Proposal for a new classification of orphan and/or rare conditions based on clinical characteristics that determine the applicability of different research methods to their study

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I put my heart and my soul in my work,

and have lost my mind in the process.

Vincent Van Gogh (1853-1890)

You are never too young to dream big

1. SUMMARY

Background: Methodologies aimed to increase efficiency of clinical studies in small populations have been only scarcely applied to the clinical development of new orphan medicinal products (OMP). The lack of references and guidance may explain reluctance to alternative methodologies, but specific guidance is impractical due to the huge number of existing orphan conditions. A systematic approach to grouping medical conditions based on their methodological requirements may be useful to allow generalisation of recommendations to type conditions, rather than to single disease models.

Objective: To propose a clustering of medical conditions based on their methodological requirements, with the aim to provide a framework for guidance on treatment development and regulatory decision making on OMP.

Methods: The characteristics of medical conditions which may be relevant to study design and regulatory decision making have been identified, and a number of sample conditions have been described in detail for these characteristics and used to produce a database that has been analysed through Multiple Correspondence Analysis (MCA) to identify clusters of conditions. These have been refined and validated from a clinical and regulatory perspective.

Results: Six groups of medical conditions are proposed which share applicability of similar methodologies to their study. A total of 125 medical indications with positive opinions issued by the EMA on OMP applications have been clustered to test applicability of inferences.

Conclusions: A new clustering of conditions based on their methodological requirements is proposed as a framework for guidance on treatment development and regulatory decision making on OMP.

2. ACKNOWLEDGEMENTS

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4. INTRODUCTION

4.1. Rare and orphan diseases

Rare diseases are those that affect a small number of people and have a particularly low prevalence compared to the general population. While individually these entities are uncommon, as a group they are an important cause of chronic illness, disability and premature death in both children and adults. The European Union considers diseases to be rare when they affect not more than 5 in 10000 (i.e 1 in 2000) individuals and no more than about 1 in 1250 in the US[1].

Rare diseases involve few patients but there are so many that their epidemiological impact is impressive and this makes rare diseases a major public health issue[2]. The geographical distribution of rare diseases is not equitable throughout the territory. It can be a rare disease in one region, but common in another one. This is the example of thalassemia, a kind of anaemia with a genetic origin, which is rare in Northern Europe, but it is frequent in the Mediterranean region.

The number of diseases considered as rare is huge. To date, six to eight thousand rare diseases have been discovered and new diseases are regularly described in medical literature. The International Classification of Diseases (ICD) that is used in most countries is not convenient for rare diseases. The absence of a universally recognised coding system is an obstacle for reliable registration of patients in national or international databases, preventing assessment of the economic and social effects of rare diseases. The number of rare diseases described depends on the degree of specificity used when classifying the different entities or disorders. Until now, in the

field of medicine, a disease is defined as an alteration of the state of health, presenting as a unique pattern of symptoms with a single treatment. Whether a pattern is considered unique depends entirely on the level of definition. The more accurate the analysis is, the more certain nuances can be detected[3].

The proportion of the overall population affected with a rare disease is large, between 6% and 8% of the population in the course of their lives, which means that the total number of people affected by rare diseases in the EU may be between 27 and 36 million. Most of them suffer from less frequently occurring diseases affecting one in 100000 people or less. Those people affected by very rare diseases are going to be particularly isolated and also more psychologically, socially, economically and culturally vulnerable[4].

Rare diseases are serious, often chronic and progressive, diseases. It is known that nearly all genetic pathologies are rare diseases, but not all rare diseases are genetic pathologies. There are also very rare forms of infectious diseases, auto-immune pathologies, rare cancers, congenital malformations or toxic diseases, among other categories. There are also many common diseases whose variants can be rare. For many congenital rare diseases, signs may be observed at birth or in childhood, as is the case of proximal spinal muscular atrophy, neurofibromatosis or Prader-Willy syndrome. However, over 50% of rare diseases appear during adulthood, such as Huntington disease, Crohn’s disease, amyotrophic lateral sclerosis, Kaposi's sarcoma or different types of cancer. There is no cure for most of them, but the appropriate treatment and medical care can improve the quality of life of those affected and extend their life expectancy. Important progresses have already been made for certain

diseases, and research and development of new medicinal drugs for these diseases must continue. However, clinical research may present a number of challenges and unique issues that are explained in next sections[5].

4.2. Orphan Drugs

Orphan drugs are used for the diagnosis, prevention, control or treatment of low prevalent (5 per 10000 persons in Europe) life-threatening or chronic disability diseases for which the marketing of the drug would not generate enough income to justify the investment needed to develop it. In absence of specific incentivation, those drugs would not be developed by the pharmaceutical industry for profitability reasons. Yet, their development is needed to respond to public health needs. Although the concept of an orphan drug is usually associated with a rare disease, it is not necessarily so. In fact, the designation of an orphan drug is also used to encourage the development of drugs for neglected diseases, which unfortunately are common outside developed countries[1].

The difference between an orphan drug and a drug for a common disease is basically economic. In the regular marketing scenario, pharmaceutical companies developing orphan drugs would not ever obtain economic revenue making the investment in research and development profitable enough. Cost of drug development for diagnosis, prevention, control or treatment of such diseases is expensive and risky, and the investment would not be recovered by the small expected sales of the medicinal product. Without proper incentives that encourage companies to develop new orphan drugs, and with hurdles in different points of the process, drug development of new treatments cannot be expected.

Rare disease's drug research has the inherent problem of its low incidence, making it difficult to perform a clinical trial of sufficient potency. It can occur that a rare disease has a higher incidence but short survival, in which case a clinical trial could be more feasible. It is true that patients with rare diseases are often identified in different datebases and are part of patient groups that allow rapid identification, facilitating their recruitment and motivating them to participate in clinical trials. Despite of this, it still is very difficult to conduct clinical trials for the development of new therapies. So they are still a group of unprotected patients with no new treatments for their rare diseases, since risk-benefit balance in investigation is not profitable for the pharmaceutical industry[6].

4.3. Development and regulation process for general drugs

4.3.1. *Development process for general drugs*

The process of developing a new molecule is complex and long. The development process can last, in average, more than ten years. Moreover, not all molecules initially selected in the discovery phase will reach the clinical phase and even less will overcome all the clinical development phases and end up in market. It is assumed that one in six molecules that begin the arduous path to marketing will finally have a successful outcome.

Some publications highlight the difficulties that arise during the development process and even until marketing goal. These difficulties may be greater depending on the type of drug and the indication requested. Hay et al. reported that only one in ten of all indications development paths in phase I were eventually approved by the FDA. This

study also found that the success rate for lead indications was around 15% and that wide differences exist depending on the therapeutic area and type of drug. Hay et al. suggested that progress in clinical science together with regulatory risk-benefit assessment may improve the situation. Some of the steps proposed aimed at improving the success rates are the development of more predictive animal models, earlier toxicology evaluation and identification of biomarkers to be used during the early phases[7].

Dimasi et al. showed results in line with those reported by Hay et al. They reported that the duration, rate of failures and milestones vary greatly depending on the type of drug and the indication for which it is developed. They argue the estimated clinical approval success rate for large molecules was 32%, much higher than for small molecules (13%). The estimated clinical approval success rates and phase transition probabilities differed significantly by therapeutic class, and they proposed three therapeutic classes with higher successful rates: systemic anti-infective drugs, musculoskeletal and antineoplastic/immunologic drugs[8].

The whole process of drug discovery and development can be divided in three big phases: *Drug discovery, preclinical development and clinical development*. These phases often overlap and, as mentioned before, may vary depending on the type of drug. Research for a new medicinal product begins in the laboratory with the discovery of a new molecule, and that preclinical research is carried out in laboratory and animal testing to answer basic questions about safety. During clinical research drugs are tested on people to make sure they are safe and effective. Regulators thoroughly examine all of the submitted data related to the drug or device and make a decision to

approve or not to approve it. Marketing phase begins when the new drug is granted a positive opinion and governments issue price and – eventually, depending on local laws – reimbursment decisions.

The main objectives and main activities performed in each of the development phases for a molecule of chemical synthesis are simplified in the next figure.

Drug discovery	Preclinical development	Clinical development			Regulatory & Pricing	Market
		Phase I	Phase II	Phase III		Phase IV
Target selection Hit to lead Lead optimization Lab synthesis Profiling	P.kinetics P.dynamics Short term toxicology Formulation Pilot synthesis	Clinical pharmacol P.kinetics Tolerability Safety in 10-100 healthy volunteers	Exploratory activity Dose finding in 100 to 1000 patients Long term toxicology	Confirmatory efficacy Exposure >1500 patients Safety Risk/benefit	Submission of application Dossier review Authorization Pricing & reimbursement	Pragmatic trials Safety surveillance Observational studies Therapeutic positioning
2-5 years	1.5 years	5-7 years			1-2 years	decades
100 projects	20 compounds	10	5	2	1.2	1

Figure 1. The phases of drug discovery and development process. Modified from Rang and Dale 7th edition[9]

4.3.1.1. Discovery phase

Research for a new medicinal product begins in the laboratory when a pharmacological target is selected and after that, the search for a molecule able to modulate the biological target is carried out. The discovery phase finishes with the selection of one or more lead compounds that will be optimized in the later phases. At this stage, compounds identified are tested in *in vitro* and *in vivo* tests to discard those ones that don't have a promising future or do not successfully complete the preliminary

screening of safety, activity and physicochemical characteristics to be investigated further.

4.3.1.2. Preclinical development

Medicinal products emerged from discovery phase have promising activity against a particular biological target that is believed to play an important role in disease. However, little is known about the safety, toxicity, pharmacokinetics and metabolism of the molecule in humans. It is the function of preclinical drug development to assess all of these parameters prior to human clinical trials. The preclinical development has the main objective of meeting all requirements for first in human studies. These requirements are mainly:

- Safety pharmacology studies to check that the new drug does not produce any acute effect potentially dangerous or clearly serious
- Preliminary toxicology tests to discard genotoxicity and determine the maximum nontoxic doses of the drug.
- Pharmacokinetic studies to characterize the absorption, distribution, metabolism and elimination of the drug.
- Chemical and pharmaceutical development of the drug, to test purity, stability in different conditions
- Formulation studies to search the best galenic option for the new drug and its clinical use.

After a drug candidate goes through all the preclinical testing with satisfactory results, an exhaustive evaluation of all the information provided is done to decide if it is

acceptable to test it in humans. However, the preclinical or non-clinical work continues even after the clinical phase is ongoing, especially to generate toxicology data on long term use before late phase clinical studies are initiated, and before the medicinal product can be placed into the market.

4.3.1.3. Clinical development

Clinical development involves four main steps[10]:

1. Phase I or clinical pharmacology studies: They are performed in a small number of healthy volunteers, usually below 100 subjects, to determine safety and discard potentially dangerous effects, and to assess tolerability and pharmacokinetic characteristics in humans. Pharmacodynamic effects can also be measured.
2. Phase II or exploratory studies normally involve some hundreds of patients, and are intended to describe activity in patients and to identify the dose/s to test in phase III clinical trials.
3. Phase III or confirmatory studies are large. They are mainly randomized double blind clinical trials, performed in more than one center and in different countries, including hundreds or thousands of patients. Sometimes Phase IIa and Phase IIIb are distinguished, where the former (pivotal confirmatory) is usually compared to placebo, and the latter (therapeutic positioning) may be comparing the new drug to the standard of care.

4. Phase IV or post-marketing studies: Additional information and ongoing safety and tolerability assessment must be performed to proof that the drug keeps the favorable benefit-risk balance after commercialization, when larger number of patients are treated during long periods of time an under routine clinical practice conditions.

Clinical development phases are resumed in the figure below (Figure 2):

Figure 2. Clinical Development Phases

4.3.1.4. Safety evaluation during Clinical Development

Safety evaluation during clinical drug development is expected to characterise and quantify the safety profile of a drug over a reasonable duration of time, which should be consistent with the intended long-term use of the drug. Thus, duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the data base necessary to achieve such goals. It is useful to distinguish between clinical data on adverse drug events (ADEs) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently are non-concurrently controlled studies. It

is expected that short-term event rates (cumulative 3-month incidence of about 1%) will be well characterised. Events where the rate of occurrence changes over a longer period of time may need to be specifically characterised or qualified, depending on their severity and importance to the risk-benefit assessment of the drug. The safety evaluation during clinical drug development is not expected to characterise rare adverse events, for example, those occurring in less than 1 in 1000 patients.

