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Rare Disease: Impact on Development of New Drug Treatments

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ABSTRACT: *Low prevalence, lack of knowledge about the disease course, and phenotype heterogeneity hamper the development of drugs for rare diseases. Rare disease registries can be helpful by playing a role in understanding the course of the disease, and providing information necessary for clinical trial design, if designed and maintained properly. We describe the potential applications of a rare disease and what type of information should be incorporated to support the design of clinical trials in the process of drug development supported a broad inventory of written record expertise. We evaluated two existing Rare disease in more detail to check the completeness of these Rare disease for trial design. Before and during the application for regulatory approval rare diseases can improve the efficiency and quality in clinical trial design by informing the sample size calculation and expected disease course. In exceptional circumstances information from rare diseases has been used as historical controls for a one-armed clinical trial, and high quality rare diseases may be used for registry-based randomized controlled trials. In the post marketing phase of (conditional) drug approval disease-specific rare diseases is likely to provide more relevant information than a product-specific registry.A rare disease registries can be very helpful to improve the efficiency and quality of clinical trial design in several ways. To alter the pertinence and optimum use of rare un-wellness longitudinal information assortment is indispensable, and specific data collection, prepared for repeated measurement, is needed. The developed listing will facilitate to outline the suitable variables to incorporate. Attention should be paid to the inclusion of patient-relevant outcome measures in the rare diseases from the start. More research and experience is needed on the possibilities and limitations of combining rare diseases information with clinical trial data to maximize the availability of relevant evidence for regulatory decisions in rare diseases.*

KEYWORDS: rare disease, impact, development, new drug treatments

INTRODUCTION

In rare illness the clinical development of effective medicine is difficult because of low prevalence of the disease and sometimes sizable composition heterogeneousness. The small numbers give

limited opportunity for confirmatory clinical trials, as it is difficult to recruit sufficient patients. For much rare illness the disease course is insufficiently identified, resulting in uncertainties with relevancy the optimum run style, including choice of endpoints, for a new drug. Even if the endpoints are clear, there is often insufficient information about their occurrence - in case of binary endpoints-, or distribution - in case the endpoint is a continuous variable. This lack of information, combined with heterogeneity, has consequences for the efficiency of preparing and designing a clinical trial. More specifically, assessing the practicableness of a shot, which is directly connected with robust sample size calculations, becomes a difficult task. When the sample size is calculated based on limited information, this increases the risk of under- or overestimation of the sample size, and possibly a failed trial. Furthermore, such scarcity of information can have considerable impact on the regulatory process and evaluation of the available evidence for the risk/benefit assessment of a new drug, and possible market authorization.

In this respect rare diseases can be an invaluable source of information. With an estimated number of 5000–7000 distinct rare diseases, in Europe over 700 rare diseases are active for a similar number of rare diseases. Rare diseases can give insight in the natural history of the disease and the variability of the patient population. The decision to start rare diseases is often made at a stage when the available information about the particular rare disease is still scarce, and the development of a treatment might lie secluded within the future. Even in such an early phase, it is important to be aware of and prepared for all possible future functions of the information contained in the rare diseases; the identification of relevant endpoints or the use as a data source for the design of a therapeutic clinical trial are two notable examples. Therefore, rare diseases should be designed in such a way that all relevant information is incorporated and can be used most efficiently. The term ‘registry’ will denote any form of information assortment. However, not all information collections that are given as illness registries are appropriate for run style or as further info for restrictive analysis. Several types of registries can be distinguished, and there is no consensus on the nomenclature and classification.

