steps in the implementation of our results and directions for future research.
References

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