The design of the clinical studies can significantly influence the ability to make causality judgements about the relationships between the drug and adverse events. A placebo-controlled trial allows direct comparisons between the adverse event rate in the drug-treated group and the background event rate in the patient population being studied. Studies including a positive or active control will allow a comparison of adverse event rates to be made between the test drug and the control drug, which may prove to be useful information for medical decision taking, but no direct assessment of the background event rate in the population studied can be made. A study that has no concurrent control group makes it difficult to conclude on the causal relationship between adverse events and the test drug

Available information suggests that most ADEs first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use should, in general, be adequate to characterise the pattern of most ADEs over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether adverse events increase or decrease over time, as well as to observe delayed events with frequencies within the range of 0.5%-5%). Usually 300-600 patients should be adequate. In some

cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small.

However, some ADEs may increase in frequency or severity with time, and some serious ADEs may first appear after drug treatment for longer than 6 months. Therefore, for drugs intended for chronic or intermittent treatments, the general requirements for development include that some patients should be treated for a minimum of 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgement based on the probability of detecting a given ADE frequency level and practical considerations, so that 100 patients exposed for a minimum of one-year is generally considered to be acceptable. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a one-year exposure period, this number of patients can provide reasonable assurance that the true cumulative one year incidence is no greater than 3%[11].

4.3.2. Regulation process for general drugs

Healthy authorities are responsible to watch over the health of the population. The regulatory agencies (RA) decide if the entry of drugs into the market is acceptable based on the guarantees on quality, efficacy and safety of the products, as demonstrated by scientific documentation. Also, the RA and the Institutional Review Boards (IRB) or independent Ethics' Committee (EC) supervise the minimum amount of safety information that must be obtained before initiating a trial in humans, in order to protect the integrity of individuals exposed to investigational products.

Responsibilities of the IRB/EC according to the Good Clinical Practices (GCP) guideline include the safeguard of the rights, safety and wellbeing of all trial subjects. They are responsible for the assessment of the risks and benefits that the participation in a given clinical trial will imply for participating subjects[11].

Placing medicinal products on the market is subject to the granting of a marketing authorization by the competent authorities. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was created to bring together the regulatory authorities and pharmaceutical industry of Europe, Japan and the United States to discuss scientific and technical aspects of drug registration. It was created in 1990 and since then several tripartite harmonized guidelines have been implemented that summarise the common minimum requirements that would be deemed internationally acceptable regarding the authorization of a new medicinal product or the authorization of a new clinical trial with an investigational product. Such international agreement reduces variability and redundancy of experiments due to discrepancies across countries in definition of standards.

The regulation of medicinal products in the European Union

The legal framework governing medicinal products for human use in the EU is settled by the European Council. While National Authorities remain sovereign on their territories, the regulation of certain medicinal products are decided in a centralized way for all Europe.The European Medicines Agency (EMA) is an independent body in charge, since the mid-90s, of providing the European Union (EU) institutions with scientific advice on medicinal products.

There is a guideline[12] that lay down the requirements and procedures for the marketing authorisation for medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorized.

Community legislation also provides for common rules for the conduct of clinical trials in the EU countries. All Community legislation in the area of medicinal products for human use is contained in the first volume of "The Rules Governing Medicinal Products in the European Union". In addition, to facilitate the interpretation of the legislation and its uniform application across the EU, numerous guidelines of regulatory and scientific nature have additionally been adopted, some of them ICH guidelines[13]. Scientific guidelines are intended to provide a basis for practical harmonization of the manner in which the EU Member States and the EMA interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community Directives. They also help to ensure that applications for marketing authorisation are prepared in a manner that will be recognized as valid by the EMA[14].

The regulation of medicinal products in the United States

The Food and Drug Administration (FDA) is an agency within the US Department of Health and Human Services whose responsibilities are protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices. The FDA is also responsible for the safety and security of food supply, cosmetics, dietary supplements and products that give off radiation.

The FDA also issues guidance documents representing FDA's current thinking on regulatory issues. These documents usually discuss issues that relate to the design, production, labelling, promotion, manufacturing, and testing of regulated products. Guidance documents may also relate to the processing, content, and evaluation or approval of submissions as well as to inspection and enforcement policies[15].

4.4. Regulation and development process for Orphan Drugs

4.4.1. Regulation process for Orphan Drugs

The US was the first country to address the need to develop specific legislation for Orphan drugs. In 1983 the Orphan Drugs Act was promulgated and subsequently similar standards were published in Japan (1993) and in Australia (1997). The European Parliament and Council adopted a Regulation (EC) No 141/2000[1] to establish a procedure for the declaration of certain medicinal products as orphan products, and to establish incentives to promote their research, development and marketing.

The EU legislation determines that market access to new drugs requires the same level of evidence regardless of whether they are intended for rare or highly prevalent diseases, since patients with rare diseases deserve the same quality, safety and efficacy in medicinal products as other patients. Thus, orphan medicinal products must also be submitted to evaluation process, so that sponsors and developers of orphan medicinal products need to obtain a Community authorization for commercializatoncompliant with the same rules of quality, efficacy and safety as drugs for highly prevalent diseases. While patients' safety and best interests lead these provisions, the EU legislation requires substantial efforts to companies that should

conduct pivotal trials to gather evidence on the product efficacy and safety. Such requirements can be difficult to accomplish due to the inherent low prevalence of rare diseases, which hinder the performance of clinical trials with sufficient statistical power, and may represent difficulties to developers that may discourage the research of new treatments, and/or lengthy developments that may delay the access to new or improved therapies for rare disease populations

The Regulation (EC) No 141/2000[1] on orphan medicinal products adopted by The European Parliament and Council proposes a *"Community procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the research, development and placing on the market of designation orphan medicinal products"*. According to this document a medicinal product shall be designated as an orphan medicinal product if two premises are fulfilled (Figure 3):

1-The new drug proposed is intended for the diagnosis, prevention, control or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention, control or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community, and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.

2-It does not exist a satisfactory method of diagnosis, prevention, control or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

The opinion endorsing an orphan drug designation is carried out by the Committee for Orphan Medicinal Products (COMP) of the EMA, while marketing authorization opinions are issued by the Committee for Medicinal Products for Human Use (CHMP), the same committee that is in charge of issuing approval opinions for non-orphan drugs. The final decision, based on the CHMP recommendation, is issued by the European Council end endorsed by national regulatory authorities.

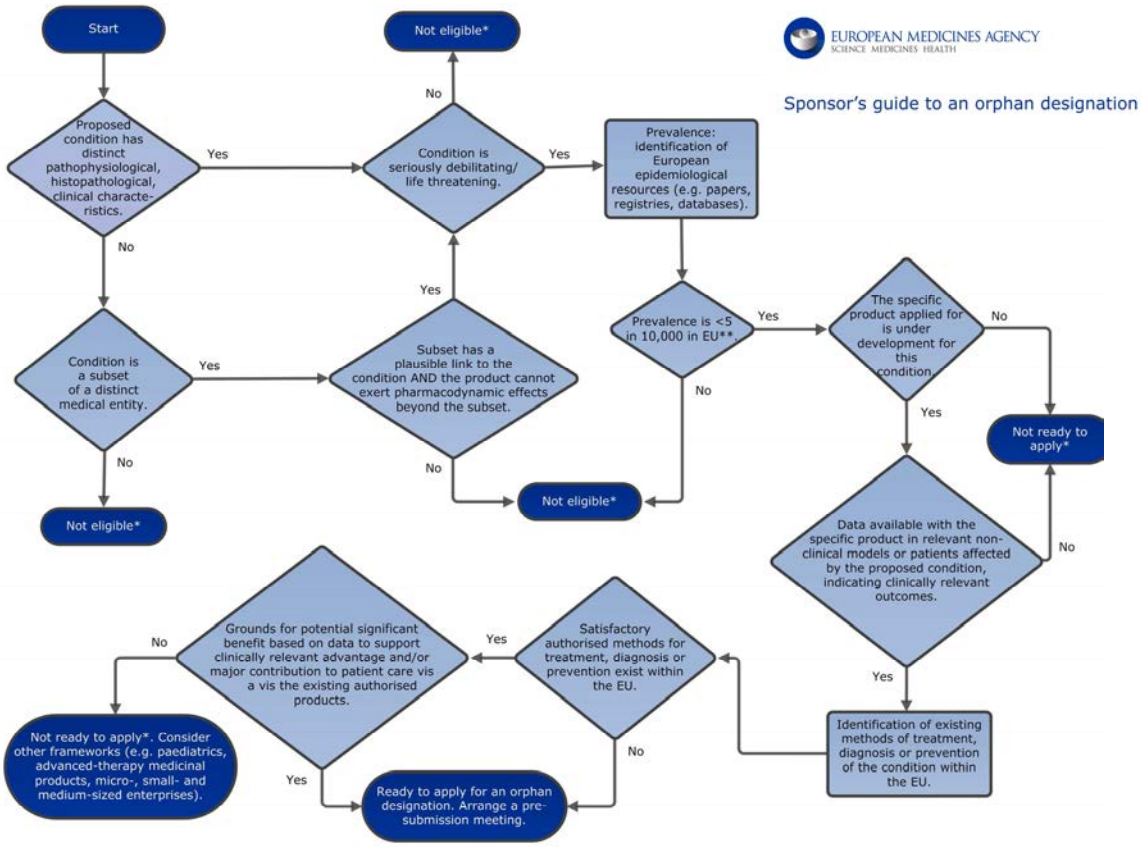


Figure 3. Sponsor's guide to an orphan designation

The COMP consists on one member nominated by each Member State, three members nominated by the Commission to represent patient's organisations and three

members nominated by the Commission on the basis of a recommendation from the Agency. The role of the COMP is to examine applications presented by pharmaceutical industry to obtain an orphan medicinal product designation, so that they can benefit from incentives for research, development, and later to place it on the market. The COMP is also responsible for assisting the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products[16].

The EU Commission recognises the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would usually not be recovered by the expected sales of the medicinal product. Thus, in absence of incentives, the commercial interest of developing new treatments for rare diseases is recognised to be small and the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions[1,4].

The incentives that can be finally granted to industry after obtaining orphan medicinal product designation consist on:

- EMA assistance in the development of research protocols.
- Reduced rates for applications.
- Access to public funding for research.
- Market exclusivity for 10 years in case the drug is approved. Other orphan drug for the same indication will be approved only if it brings a considerable and significant benefit.

- Extension of the market exclusivity for two more years if a paediatric investigation program has been carried out with the drug, regardless of whether or not the indication is obtained in children.

Incentives are actions that favor and accelerate the authorization of orphan drugs, aimed to ensure availability and access to new treatments. They can be financial and non-financial incentives:

On one hand, finantial incentives include research grants, tax reductions, marketing exclusivity, and user fee waivers, aimed to ensure that industries can recover research and development investmentsdespite the small market size. Blankart et al. found that only 10% of clinical trials for orphan drugs would have been conducted without such financial incentives[17].

On the other hand, non-financial incentives include the reduction of evaluation times for regulatory approval, like accelerated assesments, or conditional marketing aprovals where exceptional circumstances are recognised in the context of an urgent medical need that justify granting a rapid access to the treatment with certain commitments to complete scientific data. Also, pre-licensing accesses (compassionate or off-label access) may be applied[18]. All of these circumstances are going to be explained below.

An important aspect in the process of evaluation and approval of new orphan medicinal products is the time that elapses between the submission of approval for a new therapeutic target and the actual access to that new medication by patients.

One important determinant is the time that Regulatory Agencies require for evaluation. Despite of the advances in basic science there is a lack of resources by the Regulatory Agencies to address innovation, slowing access to new therapies to patients with few alternatives. Some critics argue that given the advances in basic science, it

should be possible to develop new drugs more quickly than it is done[19]. Not all the Regulatory Agencies have the same times of authorisation for orphan medicinal products. Differences can be found between the two main Regulatory Agencies, the FDA and the EMA. Some of these differences are described in Roberts et al.[20] publication which compares the time to approval of new oncological drugs between FDA and EMA, and the time to bringing them to the market after a positive opinion. They identified thirty-five new cancer drugs approved between 2013-2010 by the FDA and EMA and concluded that the FDA proved to be more efficient than the EMA facilitating early access to new drugs. They proposed two reasons why there were differences in time between the two approval agencies. Firstly, it was detected that laboratories researchers often submit their proposals to the FDA before than submitting to the EMA, and secondly it was proved that assessment time was shorter by the FDA as compared to the EMA. Consequently, the FDA approved a greater number of cancer drugs and biological studied during the same period[20,21]. It is known that early drug authorisation is of obvious importance for drugs that represent a breakthrough therapeutic advance[22]. The aim of researchers is to reduce the access time for patients to new alternatives as therapeutic options for their rare diseases. In some cases, access to orphan drugs is requested based on incomplete developments at an early stage, based on preliminary efficacy and on the lack of therapeutic options of the intended population.