In a study for the EPIRARE project, addressing regulatory, ethical, technical and financial issues related to the development of rare diseases, registries were classified into three clusters: public health registries, clinical and genetic registries, and treatment registries. Public health registries are aimed toward medicine analysis, healthcare service planning, and disease surveillance. These registries usually are population based mostly and collect info on over one illness or condition, for example on cancer or congenital anomalies. Clinical and genetic registries focus on etiological research questions. They collect information on phenotype, geno-type, family history and clinical data. Treatment registries are preponderantly aimed toward treatment analysis and watching. For example, in registries for post-marketing surveillance, often required by regulators for (conditional) market approval, information is collected on outcomes from patients who use a particular medicinal product. Often, these registries are targeted on one, or few, specific treatments. Not every type of registries collects the suitable info to be helpful in run style or drug development. For instance, the knowledge collected in population-based registries usually isn't specific enough to tell natural course and relevant disease-specific outcomes. The same holds for

genetic and clinical registries in which no outcomes are collected at a regular basis. In the Uses of Guide of the US Agency for Healthcare Research and Quality, aimed at registries that evaluate patient outcomes, but not limited to rare disease registries, a different categorization is used. Registries are divided into product or health service registries, patient or disease registries, and combinations of these. Product registries generally focus on the determination of (cost-) effectiveness, quality of care, and safety and harm of a product and only contain information on individuals who make use of a particular product or set of products. Patient or illness registries specialize in explanation, but could also be used for collecting information about efficacy and/or safety of interventions. Here, we tend to outline rare illness as standardized information collections together with info regarding patients with a selected rare disease, without selection based on treatment received. The EPI-RARE defined a set of common data elements to improve standardization and data comparability among rare diseases and to support new registries and data collections. This set of common data elements is intended to provide the basic elements for the construction of registries for a variety of purposes, but their main focus is on population-based rare diseases, such as public health registries. Besides a mandatory set of baseline elements, such as demographic characteristics and recruitment information, other domains can be chosen accordingly to the rare diseases purpose. When putting in a rare illness for a precise rare disease with the intention to use the data for clinical analysis soon, additional, disease-specific data elements, not included in the common data elements, may be necessary. For example, in chronic, slowly deteriorating rare diseases mortality and quality of life (advised as common data elements) might not be specific enough when describing the disease course and testing the efficacy of a drug at a later stage.

In this paper, we tend to describe prospects for the applications of disease-specific rare diseases for run style and drug development in rare diseases, and that we offer suggestions regarding that information elements at least should be collected for that purpose. We also give recommendations for the optimal design of rare diseases to enhance intervention research, including trials for regulatory approval, in the future.

Methods: This overview was developed & possible relevant information from models from the literature was added to the checklist, which was discussed until there was consensus. Finally, we checked the completeness of two existing rare diseases for trial design.

Focus groups, interview, European Public Assessment: First, we conducted two focus groups with 3 different statisticians each and an interview with two regulatory experts with extensive experience at the European Medicines agency (EMA), all involved in the Asterix project. The principal question was in what means rare diseases may be informative for the planning of a polar clinical test for restrictive approval and what data ought to be included to serve this goal. Minutes were taken from both focus groups and circulated among the participants for feedback. The interview with the regulatory experts was recorded and the summary report was also checked by the participants for completeness and correctness. The overview of possible applications of rare diseases in trial design and the checklist of elements to be recorded was based on the reports of the focus groups and the interview. The overview was completed with selected European Public

Assessment Reports describing examples in which rare diseases data had been used for drug approval.

Draft checklist and consensus: A first draft checklist of data elements to incorporate in disease-specific rare diseases for trial purposes was made. In a literature review, {two|2} models have a tendency to| tend to} re found describing general domains {of data/of knowledge of information} {elements/parts/components} in rare{disease/illness/un-wellness/malady/sickness} registries and/or outcome measures {which/that} we compared with our draft {checklist/list/listing}. One model gives recommendations for general data elements for rare disease registries (EPIRARE) the other model describes domains of outcome measures as a basis for the choice of core outcome sets. Both models did not provide a complete overview on variable domains to include in disease-specific rare diseases for enhancement in trial design and drug approval. Therefore, we have a tendency to incorporated potential relevant data from these 2 models with our draft list. The checklist was completed with information on the frequency of and reasons for data collection, and the applicability in the drug approval process. This version of the draft list was circulated among the consulted experts in order to obtain consensus on the final checklist.