There are some regulatory options to obtain early marketing authorization and reduce the access time to new therapies. The EMA has defined an accelerated procedure that allows reducing the overall process of assessment; similarly, the FDA has defined some

procedures, including priority review, fast-track approval and accelerated approval. Although the process is applicable to both orphan and non-orphan medicines, the process is more accepted for orphan drugs; nevertheless orphan drugs are not automatically qualified for accelerated procedures. Also, reduced pre-marketing requirements with post-marketing commitments to complete the required information may be applied.

The procedures involved are:

- Accelerated assessment: reduces the timeframe for the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorisation application. Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation**.** Evaluating a marketing-authorisation application under the centralised procedure can take up to 210 days, not counting clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment[14].

- Conditional marketing: when the data is not yet complete. The company is obliged to carry out additional studies and the authorisation is renewed annually until the studies are completed and, then, it has a normal authorisation. They are only awarded for unmet medical needs with the goal of providing early access to the drug[14].

- Exceptional circumstances: where the applicant can demonstrate that it is not possible to provide complete data on the efficacy and safety of the medicinal product for which authorisation is sought. It is usually motivated by the rarity of the disease for which it is intended, limited scientific knowledge in the area concerned or ethical

considerations involved in collecting such data. The information is reviewed annually to re-evaluate the risk-benefit balance. The fulfilment of any specific procedures/obligations imposed as part of the marketing authorisation under exceptional circumstances is aimed at the provision of information on the safe and effective use of the product and will normally not lead to the completion of a full dossier. In the rare cases where the applicant has finally been able to provide comprehensive data on the efficacy and safety under normal conditions of use (a "full dossier") and no specific procedures/obligations remain, a "normal" marketing authorisation could be granted[12].

The differences between conditional authorization and authorization under exceptional circumstances are compared below (Table 1):.

Conditional marketing authorisation	Marketing authorisation under exceptional circumstances
Authorisation while the collection of comprehensive data is ongoing in order to address unmet medical needs. Comprehensive data are still being generated post authorisation in agreed timelines.	Authorisation when comprehensive data on efficacy and safety cannot be obtained, but it is still appropriate to grant the authorisation due to exceptional circumstances.
Medicinal products without comprehensive data belonging to at least one of the following categories: - seriously debilitating or life-threatening diseases; -emergency situations. -orphan medicines. And fulfilling all of the following criteria: -positive risk-benefit balance.	Medicines without comprehensive data on efficacy and safety under normal conditions of use, respectively because: - Indications encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. - In the present state of scientific knowledge, comprehensive information cannot be provided, or it would be

Conditional marketing authorisation	Marketing authorisation under exceptional circumstances
-the applicant is likely to be able to provide comprehensive data. addressing an unmet medical need. Benefits of immediate availability outweigh the risks that additional data are still required.	contrary to generally accepted principles of medical ethics to collect such information.
Authorisation valid for one year, can be renewed annually	Authorisation valid as normal, but EMA annually reassesses how well the specific obligations have been met and how the data which generated as a result of those obligations impacts the medicine's benefit-risk-balance
Once applicants provide comprehensive data, it can become a 'standard' marketing authorisation	Will normally **not** lead to the completion of a full dossier to become a 'standard' marketing authorisation

Table 1. Differences between conditional marketing and under exceptional circumstances[14]

Off-label use, expanded acces and pre-licensing use.

Off-label or “unlabeled” drug use is the use of a drug approved by the EMA or FDA for other indications that are not included in approved labelling.

Expanded access refers to the use of an investigational new drug outside of a clinical trial by patients with serious or life-threatening conditions who do not meet the criteria for inclusion of the clinical trial in progress, and don't have any alternatives therapeutic option.

Pre-licensing allows importation of orphan drugs available in other countries, but currently unauthorized in the country where it is needed[18].

4.4.2. Development process for Orphan Drugs

As recognised by the EU legislation, the principles and overarching values of universality, access to good quality care, equity and solidarity, are of paramount importance for patients with rare diseases[4].

However, finding treatments for rare diseases is difficult due to many reasons. There are many obstacles to research in rare diseases. It is an area where experts are scarce, and in terms of academic research there is less interest for clinical studies, fewer funding opportunities, and a disadvantage for researchers at evaluation due to the presumed low societal impact. In terms of industry research, rare diseases represent a small, niche market, and there is a recent shift towards leaving basic research to academic teams (Figure 4). To this adds the lack of collaborative efforts, limited access to platforms, the need for alternative designs for clinical trials suitable to be applied to small populations, and the difficulties of conducting research when only a limited number of patients is affected by each medical condition, as well as the problems posed by the additional difficulties met at regulatory assessment to achieve acceptability of innovative approaches.

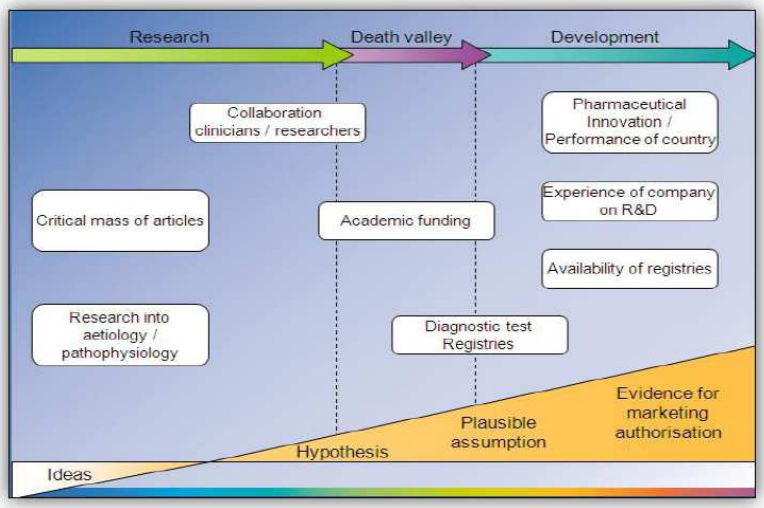


Figure 4. Bottlenecks to research and development in rare diseases. Taken from Rodwelll et al[16] 2014.

A number of actions have been done at the European level to enhance research networking and expertise connection across the region, as well as to optimise the precision and harmonization of diagnosis, availability of diagnostic tools, screening programs and disease registries[3]. Amongst these activities, a distinctive one was the setting of the **Orphanet, the portal of rare diseases and orphan drugs**[23], which offers an inventory and an encyclopaedia of diseases in 6 languages (English, French, Spanish, German, Italian and Portuguese). Each disease in Orphanet has a unique identifier and is placed in a poly-hierarchy classification system, accessible on the website. Orphanet has also developed an encyclopaedia published in an electronic, open-access journal, the Orphanet Journal of Rare Diseases, which allows searching by disease name, but also allows searching by clinical signs and symptoms, providing an output consisting of a list of possible diseases sorted by probability, so that it may serve as a diagnostic aiding tool[24].

Also, Orphanet has built a directory of expert clinical centres and keeps it actualized. The aim is to allow access to expertise and appropriate patient referrals across 37 countries[25]. This is available for clinical laboratories for genetic testing as well[26]. A listing of all on going national and European-level funded research projects by type of research and by disease is also available, aimed to facilitate collaboration between researchers and between researchers and Industry. The listing displays patient registries, biobanks and highly specialised platforms and know-how, which may be of interest in R&D, as well as licensing opportunities[27]. Networking amongst patients and professionals are also supported through specific pages. Orphanet data is continuously collected in each European Member State and contents are validated by experts.

Besides from research focused on disease diagnosis and basic patophysiology understanding, the research and development of new Orphan Medicinal Products (OMP) is considered as an area requiring specific initiatives to attract interest from researchers and from Industry[16].

An action taken to enhance research networking and expertise connection across the region is the creation of **European Reference Networks (ERN).** ERNs are networks of centres of expertise and healthcare providers that are organised across borders. They have a clear governance structure for knowledge sharing and care coordination across the EU to improve access to diagnosis and treatment, as well as the provision of high-quality healthcare for patients. ERNs for rare diseases should serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERN should also reflect the need

for services and expertise to be distributed across the EU. Due to the low prevalence and complexity of rare diseases, as well as to the nature of small and scattered patient populations, the system of ERN that is being established can bring real added value to the care, but also to the research of new treatments for rare disease patients. By ensuring doctors have the most recent and expert knowledge possible, they will be better informed to make decisions on how to adapt treatment and care pathways, and to develop new approaches and solutions to clinical problems[28].

In spite of the resources that facilitate the knowledge and the relationship between different professionals, and allow availability of subsequent treatment facilities where necessary, there is yet a number of methodological obstacles to the development of rare diseases, pivoting mainly on the small size of the population to be studied.

There is thus a need for suitable alternative study designs to the classical parallel group comparative clinical trial, which could maximise the value of the limited information which is feasible to obtain from small numbers of patients. However, there is a need also to address the problems posed by the additional difficulties met to the applicability of innovative approaches, in terms of uncertainty on their robustness and also regulatory acceptability, but also on how these new designs may address individual ethical and clinical circumstances of patients with rare diseases, that require specific attention at the time of study design[29].

These handicaps joined to the lack of regulatory predictability often discourage the research of new treatments since it is difficult to predict what will happen with a drug intended for the treatment of a rare disease once the dossier is submitted for its authorization, and the financial risk is difficult to measure. One of the biggest problems

for developers is not the economic risk itself, but the uncertainty in quantifying such risk in their predictive models of return of investment. It is often this uncertainty that blocks the development of new molecules in the orphan field. Predictability may be improved if reference documents that guide the process to the end are available, but the currently available regulatory guidance for these drugs is regarded as too general to set a predictability frame on requirements to achieve a positive regulatory decision.

4.5. Methodological approaches and trial designs in Orphan Medicinal Products

Classic randomised parallel groups double blind clinical trials literally implement the scientific method and are accepted as the best design opcion, being robust, intuitive and solid. The intuitiveness and robustness of parallel design to provide consistent and reliable causal conditions when performed correctly have, for decades, been the standard methodological reference point in clinical research ahead of other designs. It is currently considered to meet the most demanding methodological requirements, especially those of regulatory authorities which, from a position of minimizing potential risks to public health, generally prefer to base their decisions on the commercialization of new treatments in the results of parallel group trials with random assignment under double-blind conditions.

A classic trial for a common disease implies a comparative study between two or more parallel groups that enter simultaneously in the same clinical setting and process of treatment and follow-up, with constant duration and maintaining the intervention studied as the only difference single factor in study. Parallel driving ensures that the groups receive the interventions and are evaluated under similar conditions. Random

assignment of interventions under masking conditions controls the risk of biased allocation and minimizes known and unknown potential biases.

The design of the study must be established prospectively and must be executed according to a detailed protocol that selects an a priori acceptable statistical error margins. The differences between the groups at the end of the process will be attributable exclusively to the interventions studied, allowing the establishment of causal relationships[30,31].

However, there are not only advantages found in the clinical tests of parallel groups, they also have certain limitations. On one hand, the execution is expensive and long. Information cannot be obtained until the end of the trial, and the available information is ignored during the execution time. On the other hand, parallel groups are inflexible, and the parameters of the design are not verified until the end of the trial, even though they are not always well known in advance. All the design options are kept until the end, even when one could have been clearly worse or better. Also, previous information is only used for the calculation of the sample size, and, finally, the inferences are based on the observed evidence.

There are many alternative experimental designs to the classic study with random assignment of parallel groups, whose purpose is to adapt the studies to certain particularities of the studied situations. Many alternative approaches to the classic parallel clinical trial may also result in fewer patients treated and shorter study duration.

One example are complete or incomplete cross-over studies, where patients receive more than one treatment, so that analysis is optimized based on intra-individual

variability, and variance is reduced by controlling inter-individual variability resulting in smaller sample size. The subjects are randomised to one or more sequences of consecutive treatments, separated by periods of wash-out. These designs are useful in rare pathologies, but require that the factors under study are independent of the time course and the effect of intervention is not persistent on time[32].

Other strategies to optimise sample size include choosing longer trial duration when assessing survival designs or repeated events; increased number of evens in the same population can reduce sample size requirements by capturing more events among the trial participants[33]. Using genetic testing to select poplations with higher chance to respond may reduce variability between individuals, or allow inclusion of patients before they experience symptoms[34]. Using continuous outcome measures instead of categorical or binary variables may increase the ability of the trial to detect differences with smaller samples; similarly, using surrogate markers, composite endpoints, or repeated measure outcomes may also optimise the study design while keeping lower sample sizes. Other example are flexible designs, such as sequential or adaptive designs. Both take advantage of the information as it is obtained to increase the efficiency of the study and may shorten the study duration – and sometimes reduce the required sample size. Certain adaptive designs can also increase participant's probability of receiving the most effective treatment, which can encourage enrolment in a trial[33].

Sequential studies acquire information until it is sufficiently precise to be able to reject the null hypothesis in the case of a positive study, or to conclude that the probability of rejecting it if the study is continued is too low (futility). These methods are

especially useful when the recruitment period is prolonged and the duration of the treatment of a patient is relatively short.

Adaptive designs allow the adjustment of the study to the real conditions from the information obtained during its execution, maximizing the efficiency of the experiment, and in general, reducing its risks[35,36,37].

Finally, considering operational feasibility, clinical trial networks for rare diseases can facilitate the conduct of multicentre and even multinational randomized trials and facilitate the recruitment of larger populations even in rare conditions[38].

In summary, three main aspects (type of control, setting of control and the endpoint) that are determinants of study design are resumed in Table 2 and exposed in next sections.

TYPE OF CONTROLS		
Concurrent	Placebo-controlled trial	
	Dose-response	
	Active (positive)	
	No- treatment	
	Multiple control groups	
Non concurrent	Historical	
	Group in another setting	
Intra-subject comparison		
SETTING OF CONTROLS		
Methods obtaining information	Parallel groups	
	Add-on study	
	Early escape	
	Limited placebo period	
	Randomised withdrawal	
	Cross-over	
	N-of-1	
	Population enrichment	
	Enrichment withdrawal	
	Time to onset design	
Methods using information as acquired	Adaptive	Design specifications

		Sample size
		Primary end-point
		Dose finding
		Randomization
		Inclusion or exclusion criteria
	Sequential	
	Bayesian	
ENDPOINTS		
Single	Primary	
	Secondary	
Multiple	Co-primary (results for all of them are needed)	
	Several primary endpoints (results for only one is needed)	
	Composite	
	Others	

Table 2. Resume of the determinants of a trial design

4.5.1. Type of controls

The choice of control group is always a critical decision in designing a clinical trial. That choice affects not only the conclusions that can be obtained from the trial, but many others features of the study like the ethical acceptability of the trial, the degree to which bias in conducting and analyzing the study can be minimized, the types of subjects that can be recruited and the pace of recruitment, the kind of endpoints that can be studied, the public and scientific credibility of the results or the acceptability of the results by regulatory authorities.

The choice of control group is of particularly critical importance to clinical trials carried out during drug development to demonstrate efficacy. Control groups have one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatments. The control group experience tells us what

would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective. A concurrent control group is one chosen from the same population as the test group and treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time.

Bias means the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value.

Randomization and blinding are the two techniques usually used to minimize the chance of such bias, and to ensure that the test treatment and control groups are similar at the start of the study and are treated similarly in the course of the study:

Assurance that subject populations are similar in test and control groups are best attained by randomly dividing a single population to avoid systematic differences between study groups with respect to baseline variables that could affect outcome.

Blinding allows to minimize the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment. It helps to assure that the study groups are treated in a similar manner during the trial[39].

The principal methods of determining who will be in the control group are by randomization or by selection of a control population separate from the population treated in the trial (external or historical control). Control groups can be categorized:

4.5.1.1. Concurrent controls

4.5.1.1.1. *Placebo- controlled trial*

In a placebo-controlled trial, subjects are randomly assigned to a test treatment or to an identical-appearing treatment that does not contain the test drug. The treatments may be titrated to effect or tolerance, or may be given at one or more fixed doses. Such trials are almost always double-blind. The name of the control suggests that its purpose is to control for "placebo" effect (improvement in a subject resulting from the belief that he or she is taking an active drug), but that is not its only or major benefit. Rather, the placebo control design, by including a group that receives an inert treatment, controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug, such as the expectation of the subject or the investigator on the drug effects or subjective perceptions on clinical assessments, spontaneous course of disease, regression to the mean, or the effect of concomitant treatments. Placebo-controlled trials seek to show a difference between treatments when they are studying effectiveness, but may also seek to show lack of difference (of specified size) in evaluating a safety measurement. The use of a placebo control group does not imply that the control group is untreated. In many placebo-controlled trials, the new treatment and placebo are each added to a common standard therapy.

Within this general description there is a wide variety of designs that can be used successfully: parallel or cross-over designs, single fixed dose or titration in the active drug group, or even non-randomized designs.

It is often possible to address the ethical or practical limitations of placebo-controlled trials by using modified study designs that still retain the inferential advantages of these trials, such as those with early rescue or limited periods of placebo control. In addition, placebo-controlled trials can be made more informative by including additional treatment groups, such as multiple doses of the test agent or a known active control treatment[39].

4.5.1.1.2. *Dose-response concurrent control*

In a randomized, fixed-dose, dose-response trial, subjects are randomized to one of several fixed-dose groups. Subjects may either be placed on their fixed dose initially or be raised to that dose gradually, but the intended comparison is between the groups on their final dose. Dose-response trials are usually double-blind. They may include a placebo (zero doses) and/or active control

4.5.1.1.3. *Active (Positive) concurrent control*

Patients may not wish to enroll into trials because of concerns about being randomized to a placebo[40]. Such reluctance may be especially relevant in orphan diseases and/or in paediatric trials. In an active control (or positive control) trial, subjects are randomly assigned to the test treatment or to an active control treatment. Such trials are usually double-blind. When different regimens, different routes of administration and/or different toxicities concur, then double dummy approaches or third party assessments of efficacy may be used to preserve blinding. Active control trials can have two distinct objectives with respect to showing efficacy:

a) to show efficacy of the test treatment by showing it is as good as a known effective treatment

b) to show efficacy by showing superiority of the test treatment to the active control. They may also be used with the primary objective of comparing the efficacy and/or safety of the two treatments.

4.5.1.1.4. *No-treatment concurrent Control*

In a no treatment-controlled trial, subjects are randomly assigned to test treatment or to no study treatment. The principal difference between this design and a placebo-controlled trial is that subjects and investigators are not blind to treatment assignment. This is a valuable approach and should always be considered in trials that cannot be blinded, but has many problems associated with potential biases derived from knowing the treatment assignment.

4.5.1.1.5. *Multiple Control Groups*

Often more than one kind of control are used in a single study (i ex: active control and placebo). Similarly, trials can use several doses of test drug and several doses of an active control, with or without placebo. This design may be useful in exploratory settings and especially for active drug comparisons where the relative potency of the two drugs is not well established, or where the purpose of the trial is to establish relative potency.

4.5.1.2. No concurrent controls

An externally controlled trial may compare a group of subjects receiving the test treatment with a group of patient's external to the study, rather than to an internal

control group consisting of patients from the same population assigned to a different treatment. The external control can be a group of patients treated at an earlier time (historical control) or a group treated during the same time period but in another setting.

4.5.1.2.1. *Historical control*

A historical control compares the treated group with a not concurrent separate group of patients. The comparison can be between two different times.

Five requirements have been proposed to consider valid an historical controlled study[41,42]:

1-Control group received the precisely defined treatment in a recent study.

2-Criteria for eligibility, work-up and evaluations must be the same.

3-Prognostic factors are completely known and similar in both groups.

4-No unexplained indications lead one to expect different results.

5-If there exists some differences in prognostic factors, the differences are not sufficient to explain any observed difference in outcomes

4.5.1.2.2. *Group in another setting*

A group in another setting is one in which the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent. The control group is thus not derived from exactly the same population as the treated population. It could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study. Sometimes certain patients from a larger external experience are selected as a control

group on the basis of particular characteristics that make them similar to the treatment group; there may even be an attempt to match particular control and treated patients[39]. Big databases of electronic records may be used to that purpose.

4.5.2. Setting of controls

4.5.2.1. Methods obtaining information

4.5.2.1.1. *Parallel group*

The intuition and robustness of the classic trials have done them a methodological standard in clinical research over other designs. Regulatory agencies prefer to base their opinions on traditional models in randomized double-blind conditions, where the bias for the assignment and evaluation can be controlled and because of their robustness to conclude causality. The reluctance of regulatory agencies to accept alternative methods and the risk avoidance of financial pharmaceutical investors prefer "safer regulatory methods".

Comparative parallel group designs literally implements the concept of scientific method, two or more groups enter simultaneously in the same process of treatment and monitoring of constant duration. The only differentiating factor is the intervention studied. The trial design prospective established and executed following the guidelines of an established protocol, allows the selection of acceptable statistical error margins. The differences between the groups at the end of the process are attributable to the distinguishing factor.

The main points for the parallel group:

- Robust, intuitive and solid

- Literally implementation of scientific method
- Conclusive on causality

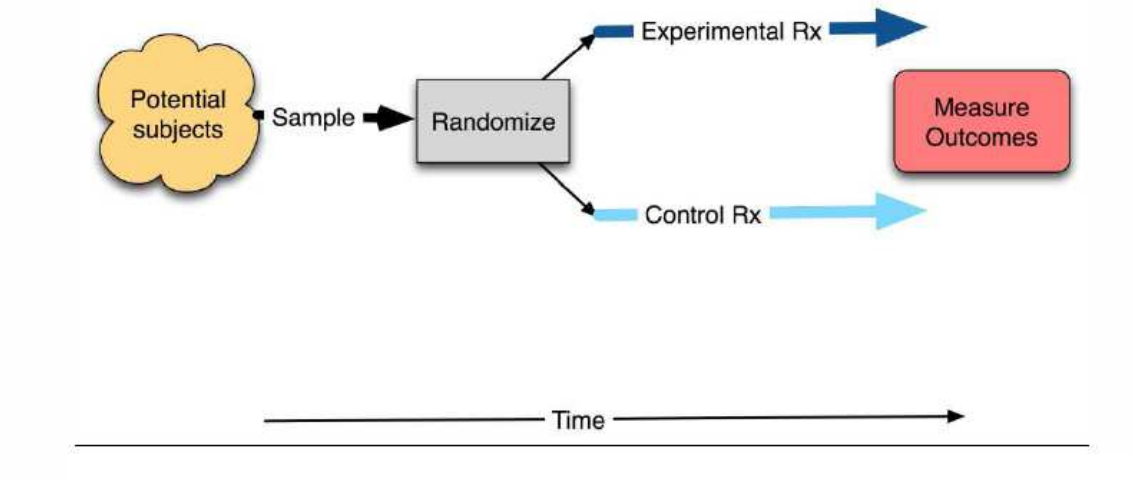


Figure 5. Parallel group. Taken from: A new toolkit for conducting clinical trials in rare disorders[43]

4.5.2.1.2. ***Add-on study***

An *add-on* study is a placebo-controlled trial of a new agent conducted in people also receiving standard treatment and randomised to receive the experimental treatment or a placebo on top of the standard of care. Such studies are particularly important when available treatments are known to decrease mortality or irreversible morbidity, and when a non-inferiority trial with standard treatment as the active control cannot be carried out, or would be difficult to interpret.

The main advantage is that patients with serious disease can be included in this kind of design, but a disadvantage is that it becomes difficult to demonstrate additional efficacy compared with the available treatments.

4.5.2.1.3. ***Early Escape***

In early escape designs, patients are continuously evaluated to detect their individual response, and are taken out from the study if they don't reach a minimal response in pre-specified times of the study, either because of worsening of clinical status, or failure to improve to a defined level.

Early escape is useful when lack of active treatment can have an important prognostic impact in the health of the patients posing ethical restrains to use of placebo or potentially useless medications; i ex: when several weeks of articular inflammation may lead to irreversible articular damage. By ensuring continuous monitoring and appropriate rescue management in case of failure, early escape improves the acceptability of taking part in studies with placebo or new medicinal agents. However, a main disadvantage is that long-term comparisons are not feasible.