Evaluation of existing rare diseases:

The final list was wont to valuate whether or not all necessary components to tell a clinical test within the future were enclosed in 2 existing disease-specific rare diseases. The two available disease-specific rare diseases selected were the European Cystic Fibrosis Society and the Diffuse Intrinsic. These two rare diseases were selected from eight rare diseases whose coordinators had participated in interviews about the goals and set-up of rare diseases, and their use in clinical trials. The selection was based on variability in disease, their possible use of rare diseases data in clinical research or trials, and the possibility to retrieve the data elements collected in the rare diseases. Possible gaps or differences between the rare diseases and the checklist were highlighted and suggestions for improvement were given.

Results

The importance of rare diseases information for the clinical development stage of a medicinal product for rare diseases was endorsed by all experts. The possible use of a rare diseases was divided in five main categories, i.e. 1) general aspects of a rare diseases for research of the particular disease, 2) the possible application of a rare diseases for sample size calculations and sample size reduction, 3) the use of a rare diseases for a registry-based clinical trial, 4) the use of rare diseases information as a historical control group, and 5) possible application of a rare diseases in the post-marketing phase (safety, off-label use, continued assurance of effectiveness). Also, an elaboration was given on the requirements of rare diseases to be applicable in trial design, followed by the results from the developed checklist.

1) General aspects of rare diseases:

Rare diseases can give insight in the natural course of the disease, providing good starting points for relevant research. Registries area unit notably relevant for rare diseases, as they will usually be the most supply of data. In the phase of protocol development and regulatory scientific advice, the knowledge gathered from the rare diseases forms the foundation for many relevant features of the development plan (and the clinical trial design), such as information on prevalence, clinical course of disease, prognostic subgroups and relevance of surrogate endpoints (when collected) or other outcome measures. Through the rare diseases, sites with expertise in managing the disease and patients who may be eligible for a trial can be located, which may allow to estimate the trial feasibility and can enhance the efficiency once the trial is open for recruitment.

2) Possible application of rare diseases for sample size calculations and sample size reduction:

For the design of future clinical studies, rare diseases may provide a database of prior information that can be used in different ways. The most direct use of this information would be as input for estimations of nuisance parameters to inform sample size calculations for a new trial. Nuisance parameters replicate aspects of the likelihood distributions that have an effect on the preciseness of estimators of the target parameter, however don't seem to be of primary interest. Examples of nuisance parameters are the standard deviation (for continuous outcomes) and the control event rate (for dichotomous outcomes). Empirical information on the nuisance parameters gives reliable input for sample size calculations. The availability of this information alleviates the need for pilot studies, thus saving time and resources. Sometimes the registry data (or part of the data) might be used directly as part of the (Bayesian) design and analysis of a new study, which may reduce the necessary sample size. This can be done in several ways – add data (e.g. on the control treatment) as “pseudo observations” in the new trial, combine part of the rare diseases data and data from the new trial in a Bayesian analysis or use the written account to model malady progression and use this as reference within the trial . This is not without controversy among trial methodologists and regulators. However, in (very) rare diseases this approach might be preferable to conducting a trial that is essentially too small, and then synthesize the evidence of this trial in a less formal way, e.g. by post-hoc analyses, after the trial is completed.

3) The use of rare diseases for trials based:

trials have many advantages over traditional RCTs, such as lower use of resources, higher rate of enrollment of patients, and, besides potential completeness of the baseline data, enhanced generalization of findings, like this structure assessment of patients World Health Organization are or aren't collaborating within the trial is feasible. The advantages of this approach in terribly to ultra-rare diseases area unit debatable. In case of ultra-rare diseases or within-disease rarity through choice of specific genotypes, randomization might not be viable. Also, although a registry-based RCT saves money, keeping up high-quality rare diseases is expensive, so it is questionable whether in the end this approach is financially favorable for rare diseases. On the other hand, for

financial and logistic reasons pharmaceutical companies may be more willing to start a RCT when this could be embedded in the already existing rare diseases.