4.5.2.1.4. *Limited Placebo Period – Delayed start randomization*

In a situation where long-term placebo treatment would not be acceptable, delayed start randomization consists of randomising the sample to either immediate start of the treatment or to the use of a placebo group for a short period at the beginning of an active control trial, after which all patients would receive the active treatmentand the trial would then continue without the placebo group. Such provision could provide evidence on early effects of the drug, allowing establishing assay sensitivity while ensuring access to active treatment to all trial participants. The observation of similar effects in both groups with a temporal delay serves as a sign of pharmacodynamic consistency. Also, differences between groups observed in the long-term may be informative on the impact of treatment delay. This type of design is relevant for severe progressive orphan conditions where few patients are affected and there is a

reasonable plausibility on the effects of the tested drug making the placebo option difficult to accept by subjects.

4.5.2.1.5. ***Randomised withdrawal***

For treatments intended for controlling symptoms otherwise reasonably constant, and not progressive in the short term, randomised withdrawal designs are an option. All patients are treated with the studied drug, and those who have treatment response

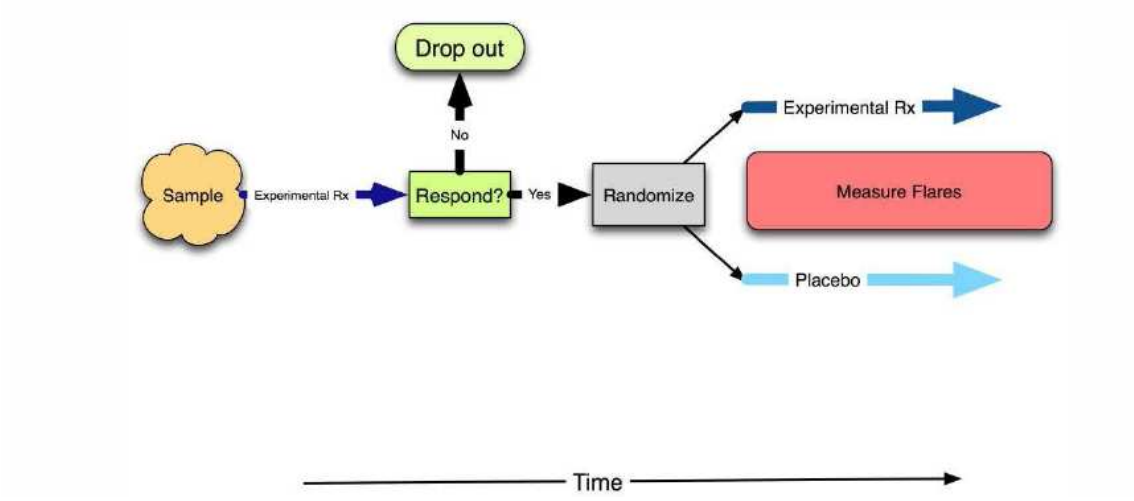


Figure 6. Randomised withdrawal. Taken from: A new toolkit for conducting clinical trials in rare disorders[43]

are randomised to either continue receiving the same treatment, or a placebo. The trial endpoints are usually the return of symptoms[44]. Return of symptoms represents a sign of causality.

There is another variant of randomised withdrawal that consists on crossing over patients, so that they are exchanged to another active treatment or placebo (randomised switch). The advantages are that patients with serious pathologies are allowed to participate but on the other side, the effect of withdrawing a treatment that has proven to be effective could be ethically questionable.

4.5.2.1.6. ***Cross-over***

Again in situations where the medical condtion is stable and the treatment has a symptomatic approach, cross-over trials are options to design trials of relatively small sample size. The subjects are randomised to one or more sequences of consecutive treatments, separated by periods of wash-out. At the end of every period of treatment the principal variable is measured up. The results are analyzed fitting for sequence and period when the experimental phase is finished and the contrast of hypothesis is realized. The assessments are only concerned with short-term response as measured during and at the end of each treatment period. Any more long-term carry-over effect of the first treatment into the second period is undesirable. If such carry-over is possible, appropriate wash-out periods between treatments should ensure that the effects are not present at the beginning of the following period[41]. As randomised withdrawal, cross-over designs are useful in rare diseases when the factors under study are independent of the temporal evolution.

One of the most interesting advantages is that the intraindividual variability is reduced, so that it allows optimization of the sample size. In addition all patients will receive the experimental treatment at some time during the trial which may lead to enhanced acceptability and improved recruitment[32].

Disadvantages include that cross-over designs may be less robust if sequence effects (due to carry-over) or period effects (due to external factors) appear, and are longer in execution that the parallel design. This type of design requires constant diseases in time and absence of dragging of the therapeutic effect to be acceptable. The trials are

more sensitive to missing data, so that the loss of a subject supposes the loss of all his periods.

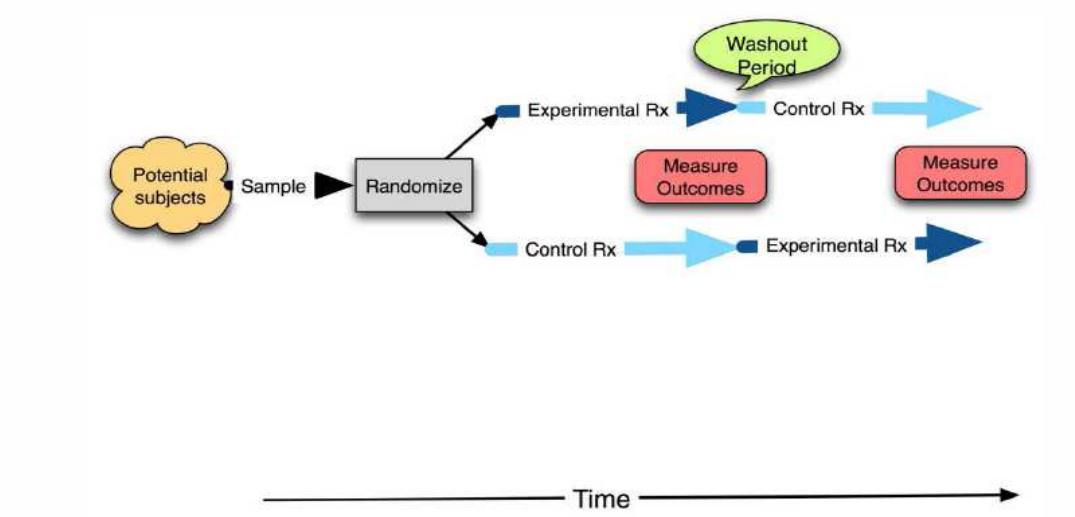


Figure 7. Cross-over. Taken from: A new toolkit for conducting clinical trials in rare disorders [43].

The design offers many advantageous features to investigators of rare diseases such as less variability (as each patient acts as his or her own control allowing for within patient comparisons) / higher precision – and therefore the need for a smaller sample size (in some cases almost half of what is needed for a parallel design).

4.5.2.1.6.1. Multiple cross-over

In a multiple cross-over study, each subject is crossed between experimental and control treatments several times, mixing features of randomised withdrawal retreatment and cross-over trials; in this way, we gain additional information for each subject, and the total number of subjects in a study may be decreased with preservation of power.

4.5.2.1.7. *Population enrichment*

In some clinical situations, intervention may be more effective in patients with certain comorbidities or specific pathophysiological features, so that the study can be enriched with selective inclusion of a subpopulation, increasing the chances to adequately assess the effect of treatment. Population enrichment is used to identify a priori subjects with higher chances to respond, or even those who are experimental drug responders, by enrolling study participants into an open-label trial where all patients receive the treatment under the study. The approach could be a useful solution in situations where ethically is advisable to minimise the likelihood of failure within the trial, when recruitment is difficult, or when the absence of effective alternatives for serious diseases makes patients reluctant to participate in randomized designs compared to placebo. Also, by increasing the chancesof response, the magnitude of the expected effect is bigger, thus requiring in principle smaller sample sizes. However, as a drawback, the design may lead to overestimate the effect size, and may be difficult to extrapolate to wider populations. These designs can be combined with others to optimize their performance, such as combination with cross-over approaches, early escape designs or randomised withdrawal. Any implementation of enrichment strategies requires detailed planning, with simulation scenarios to weigh the benefits of increased power of the study and reductions of sample size.

4.5.2.1.8. ***Enrichment withdrawal***

In this design, features of enriched design are combined with randomised withdrawal, so that initially all patients receive treatment, and only those who respond to the treatment remain in the study. At that time a random assignment is made to active

treatment or placebo (withdrawal of the active drug). Patients in both arms with relapse are undergoing active treatment again. If signs are first controlled, the return, and then are controlled again, causal conclusions can be considered as robust.

4.5.2.1.9. *Time to onset designs*

This design evaluates the time up to the beginning of the effect, in a similar way to that of when the "time up to survival" is evaluated. By using this design, it is possible to evaluate time to reach an effect when it is considered a key element, such as in time to disappearance of certain signs, symptoms or functions.

4.5.2.1.10. *N of 1*

Only one subject is randomised to one therapeutic strategy in different consecutive periods. The information accumulated of the experience of N with 1 in a series of patients in special circumstances can provide evidence on the efficacy of a treatment. It concludes high validity for the patient, but it generally does not give enough validity to extrapolate the results to other subjects or wider populations.

4.5.2.2. Methods using information as acquired

4.5.2.2.1. *Sequential design*

In sequential methods the data is evaluated as it is collected, and the study can be stopped in accordance with predefined stopping rules as soon as significant results are observed. When the initial working hypothesis had overestimated or underestimated the expected differences, a conclusion may sometimes be reached at a much earlier

stage than would be possible with more classical hypothesis testing or estimation, at consequently lower financial and/or human cost.

Sequential designs make intermediate analyses using data from completed patients at predetermined size groups, and manage the multiplicity of analysis through I error rate adjustments allowing a study prematurely ending if the null hypothesis can be rejected from the intermediate results. The futility analysis allows premature ending rejection when the probability of rejecting the null hypothesis at the end of the study is reasonably low, adjusting the type II error[35,45]. Some methods, such as the one of O'Brien-Fleming and other similar ones,are based on small alpha spending with strict significance requirements at the beginning of the trial, and don't require a relevant increase in sample size. Others, such as the one of Pocock and other similar ones do not require such small p value for early interrupton, making it easier to stop the study with initial inspections, but require lower alpha levels to conclude at the end of the standard sample size, if early interruption does not occur, and thus usually require increased sample sizes as respect to standard designs.

4.5.2.2.2. ***Adaptive designs***

The key concept of adaptive designs is the use of information collected during the execution of the study to decide to amend design aspects, without compromise its validity. Adaptive designs use the accumulated information for intermediate analyses used to decide the modification of aspects of the study during its execution. Adaptions allow flexibility to accomodate to deviations from initial expectations used at the time of study design. Any adjustments done, especaillythose concerning key points (for example type of population or changes in the principal variable), should be

predetermined and thoroughly described methodologically and justified to ensure their acceptability at the regulatory level. Due to the level of flexibility involved, these trial designs are also termed as "flexible designs." There are several differences between conventional trials and adaptive designs. The next figure shows some of them:

Features	*Conventional trial*	*Adaptive design*
Design	More rigid	Flexible
Treatment arms	Maximum two or three	Many simultaneously
Hypothesis	Test the hypothesis under consideration	Fit data into a hypothesis
Modifications	Not allowed without protocol amendments	Pre-specified allowed
Phases	Phases I–II are well defined	Can be seamless phase 2/3 design
Statistical analysis	Use routine frequentists methods	Use complicated Bayesian approach
Organization	Much simple	Complicated, requiring simulations
Interim analysis	Not a routine	Done routinely and frequently
Role of IDMC	More once trial/phase is over	Proactive role throughout the trial
Regulatory view	Well endorsed	Still speculative

IDMC: Independent data-monitoring committee

Figure 8 Differences between Conventional and Adaptive trial. Taken from: Adaptive design clinical trials: Methodology, challenges and prospect[36].

Adaptive designs determine modifications of one or more design characteristics (i.e: sample size, primary endpoint, inclusion/exclusion criteria, number of study arms, study duration…) with the final objective of correct or refine design issues without increasing type I error[46,47]. The purpose of adaption in clinical trials is to give the investigator the flexibility for identifying the optimal clinical benefit of the test treatment under study with the best possible design, without undermining the validity and integrity of the intended study[48]. The general idea is to make clinical trials more efficient.

Any adaption has to be pre-planned and should be based on data collected from the study itself. Accordingly, the new draft guidance of the FDA for industry on adaptive design clinical trials defines an adaptive design clinical trial as "*a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study*." Analyses of the accumulating study data are performed at pre-planned timepoints within the study, with or without formal statistical hypothesis testing[49].

Advantages with adaptive design

One of the advantages of adaptive design trials is that potential modifications are approved before-hand by regulatory authorities and ethics committees and thus the time to file and obtain approval for protocol amendments can be saved[50].

Logistics for changing treatments or doses can also be planned upfront. Moreover, there is complete flexibility to react to unanticipated events and options exist to introduce any new doses, change endpoints etc…[36]. Adaptions have been widely applied in the last decades, and have now a broad regulatory acceptance, particularly in case of exploratory adaptive design clinical trials[51].

When adaptive designs are used properly, efficiencies can include a more efficient treatment development process, and an increased chance of correctly answering the clinical question of interest. However, improper adaptions can lead to biased studies. A broad definition of adaptive designs allows for countless variations, which creates confusion as to statistical validity and practical feasibility of many designs[52].

Some examples of adaptive approaches are shown below:

4.5.2.2.2.1. Adaption of design specifications

If an adaptive design is used, the number of design modifications should be limited. Phase III trials are supposed to confirm hypotheses generated in earlier trials about efficacy, and to some extent safety, of a particular drug under particular experimental conditions. The need to modify a number of design aspects, e.g. re-assess sample size, change inclusion or exclusion criteria, change dosing, treatment duration, mode of application, allow for alternative co-medications, may change the emphasis from a confirmatory trial to an hypothesis generating, or exploratory, trial.

4.5.2.2.2.1.1. Sample size reassessment

One of the most widely applied adaptions is that of re-assessment of the sample size. The method consists in checking before the entire sample is recruited if the assumptions applied to the calculation of the study sample size, often based on limited data or published literature, were accurate and are being met in the already included sample. Either the variance or the expected rate of events can be derived from inspection of the data when a representative amount of subjects have been included and followed, and then a corrected sample size based on the actual distribution of values in the observed data may be implemented. The inspection of the data should in general be be blind, but sometimes unveiling the code may be required for calculations. In such cases, the exercise for sample size reassessment should be completely independent from operations and trial decision making, and done by separate teams – often also in separate organizations. The resulting decision may be either to increase the initial sample size or to reduce it, or in survival designs or repeated measurements, to change the lenght of the predetermined follow-up. The

main limitations of this method are related to keeping the trial integrity, so that the inspection should not provide interim results nor insights on the course of the trial, to avoid operational bias. Sometimes, sample size reassessment is combined with interim inspections and group sequential designs.

4.5.2.2.2.1.2. Change or modification of the primary end-point

Adaptions to the choice of events and their hierarchical approach in the analysis can also be done. I ex: anoption can be to reduce a set of multiple endpoints by excluding items that are not properly measured in terms of variability or completeness[53]. Changes can also be made to a pre-assigned hierarchical order of analysis; i ex: in an oncological trial planned initially with progression free survival as the main end-point and overall survival as a secondary one, an adaption may be to downgrade progression free survival to secondary analyses, and upgrade overall survival to the main study analysis. Also, a new endpoint can be brought in once the study has already been started. However, changes to the primary endpoint will always raise doubts over the quality of the original planning.

Adaptions on study end-points may be especially sensible in areas with no or little experience of effective medical treatments and/or in rare diseases for which growing knowledge might justify a re-weighting of endpoints during the trial process[53].

4.5.2.2.2.1.3. Drop the loser, pick the winner

Major adaptions to the study design may include changes in the number of arms studied. An adaptive dose-finding design is often used in early-phase clinical development that uses information as acquired to decide at predetermined times

which arms are unlikely to be successful, and to re-shape the randomisation procedure so that best arms are continued and more patients are included in them. The aim is to discard inefficacious or toxic doses and to identify and obtain thorough information on the minimum effective dose and the maximum tolerable dose that will be used in the next phase clinical trials[36].

4.5.2.2.2.1.4. Dynamic Randomization

Adaptive randomizations allow alterations in the randomization schedule along the trial, depending upon the varied or unequal probabilities of treatment assignment. The purpose is to increase the probability of success.

In trials using adaptive randomization, the probability of being randomized to an intervention changes during the enrolment period. The goal of adaptive randomization may be to minimize imbalance in baseline covariates among treatment groups (covariate-adaptive randomization) or to increase the proportion of patients assigned to the seemingly more effective treatments while reducing overall trial enrolment (response-adaptive randomization)[46].

4.5.2.2.2.1.5. Modification of inclusion or exclusion criteria

Inclusion and exclusion criteria should remain constant, as specified in the protocol, throughout the period of subject recruitment in order to avoid heterogeneity within the trial. When changes are proposed during the study conduction but not foreseen in the protocol, these must be implemented through formal study amendments requiring full review if relevant. Such changes may may include several unforeseen situation; for example, in long-term trials, where growing medical knowledge either from outside

the trial or from interim analyses may suggest a change of entry criteria due to new diagnostic criteria, or the discovery by monitoring staff that regular violations of the entry criteria are occurring or that seriously low recruitment rates are due to over-restrictive criteria. Any changes should be made without breaking the blind and should always be described by a protocol amendment that should cover any statistical consequences, such as sample size adjustments arising from different event rates, or modifications to the planned analysis, such as stratifying the analysis according to modified inclusion/exclusion criteria[39].

However, when modifications to the study inclusion / exclusion criteria can be anticipated already at the design phase, then these changes can be incuded prospectively in the protocol as foreseen adaptions, with clear definitions of the thersholds or rules for implementation, and any consequent modification to the analysis methods or plans.

4.5.2.2.3. ***Bayesian approaches***

Most traditional clinical trial designs are based on frequentist statistics. In frequentist statistics prior information is utilized formally only in the design of a clinical trial but not in the analysis of the data[54].

The key concept of Bayesian designs is the use of prior knowledge on the design and analysis of information from a new study, so that the methods consider how foreknowledge is modified by the appearance of new evidence. Thus, the Bayesian statistics starts from a belief or statement prior, consisting on a probability distribution, which is updated with the results observed in new experiments to

integrate a later statement, also consisting on a probability distribution that weighs evidence based on precision, and all available results are taken into account[55,56].

Bayesian statistics provides a mathematical method for calculating the likelihood of a future event, given the knowledge from prior events and current observations. These methods, thus, directly address the question of how new evidence should change what we currently believe [57].

Bayesian designs offer a major flexibility and power, and provide results in a more intuitive and natural way. However, not everyone agrees to use a priori information when it comes from external data. This hinders their acceptance for confirmatory efficacy studies, especially at the regulatory level.

4.5.3. Endpoints

When we talk about endpoints in clinical trials we are referring to an event or outcome that can be measured objectively to measure whether the intervention being studied has an effect or not. They are usually included in the study objectives. (i.e: survival, improvements in quality of life, relief of symptoms...).

Several end-points may be relevant for assessing effects, and they have to be prioritised according to eithe the expected frequency of an endpoint event or their actual relevance. Some can be grouped to create composite end-points. Endpoints can be treated differently if they are intended to establish efficacy to support approval or intended to demonstrate additional meaningful effects. Endpoints essential to establish efficacy for approval are called primary endpoints. Secondary endpoints may be used to support the primary endpoint(s), to demonstrate additional effects and/or to explain differents parts of a complex effect [58].

4.5.3.1. Single endpoints

4.5.3.1.1. *Primary*

Primary endpoint or primary endpoint family, when there is more than one, is the basis for concluding that the study reached its objective.

4.5.3.1.2. *Secondary*

Secondary endpoints are those that may provide supportive information about a drug's effect on the primary endpoint or demonstrate additional effects on the disease or condition. When an effect on the primary endpoint is shown, the secondary endpoints can be examined and may contribute to support information about a drug's efficacy, to explore additional effects or to explain some parts of the observed effect.

4.5.3.2. Multiple endpoints

Multiple endpoints may be needed when determining that the drug confers a clinical benefit depends on more than one disease aspect or outcome being affected. Multiple endpoints may also be used when (1) there are several important aspects of a disease or several ways to assess an important aspect, (2) there is no consensus about which one will best serve the study purposes, and (3) an effect on any one will be sufficient as evidence of effectiveness to support approval. In some cases, multiple aspects of a disease may appropriately be combined into a single endpoint, but subsequent analysis of the components is generally important for an adequate understanding of the drug's effect [58].

4.5.3.2.1. *Several primary*

Sometimes the selection of a single primary endpoint may be difficult because many diseases have multiple impairments that are equally relevant, and demostrate the effect on any one of these aspects with only one selected primary endpoint could no solve a conclusion of effectivenes. In such cases, the trials must show relevant and significant effects in each of the co-primary end-points to conclude positively.

4.5.3.2.2. ***Composite***

There are some disorders for which more than one clinical outcome may equally appear as a consequence of the disease, and thus in a clinical trial is important to detect the occurrence of either of them. Since all outcomes are expected to be affected by the treatment, the demonstration of efficacy on a composed endpoint may be reasonable, rather than using each potential outcome as a separate primary endpoints, each with low prevalence and requiring adjustments to avoid errors due to multiplicity of analyses. This may prove more efficacious and reasonable also than selecting just one to be the primary endpoint and designating the others as secondary endpoints. Typical examples for this approach are the combined variables in cardiovascular prevention, often including variables such as acute myocardial infarction, stroke and death.

4.6. Controversies associated to orphan drugs

4.6.1. Are prices for Orphan Drugs too high?

One of the determinants of actual access to orphan treatments is the long time required for pricing negociations with the administration, and often, the exorbitant price of acquisition for these drugs in some cases. While high prices are justified to

incentive the research of new treatments for neglected conditions with huge medical needs, high prices can hamper their access by patients, destroy sustainability of health system financing, and create problems of equity with other patients with serious but non orphan illnesses. It is argued that the high price of orphan drugs is justified by the high invests on research and the development costs for a small market. But nevertheless, there are well-founded criticisms that defend that the pricing system is not working correctly [59,60,61].

In one hand, groups of affected patients with rare diseases claim drugs for them or their relatives, on the other hand the regulatory agencies have developed special programs that allow accelerated approval for orphan drugs, so that patients may have a rapid access to them. When an orphan drug is finally approved it obtains the exclusivity in the market, and such circumstance allows establishing the most interesting price to pharmaceutical industry. In this scenario Health System Services have little room for negotiation. They cannot stop financing the drug even if its cost-benefit balance is questionable or if its effectiveness is not clear enough, because they have the pressure of a well-organized amount of patients willing for that new therapy and because there is no alternatives to cover the therapeutic gap that is claimed with this new drug[62].

Even though by definition orphan drugs are expected to generate low incomes, certain orphaned medicines achieved solid global sales in 2014 of over 1 billion dollars while analysts expect that other orphan drugs will follow the same trend. Regulations and incentives that justifiably seek to protect and help patients with rare diseases have produced an undesirable side effect: exorbitant drug prices with block-bluster

revenues (Figure 9). Drug manufacturers have taken advantage of the current situation and ultimately of patients and health care services [63].

Main substance	Brand name	Indications	Global sales (million US$)
Lenalomida	Revlimid	Multiple myeloma Myelodysplastic syndromes	4,980
Imatinib	Glivec	Chronic myeloid leukemia Malign gastrointestinal stromal tumours Dermatofibrosarcoma protuberans Acute lymphoblastic leukemia Hypereosinophilic syndrome and/or Chronic eosinophilic leukemia Myelodisplastic/myeloproliferative syndromes	4,695
Eculizumab	Soliris	Nocturnal paroxysmal hemoglobinuria Atypical hemolytic uremic síndrome	2,225
Bosentan	Tracleer	Pulmonary arterial hypertension Systemic sclerosis	1,649
Dasatinib	Sprycel	Chronic myeloid leukemia Acute lymphoblastic leukemia	1,520
Nilotinib	Tasigna	Chronic myeloid leukemia	1,511
Sunitinib	Sutent	Malign gastrointestinal stromal tumours Metastatic renal cell carcinoma Neuroendocrin pancreatic tumours	1,183
Sorafenib	Nexavar	Hepatocelular carcinoma Renal cell carcinoma Differentiated thyroid carcinoma	1,026

Figure 9. Orphan drugs ranked by global sales in 2014. Taken from: Drug and therapeutics bulletin of Navarre. Orphan drugs: regulation and controversies [64].