Registry-based irregular controlled trials might face some moral problems. One of these is the design of the consent procedure. Is a formal informed consent for the 'control' treatment needed when a patient has consented the data collected in the registry could be used comparatively? In a study. Among a cohort of women with menopausal hot flushes a Zelen design for the consent procedure was used. At the time of random allocation of patients to the active and management arm, only the patients assigned to the active treatment were informed about this & the opinion of the 'control' patients on this procedure had not been evaluated. Although some patients might just be fine with not knowing, others may feel not-informed and left out of the loop. However, both the Declaration of Helsinki and the ICH Guidance on Good Clinical Practice are clear in that the subject must receive detailed explanations on the experimental nature and design of the trial, including its purpose, the tested treatments and the probability for random assignment to each treatment. Also another study mentions the importance of informed consent in pragmatic randomization. Whether a general acceptance of data collection in rare diseases for comparative use may overcome such recommendations can be controversial. So, these (among other) challenges have to be taken into consideration before proper execution can take place.

4) The use of rare diseases information as a historical control group:

The RCT with an appropriate comparator arm is the design of first choice, as is also stated in the EMA guideline on clinical trials in small populations. The random allocation minimizes choice bias and also the synchronous comparison cluster permits the researchers to work out any effects of the treatment compared with the management treatment unbiased by the effects of unmeasured confounders. With relation to rare diseases, irregular studies will still be conducted, as in several diseases the patient population is massive enough to perform self-made random allocation. However, in bound circumstances, betting on sort of malady and treatment potentialities, rare diseases might introduce complexness within the thought whether or not a RCT could be a viable choice. For instance when a disease is ultra-rare and severely progressive for which no treatment is available yet, ethically sound alternatives might be considered to open the door for drug development. One of these alternatives is the possibility of using the data of rare diseases patients as historical controls for a single arm trial. Below, two examples are described of drugs approved after historical data had been used as a control group for a single arm pivotal study.

Example 1:

In 2006 the new drug Myozyme was approved by the EMA for Pompe's illness, a rare chromosome recessive lysosome storage illness. This decision was based on data from studies among patients with late-onset and infantile-onset Pompe's disease. These studies included, among others, a double-blind, randomized, placebo controlled study with a duration of 18 months, involving 90 patients with late-onset Pompe's disease, and a single-arm trial among 9 children with infantile-

onset Pompe's disease. Because this infantile-onset illness could be a quickly fatal disorder and former data already showed a helpful impact of the drug, the use of a placebo arm was considered unethical. Instead, associate untreated cohort of infantile-onset Pompe's illness patients from the illness written record, fulfilling the inclusion criteria of the trials, was identified to serve as a reference group. Based on these results Myozyme was licensed each in late-onset and infantile onset Pompe's illness.

Example 2:

The drug Defitelio is employed to treat severe veno-occlusive illness (VOD) in patients undergoing haemopoietic stem-cell transplantation. VOD could be a condition within which the viscos veins become blocked, leading to liver dysfunction. VOD is understood to own a high mortality (between seventy five and 85%). In one main study including 102 patients with VOD, the mortality rate after treatment with Defitelio was compared to a historical control group of patients who had received standard supportive care. The mortality within the cluster treated with Defitelio was sixty two compared to seventy fifth within the historical management cluster. The committee for medicinal products for human use (CHMP) concluded that Fidelity's benefits were greater than its risks. So, despite lack of a concurrent placebo comparison, the results were convincing enough for market authorization, but under 'exceptional circumstances'. This meant that, because it was not possible to obtain complete information, a registry including the patients receiving the treatment was required to provide further data on safety, health outcomes, and the way the drug is used in practice.

5) Possible application of rare diseases in the post-marketing phase:

Applying rare diseases data in the post-marketing phase is useful for the systematic collection of real-world data on the use of new treatments. The participants in a trial usually constitute a selection of relatively homogeneous and fit patients (although in rare diseases this is less the case), who are selected based on genotype or alternative unwellness aspects and are closely followed and controlled. When supported the trial it's terminated that the intervention has shown profit in such a patient population, it is under the relatively artificial conditions of the trial, and generally for a shorter period of time than the intended time that patients will be treated in clinical practice. Thus, at the time of marketing approval, the information on safety and effectiveness of the product is inferred to be applicable also to many other patients with different characteristics and for long term treatments. With regard to rare diseases, valid information from rare diseases may provide evidence to clear uncertainties on the effectiveness and safety of the product in conditions of routine clinical practice and in wider patient populations. This is illustrated by associate degree example of Elaprase, a drug used as enzyme-replacement therapy in Hunter syndrome. Based on a placebo-controlled trial among ninety six patients aged VI to thirty one year's previous, market authorization was given. However, as of restricted knowledge, follow-up information was requested to investigate the long-term effects of the drug. Because the clinical trial was restricted

to patients from 6 years onward, no efficacy information was available for younger patients. A broad age range of patients enrolled in the registry allowed an analysis to be performed of safety and preliminary clinical outcomes in patients younger than 6 years of age. Findings from the written record, together with an open-label study among young patients, supported marketing authorization of Elaprase in children from this younger age group. Also in Gaucher's unwellness long-run treatment info was obtained on enzyme-replacement medical aid through the International cooperative gaucher cluster Gaucher written record. This registry has been useful to confirm benefits on clinical outcomes and long-term effectiveness of the treatment in routine clinical practice, including wider patient populations than those included in clinical trials.

- **Requirements of rare diseases to be useful for trial design:**

In the design phase of rare diseases it is important to consider the research questions and endpoints of a possible clinical trial in the future. By considering a possible future trial it becomes clear what information one would preferably be able to extract from the registry in the future. Information on the primary outcome is necessary to calculate the necessary trial sample size. This means that it is important to collect the right type of information on potential primary outcomes in the right way from the beginning of the registry. One must deem the utilization of valid measure instruments, or if necessary further validation of promising instruments, and the timing and performance of the measurements must be standardized, preferably internationally. This is needed to provide a reliable source of information and to increase the chance of successful use for a clinical trial.

To leverage use of prior information through Bayesian analysis, the preferred path would be that prior distributions for the (efficacy) parameters of interest – such as change in disease severity or event incidences – can be based on actual data, rather than prior beliefs. A rare diseases may provide such data, but then needs to register the outcomes that will be of interest in the clinical trial to be designed, as well as include broad variability within the patient population registered to be able to represent all potential patient teams during a future trial. Preferably patients are included in all disease progression states, from multiple centers and internationally, with standardized outcomes. This is necessary for the, essential, exchange ability assumption to be fulfilled, which means that the prior information is based on a population that is comparable to the one included in the trial.

For the use of rare diseases data in a registry-based clinical trial, as a historical control group for clinical trials or in the post-marketing phase, similar considerations are important as for its use in a sample size calculation. With regard to the registry-based RCT a high-quality database is a prerequisite including flexibility to add variables if necessary, as well as an adequate number of patients who are eligible for the registry- based RCT. There are three main concerns with the use

of historical data. The first is the comparability of the trial participants with the patients in the rare diseases, and the second is the comparability of the collected data. The third is the evolving standard of care that may induce bias when the control group is not concurrent. To overcome the first two issues, standardization of measurements and data collection from the very start of the registry is paramount, and measures intended to check comparability and allow matching by baseline variables that may be related with patient evolution over time, such as severity of the disease, age, and genotype, need to be available. Again, sufficient patients need to be included in the registry to enable a useful selection of patients allocated as comparative group.