4.6.2. Are there too much orphan drugs?

Given the incentives to develop orphan drugs, the exorbitant prices, and the difficulty in discovering new drugs for common diseases, orphan drugs account for a large number of applications in the regulatory agencies. In the strategy of pharmaceutical companies, orphan drugs are being given priority over drugs targeted at wider populations. The perceived difficulties to develop new treatments are now opposed to the willingness to fulfil unmet needs as claimed by patients, so that regulatory

requirements may be not so stringent as regards to demonstrated efficacy in certain situations, making the chances of success higher for a new orphan drug.

Probably as a consequence of these factors, there has been a constant increase in the number of orphan drug designations by the EMA. The number of applications in 2014 reached a record of 327 (Figure 10), reflecting the industry interest in the field of orphan conditions. However, the annual number of authorized drugs has remained steady at approximately 10[65,66]. Some may argue that the displacement of research towards orphan conditions, a desirable effect of the European orphan regulation, has reached a saturation point and may be now contributing to strain of the system.

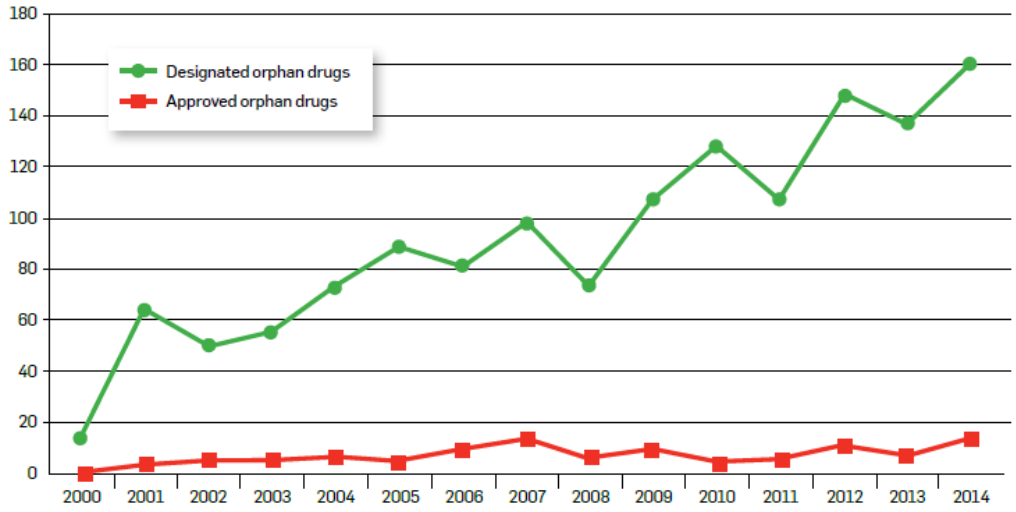


Figure 10. Orphan drugs designated and approved by the EMA. Taken from: Drug and therapeutics bulletin of Navarre. Orphan drugs: regulation and controversies[64].

4.6.3. Are orphan drugs only for rare diseases?

Patients who suffer from some rare diseases are benefitting from the development of orphan drugs. However, as pointed out above, drug companies may be employing excessive stratification of these diseases, so that common diseases may be divided into various conditions so that each one complies with criteria as a rare disease[61]. For instance, lymphoma has been classified in dozens of subgroups in relation to the cell affected. In addition, a drug can earn a place as an orphan drug when indicated for patients who do not respond to previous treatment. Also, once in the market and after obtaining orphan benefits, many of these drugs have expanded their indications to similar conditions, targeting quite large populations. I ex: more than half of the drugs approved for cancer in the US are orphan[67], and some are among the most profitable products ever. So, it is not surprising that only half of the authorized orphan drugs in Europe are designated for rare diseases of genetic origin. This does not mean that there are no other research fields to explore. Before 2012 only a quarter of very rare metabolic diseases of genetic origin (prevalence <1/100000) had an orphan designated drug (not even approved) by either EMA or FDA. It has been shown that development of orphan drugs tends to focus on more lucrative therapeutic areas[68].

4.6.4. Difficulty of regulatory and financing decisions

As it has been explained before, high prices associated with orphan drugs may cause serious problems by making it difficult for patients to gain access to them, undermining financial sustainability of the health care system and creating uneven access to treatment among patients[63,64]. The high price of orphan drugs is justified by the elevated research and development costs for a small market.

Despite the technical difficulty of developing orphan drugs, it should not be an excuse to accelerate the process at the expense of supporting effectiveness only based on surrogate endpoints and few safety data that has not yet been completed. But the reality of the Regulatory Agencies is that they have to deal with a continuous ambivalence. On one hand, they must ensure the effectiveness of the new orphan product through their rigorous evaluations with poor information, and on the other hand, they have the pressure of the society through informed and empowered groups of patients that demand the availability of new treatments as soon as possible to meet the existing needs.

Recently it was published a clear example which highlights the regulatory difficulties that FDA had when approving eteplirsen, a new drug for Duchenne Muscular Dystrophy (DMD)[69]. DMD is a rare genetic disorder characterized by progressive muscle deterioration and weakness. It is the most common type of muscular dystrophy. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The first symptoms are usually seen between three and five years of age, and worsen over time. The disease often occurs in people without a known family history of the condition and primarily affects boys, but in rare cases it can affect girls. DMD occurs in about one out of every 3,600 male infants worldwide.

Eteplirsen was designed to offer a promising new therapeutic approach. In particular, eteplirsen targeted exon 51, the location of the stop codon in about 10% to 15% of patients with DMD (an estimated 2000-2500 cases in the United States). Despite this innovative mechanism, the development of eteplirsen was controversial, starting with its manufacturer-supported pivotal double-blind study, which involved only 12

patients: 8 were randomized to 2 different eteplirsen doses and 4 were randomized to placebo for 24 weeks. They latter were then switched to eteplirsen and all were to be followed for an additional 24 weeks. The sample size was substantially smaller than the study sample size in which a similar DMD drug, drisapersen, had been tested in 3 randomized trials that together enrolled 290 patients. The FDA declined to approve drisapersen in 2015, after these studies showed no clear benefit and because of the possibility of safety problems. In the eteplirsen study the primary trial endpoint was a surrogate measure: an increase in the presence of dystrophin in muscle biopsy specimen. In a 2013 publication, the authors reported increases to about 50% of normal in dystrophin containing fibers in the biopsy specimens[70], results that were met with enthusiasm by the DMD community. However, these results were based on an immunohistochemical assay that assessed only an increase of newly produced dystrophin compared with baseline values.

Controversy over eteplirsen came into broader public view when the FDA convened an advisory committee in April2016 to review these data, including in the meeting patients, families, lawyers and legislators. Almost all the public presenters said yes to drug approval. The advisory committee was not impressed by the results of the study presented and they did not reach an agreement. They delayed its decision and requested additional data that did not prover better results. Later more, there was also controversy between members of the FDA, FDAs cientific reviewers and the director of the FDA's Center for Drug Evaluation and Research. While the reviewers were not in favor of eteplirsen approval, the director suggested that in the basis of an absence of alternatives, they should approve it. Finally, the drug was approved under

the accelerated approval provisions. The FDA requires developers to conduct a clinical trial to confirm the drug's clinical benefit. The required study is designed to assess whether the product improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, with a deadline of May 2021 for submission of its results. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug. Immediately after approval, the developer announced the price of $300.000[71] per year for eteplirsen. The product marketing application is now being assessed by the EMA, but if granted approval, the pricing strategy may be similar to that in the US, regardless of lack of substantial evidences on efficacy and safety.

This is a clear example that shows how accelerated acces of a new treatment to the market on the basis of surrogates' endpoints does not ensure meaningful benefit, and can carry out a risk of adverse effects and a high cost[72]. Thus, it is necessary to ensure that, for products offering small evidence, the society do not have to accept uncertainties in benefit/risk nor bear a huge financial burden that does not respond to actual efforts of the company in obtaining appropriate evidences through development. On the contrary, clear standards of what can be considered a reasonable development should be in place, so that both the pre-marketing assessment and any post-marketing commitments can be referenced and transparent.

To that purpose, it is relevant to be able to determine what type of studies can be applied and expectable for each type of disease, in a way that can be at the same time helpful to incentivate research in difficult settings, but also able to confirm initial assumptions and prove that that the new treatments are secure to patients.

4.7. Selection of the best methodology to study a rare disease

Methodological approaches to rare diseases struggle with the need to conclude efficacy and positive benefit-risk, and the difficulties of achieving statistical demonstration with conventional statistics[73]. The current standards of evidence, including required significance levels to demonstrate efficacy and acceptability of different designs (such as non-inferiority), do not distinguish between rare or regular diseases. Nevertheless, actual decision making does seem to do so, but is lacking systematic guidance.

New methods, despite have often been valued as especially relevant for easing the development of treatments in small populations, have been paradoxically applied mostly in highly prevalent diseases, where conventional standards are fully feasible, because new methods may reduce substantially the overall costs of large trials. Since more efficient and smaller trials often lead to smaller pre-marketing safety populations, conventional trials with wider sample sizes reduce uncertainty in benefit-risk assessment, allow more confident decision making and have been preferred to new designs by regulators.

A direct consequence of this fact is the likely perception by regulators of new statistical methods as not providing reliable data and not being fully validated, and thus not being fully compliant with standard evidence requirements. It has to be understood, however, that commercial sponsors seek regulatory agreement for their plans and thus regulators also have to share some risks of drug development in that an eventually limited basis for decision making may be available in the end. Naturally then regulatory advice can only refer to designs where regulators have experience, which is sometimes

called regulatory conservatism. Risks of negative outcomes of regulatory assessment of evidence obtained through non-standard methods have been aversive to investments in research for rare and very rare diseases, for which conventional designs are unfeasible.

Gupta et al.[74] and Cornu et al.[75] summarized in their publications some novel designs methods in clinical trials and provide examples of applications for rare diseases. Besides those examples, Cornu et al proposed an algorithm for the choice of an appropriate trial design in the development of orphan drugs, and Gupta et al provided a framework for selecting among those new approaches for studies of rare diseases[74,75]. The use of a particular trial design is recommended depending on the duration of clinical effect, required follow-up versus accrual time, anticipated sample sizes, difficulties of retention of patients and prior level of confidence in the effect of treatment. However, these recommendations are useful at the trial level only, and do not allow to have a broader approach to the whole process of development and regulatory assessment. Aspects such as integration of the previous knowledge arising from non-clinical or pilot studies, cumulative evidence, completion of evidence at later stages or the size of the safety database required to assess benefit/risk at the time of approval are out of the scope of their publications.

Nony et al.[76] proposed a framework with systematic approach to previous therapeutic and research information for a given condition, in order to select through *in silico* modelling and simulation the key aspects of design or future studies. Whether such a sophisticated approach can be generalised, may be applicable in areas with no

previous data available, and how reliable the predictions may prove across different conditions are still open questions.

General guidance for clinical investigation on a particular disease is an effective method to guide structured and predictable decision-making. Regulatory guidance for clinical development of new medicinal products has been issued by the EMA[14] and many other regulatory agencies for many prevalent diseases, which represents and useful aid to both developers and regulators. However, there are thousands of rare diseases[26] and this fact makes the development of guidelines for clinical investigation on each condition unrealistic. Currently the EMA deals with the particularities of rare diseases from a general perspective through a single guideline[73]. This document provides general advice on the best methodological approach to the development of new medications aimed to small populations and sets a number of key points, but is wide in scope and thus not directly applicable to determine the expected requirements in a given case for a full product development, and how to proceed with high chances of being acceptable from the regulatory point of view. There is consensus in that there is room for a more structured process for decision-making [77,78], and on the need to issue practical references to the most appropriate selection of methodologies and study designs in specific orphan conditions.