For all applications of rare diseases information mentioned above, longitudinal data collection, preferably in prospectively defined intervals, is key. This means that information on the outcome measure needs to contain at least two points in time. In this way the development of the outcome measure can be assessed for all patients, irrespective of what treatment they received. In its most straightforward kind, this might be date of birth and date of death so as to assess mortality during a severe fatal unwellness, like DIPG. A more complex example is the 1 min forced expiatory volume (FE1) in patients with cystic fibrosis, which is regularly measured in all patients during clinical follow-up and could be thoroughly registered in the rare diseases if needed.

- **DISCUSSION:**

  Our research question focused on the possible applications of disease-specific rare diseases for clinical trial design and regulatory approval and on the minimum information that should be recorded to maximize their potential for these purposes.

  The results show that rare diseases can be very helpful to improve the efficiency and quality of trial design in several ways. It can inform the sample size calculation, or, when prior information on the endpoints is available, even reduce the number of patients included. Besides informing a sample size calculation, the data of the rare diseases could, in certain circumstances, be used as an external control when placebo or active comparator groups are e.g. not ethically acceptable, and in larger RDRs, once of top quality, for registry-based RCTs. Also, within the post selling part a disease-specific rare disease is useful to supplement, confirm or (theoretically) refute data supporting the initial marketing authorization.

  Designing a registry with a future clinical trial in mind can considerably reduce the time needed for the clinical development phase of a long awaited drug. One of the first steps in making a disease-specific RDR applicable to inform a drug trial for market authorization is to think of the research question and endpoints of that future trial. It is pivotal to consider what could be appropriate outcome measures in a very early stage, even when a trial is still far away. When it is still unclear what would be the best outcome measures, data from the RDR can help defining the most relevant ones. In addition to the goal(s) and desired

outcome, factors need to be included that might influence the outcome but are not necessarily the focus of the study. When these potential confounders are also collected, their effect can be assessed and taken into account in the design of the study (i.e. used as stratification factors), but they could also be useful for matching historical cohorts. The developed checklist provides a tool to check whether all types of important variables have been included. However, although the checklist has an expert and literature base, further validation of this tool by its actual use in designing rare disease trials is advised.

In the analysis of 2 existing RDRs it absolutely was shown that knowledge components associated with life impact were missing. Variables, with immediate connectedness to patients, such as health related Quality of Life and variables concerning daily functioning are particularly important for patients and could improve RDR design and usefulness in a clinical trial. In Duchene hereditary condition as an example, patient advocacy groups identified the need to develop a scale to measure motor function of the upper limb to be able to also embrace non-ambulant youngsters within the target cluster for brand new registration studies. The involvement of patients and families helped to pick things reflective clinically substantive activities of daily living. Therefore, it is advised to ascertain patient involvement in the development of a RDR so that patient-relevant outcome measures, generally considered very important by the regulators, are incorporated in the RDR. Besides, a RDR might represent opportunities for sceptered patient organizations, World Health Organization might initiate or sponsor registries as means that to boost information of sure rare diseases and to ease the conduct of clinical trials in certain conditions.

The use of validated measurement instruments and standardized measurement and data collection are other key aspects in RDR development, which prevent comparability issues later on when a trial is being set up. Several initiatives have been launched for standardization of outcome measurement. One of these is the COMET initiative. The COMET Initiative brings together researchers, clinicians and patients interested in the development and application of agreed standardized sets of outcomes, known as a ‘core outcome set.’ These sets represent the minimum that ought to be measured and reportable altogether clinical trials, audits of practice or other forms of research for a specific condition. This allows the results of trials and other studies to be compared and combined as appropriate. Besides the core outcome set, researchers are free to explore other outcomes as well. The International Consortium for Health Outcomes Measurement (ICHOM) is also aimed at harmonization of outcomes and data, in particular standardization of important outcomes of clinical care for patients on a global level. Although the appliance of those initiatives (predominantly in non-rare diseases) could also be difficult for rare diseases, their methods could very well serve as a basis. Furthermore, new opportunities may lie in

the rise of the European Reference Networks (ERNs), networks of centers of expertise and healthcare providers with a clear governance structure for knowledge sharing and care coordination across borders. The ERNs, focusing on specific (clusters of) disease(s), can unite relevant stakeholders, including patient representatives and could initiate standardization to improve comparability and data linkage and sharing of RDR data.

With regard to the instruments used to measure the relevant outcomes, the measurement properties, such as reliability, validity, and responsiveness need to be assessed and found adequate before they can be used in clinical trials. Important decisions are based on the results obtained with these instruments; therefore one needs to be confident that these results are reliable and valid. The USA Food and Drug Administration (FDA) and EMA need that measure instruments square measure well valid for his or her purpose. Especially for outcome measures that could have a subjective nature, such as patient-reported outcomes, it is important to evaluate the reliability and validity of these instruments. If no useful measurement instruments exist to measure the effect of interventions in a particular disease, the development and validation of measurement instruments should start as early as possible, since this process takes considerable time, especially in rare diseases.

The importance of longitudinal data collection for the applicability of RDR in clinical trials has been stipulated. The key strength of collecting an outcome measure at multiple follow-up times is the possibility to measure individual change in outcome, which enables comparison between different patient groups. Although we strongly recommend collecting data in a longitudinal manner, this type of data collection is costly and requires a high level of organization, such as in logistics and personnel. To financially sustain a basic RDR is already challenging, so it needs a creative approach to keep such a registry running and maintain a high quality data collection. For example, agreeing on standardized approaches to collect medical information into electronic medical records during routine clinical practice may be a strategy that can be explored in order to improve the feasibility and efficiency of a RDR. For the statistical analysis of longitudinal data specific methods are required that properly adjust for the intra-subject correlation between the measurements.

Although the possible benefit of a RDR in the post-marketing phase has been described, some caution has to be put in place as well. Especially regarding efficacy assessment after drug approval in populations not evaluated in the trial. Some may argue that systematic compassionate use after market approval may weaken the robustness of information supporting regulatory and clinical decision making in these neglected populations, as it may preclude the conduction of randomized trials able to conclude efficacy. Meanwhile, in bound little subgroups the comparison with RDR knowledge for enlargement of the market authorization could be one in every of the few potentialities left. Therefore, careful deliberation on the pros and cons of different scenarios is desirable.

- **Future directions:**

The option of reducing the required sample size of a RCT in (very) rare diseases by using rare diseases as historical control group is under debate. In very small populations with life threatening or seriously disabling diseases it may be the only ethically acceptable approach and it is worthwhile to further investigate its options.

At this moment, alternatives for a RCT such as historical controls are only taken into consideration in specific circumstances, and acceptability by regulators is determined on a case by case basis. Aspects like limited life-expectancy, limited or no availability of current treatments, and expected magnitude of the treatment effect could be possible reasons to consider the possibility of using information from rare diseases as comparator.

The regulatory agencies often ask for longitudinal data collection after (conditional) drug approval to assess safety on the long term. Several business firms accommodates this request by fitting specific product or drug registries, in which only patients using the drug are included. In our opinion this post-marketing safety assessment should be conducted by means of (already existing) disease-specific rare diseases. Besides the fact that most of the time, safety parameters are already included (saving time and money), disease-specific registries, rather than product-specific registries, may be useful to compare effectiveness in a clinical setting across styles of patients and coverings, and could protect the evaluation process from commercial influences. Furthermore, the information on a rare disease could then be collected in one place, instead of being divided among several commercial companies who might be unwilling to share 'their' data. Collaboration between stakeholders, like health authorities, (several) pharmaceutical firms, educational researchers and rare malady patient organizations to develop possible ways for this matter ought to be the primary priority aiming at a considerable improvement in achieving sustainable longitudinal rare diseases, which may ultimately enhance the speed of getting effective orphan drugs to those who need them.

CONCLUSIONS:

Rare diseases can be very helpful in trial design by informing the sample size calculation, it can increase efficiency by being a data collection tool in clinical trials, may provide a historical control group in instances when placebo or active comparators are e.g. not ethically acceptable, and it are often informative within the post selling section.

To modify the relevancy and best use of a rare diseases longitudinal knowledge assortment is indispensable, and specific knowledge assortment, prepared for repeated measurement, is needed. The developed list will facilitate to outline the suitable variables to incorporate.

Disease-specific rare diseases are preferred over product-specific registries. In a malady-specific rare diseases all willing patients with the disease are enclosed, and not only the patients who receive a certain treatment.

Valid measurement instruments should be used, and measurements, data collection and data management should make use of global data standards to optimize comparability with clinical trial data.

Agenda for researchers, regulators and funders with relation to rare diseases

Prior information used as observations in the new trial, or combining rare diseases data and trial data could be a possibility to reduce the sample size of a rare disease trial under certain conditions. More research is needed to define the circumstances in which this approach could be used and what are the content requirements.

There are some examples where rare diseases data, either collected retrospectively or prospectively, were used to replace the use of placebo or active comparators. However, for many patients and patient organizations, as well as for many scientists, it is not clear in what circumstances this might or might not be acceptable. A description of situations in which the use of historical data in trial design might be acceptable would be helpful for future rare diseases builders to foresee the (im) possibilities of the rare diseases use and what should be taken into account for that.

To maximize efficiency, post-marketing safety assessment should be conducted by means of (already existing) disease-specific registries instead of product-specific registries, not only to allow for comparisons and protect the evaluation process from commercial influences, but also to enhance possibilities for gathering information on the use of the products in special circumstances (such as extended licensing) or even for collecting clinical trial data. Health authorities, pharmaceutical companies, researchers and patients should make this a common accomplishment.

It is recommended to conduct an international consensus procedure on the content, inclusion criteria, governance, traceability of, and access to disease-specific rare diseases needed for post-marketing surveillance.

- **ABBREVIATIONS:**
  Asterix:
  Advances in tiny Trials style for regulative Innovation and excellence
  CDE:
  Common data elements
  CHMP:

Committee for medicinal products for human use
DIPG:
Diffuse intrinsic pontine glioma
ECFS:
European Cystic Fibrosis Society
EPAR:
European Public Assessment Report
ERN:
European Reference Network
FDA:
US Food and Drug Administration
FEV:
Forced expiratory volume
ICHOM:
International Consortium for Health Outcomes Measurement
RCT:
Randomized controlled trial
RDR:
Rare disease registry
VOD:
Veno-occlusive disease

- **REFERENCES:**

1 Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, Freyer DR, Arnold GL, Pivnick EK, Ottinger CJ, Robinson PH, et al. Clinical outcomes once long-run treatment with alglucosidase Alfa in infants and kids with advanced Pompe unwellness. Genet Med.

2. Van der Lee JH, Tanck MW, Weaseling J, Offringa M. Pitfalls in the design and analysis of pediatric clinical trials: a case of a 'failed' multi-Centre study, and potential solutions. Acta Paediatr.

3. Joppi R, Bertele V, Garattini S. Orphan drugs, orphan diseases. The first decade of orphan drug legislation within the EU. Eur J Clin Pharmacol.

4. European Organization for Rare Diseases: Rare diseases: understanding this public health priority.

5 Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG, Consolidated Standards of Reporting Trials G. CONSORT 2010 clarification and elaboration: updated tips for news parallel cluster randomized trials. J Clin Epidemiol.