4.8. Justification of the project

The European Comission has repeatedly recognised that the development of treatments for rare or neglected conditions is a clear priority, and has taken actions to promote the development of new treatments in the field. Amongst these, the FP7 Call – Health.2013.4.2-3 was issued specifically to foster innovative approaches to adapt

and assess clinical trials on small populations and rare diseases. ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence, FP7 HEALTH 2013 – 603160, *http://www.asterix-fp7.eu/)* is one of the 3 multinational projects funded by the European commission with the aim to develop innovative approaches to adapt and assess clinical trials on small populations and rare diseases, by means of the FP7 Call – Health.2013.4.2-3. The other 2 projects are IDEAL *(Integrated Design and Analysis of small population group trials, FP7 HEALTH 2013 – 602552, http://www.ideal.rwth-aachen.de/) and InsPIRe (Innovative methodology for small population research): FP7 HEALTH 2013 – 602144, http://www2.warwick.ac.uk/fac/med/research/hscience/stats/currentprojects/inspire/).* The Universitat Autònoma de Barcelona collaborated in the former project ASTERIX, leading the working package 5, dedicated to validation of new methods within clinical as well as regulatory settings.

In order to approach the limitation to issue disease driven guidance resulting from the huge number of conditions, the idea of grouping medical conditions based on methodological similarities resulting in common recommendations was proposed within the ASTERIX FP7 project as one of its three main deliverables. The aim was to set a framework able to get to an intermediate point between a single guidance and thousands of guidances, ideally by identifying a number of groups of conditions below 10. Thus we proposed that a systematic grouping of conditions based on their methodological requirements may become a useful tool to allow a more structured approach for the development of medicinal products and decision making, by allowing generalisation of recommendations to types of medical condition, rather than to single

disease, improving their level of detail and thus easing development planning and improving the predictability of regulatory requirements. We proposed an approach to clustering medical conditions linking clinical and treatment characteristics with applicability of different methodologies and designs of clinical studies, considering the process of development of new treatments, with the aim to obtain a limited number of orphan clinical situations that may be approached from a regulatory point of view to provide a more specific methodological guidance.

5. HYPOTHESIS

Orphan conditions can be grouped through a systematic approach based on their methodological requirements, and the resulting clustering can be an effective tool for establishing specific recommendations for the study of groups of conditions rather than for individual conditions, that would facilitate a more structured approach to regulatory development and decision making.

6. OBJECTIVES

6.1. General Objective

The main objective is to propose a new grouping of orphan and / or rare conditions by linking the characteristics of the medical condition with the requirements of applicability of the experimental methods and different research designs and methods for its study.

6.2. Specific objectives

- To list the relevant characteristics of rare medical conditions which are the key to define the best methodology for clinical trials and produt development.
- To create a detailed dictionary of characteristics of rare medical conditions to be applied to the description of a sample of diverse and heterogeneous rare conditions.
- To create a base-case grouping not led by previous assumptions through an unsupervised analysis method such as Multiple Correspondence Analysis (MCA) of the database of clinical characteristics and rare medical conditions
- Taking the base-case grouping resulting from the MCA analysis, to refine and validate a proposal for clustering of rare medical conditions able to describe most regulatory situations where similar research methodologies can be applied.
- To describe the methodological approaches generally applicable to each one of the clusters proposed.

7. METHODS

7.1. General approach

The work was done by a group of research involving 10 people that included expertise in clinical pharmacy, clinical pharmacology, statistics, epidemiology and regulation. The team and background expertise is summarised below.

	Clinical Pharmacy	Clinical Pharmacology	Statistics	Regulator	Epidemiology
Mònica Gómez-Valent	X				
Manel Fontanet	X				
Caridad Pontes, MD		X		X	
Rosa Morros, MD		X		X	
Arantxa Sancho, MD		X		X	
Josep Torrent, MD		X		X	
Ferran Torres, MD		X	X	X	
Jose Rios			X		
Roser Vives, MD				X	X
Jorge Martinalbo				X	

Table 3. Team developing the clustering exercise

A list of relevant clinical characteristics of diseases that are key to define methodology of clinical trials in drug development and an operational definition for each characteristic was created, with the objective of making a list of instrumental variables aimed to describe in detail which are the main determinants of the applicability of a given method to the clinical study of a new treatment in a given condition (Annex 1). The characteristics of the dictionary are better explained in section 7.2.

The resulting dictionary was then applied to extensively describe a selected sample of diverse and heterogeneous rare conditions, in order to create a representative database of rare conditions and their characteristics that limit the applicability of different development approaches and trial designs.

Seventeen different conditions were initially proposed to apply the dictionary. The database was created in duplicate for each clinical condition by a pair of investigators, and then confronted and discussed for discrepancies until consensus. A peer review procedure with intervention of a third investigator was applied in case of persistent discrepancies.

To solve this discrepancies the process was iterated in two sequential steps. Firstly with the reassessment of the listing of clinical characteristics and the definition of terms included in the dictionary after a first pilot round of classification, in order to ensure completeness of features analyzed. And secondly, increasing the number of the conditions included in the working sample with ten more examples, to ensure that many different situations were studied.

After a triple consensus of opinion between both investigators and peer review, the database was then used to conduct a Multiple Correspondence Analysis (MCA), aimed to explore if different rare conditions could be clustered in a reasonable number of groups of conditions studied with common methodological characteristics that are key to develop a clinical trial.

The graphical representation from the results of the analysis were the basis for a consensus process where numerically and graphically driven proposals for grouping were reviewed and refined from methodological, medical and regulatory perspectives by the investigators.

The resulting proposal for clustering of rare conditions was then applied to the 125 conditions for whose an EMA regulatory opinion was available, as derived from the European Public Assessment Reports (EPAR) identified in the EMA webpage, in order

to test if the proposed groups were wide enough to cover most of the regulatory conditions for which orphan medicinal products have been assessed in Europe up to now.

Figure 11 summarizes the overall project approach.

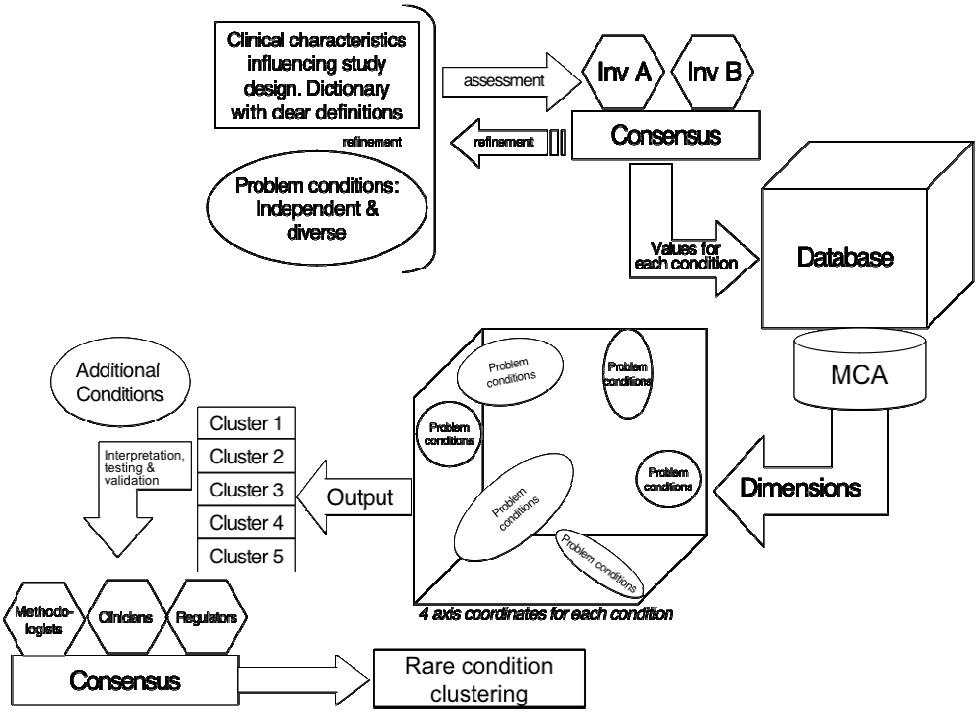


Figure 11. Overall approach to create the clustering

7.2. Dictionary of clinical characteristics of conditions

A list was created including a number of clinical characteristics determining, influencing or modulating the applicability of designs and methods to clinical trials aimed to study the efficacy and safety of a given treatment. Those characteristics responded to different areas that are necessary when planning a methodology for a clinical trial. The dictionary has been divided in six different blocks referred to:

- Clinical characteristics that describe a given condition.
- Availability of treatments for such conditions.

- Endpoints and variables of clinical trials carried out for a given study.
- Feasibility of recruitment of patients to achieve a good sample size.
- Knowlegde of condition.
- Additional variables on standard of care and therapeutic approaches for treatments.

Each variable of the dictionary was identified through literature review, and through joint open discussions between clinicians, statisticians and regulators. All items were treated as qualitative variables, and had written definitions for each category which were agreed by focusing on their methodological implications for clinical study design and analysis.

A dictionary was created for reference, in order to harmonize the criteria between investigators and reproducibility of condition's description. The initial list of variables and the definitions of the dictionary were tested by using them to classify the clinical characteristics of a limited sample of orphan medical conditions, and refined according to the feedback of the involved investigators. A final dictionary was issued including 76 dichotomous variables to be applied by the investigators in the creation of the final dataset for analysis (Annex 1)

7.2.1. Blocks of the dictionary

Different blocks of the dictionary were created to reflect different clinical characteristics that determine, influence or modulate the applicability of designs and methods applicable to clinical trials aimed to study the efficacy and safety of a treatment for rare conditions.

Each block was defined by two items, set in columns of the dictionary. The first one (Terms) contains the final list of dichotomous variables of the characteristics that were selected after refining the intial list, according to the feedback of the involved investigators, and the second one (Definition) contains its detailed descrption, necessary to ensure uniform criteria between investigators when applying the dictionary and thus decrease subjective interpretation.

The final dictionary includes 76 dichotomous variables to be applied in the description of rare conditions.

7.2.1.1. Clinical characteristics of the condition

This block describes the clinical characteristics that were determining different aspects of the applicability of certain methodologies to the study of the condition. I ex: terms related to the temporality and the clinical course may condition the applicability of methods that require short time between treatment and outcome to apply methods that use information as acquired, such as sequential or adaptive designs. Another example may be the applicability of cross-over based methods to the study of conditions with intermittent or constant course; also clinical irreversibility precluded crossing-over. The severity of the disease and whether they were progressive also were determinants of acceptability of controls and required ethical considerations, but also were determinants on the need of concurrent controls. The predictability o the clinical course, as determined by previous knowledge of the condition and the degree of intersubject variability, was determinant to the applicability of uncontrolled studies or external controls, as well as to the suitability of Bayesian approaches. Subgroups

within the condition were also considered important to define stratification methods and prospective testing of heterogeneity.

Whether reliable diagnostic criteria were available, and the type of clinical elements included in the diagnosis were relevant to the definition of end-points. Other descriptors included the organ systems affected.

The table below summarises the clinical information block.

	Terms	DEFINITION
1.	***Temporal scope of condition*** ***A:*** Chronic condition ***B:*** Acute condition	***A:*** Condition with long-term (years, decades) clinical course. ***B:*** Condition with short-term (days, months) clinical course.
2.	***Clinical course*** ***A:*** Constant course ***B:*** Intermittent condition	***A:*** Regular or homogeneous impairment along the temporal scope of condition; separate episodes can not be distinguished ***B:*** Condition whit clear-cut worsening episodes or flares
3.	***Seriousness*** ***A:*** Life threatening condition ***B:*** Debilitating condition ***C:*** Mild significant condition	***A:*** With current SOC the condition progresses to either death or requirement of vital support, which is clinically more relevant than the burden of disease. ***B:*** With current SOC the condition progresses to serious disability, organ substitution or transplant, which is clinically more relevant than the threaten to life it represents. ***C:*** The condition does not seriously compromise the patient life or function, but may derive into life-threatening or debilitating condition if untreated.
4.	***Speed of progression*** ***A:*** Stable clinical course ***B:*** Progressive condition ***1:*** Very rapid or fulminating progression ***2:*** Rapidly progressive condition ***3:*** Slow progression	***A:*** Condition that does not increase in severity along time; does not exclude conditions with flares that return to baseline once resolved. ***B:*** Condition that once diagnosed does not revert to healthy status and progresses, either steadily or due to subsequent flares that do not revert to pre-flare status ***1:*** Condition that progresses towards maximum deterioration in a period up to 12 weeks ***2:*** Condition that progresses towards clinical deterioration in a period longer than 12 weeks but shorter than 36 months ***3:*** Condition that progresses towards clinical deterioration in a period longer than 36 months
5.	***Reversibility*** ***A:*** Reversible condition ***B:*** Irreversible condition	***A:*** Self limited condition *(that may revert or reverts to pre-disease status)* either due to natural history or after SOC. ***B:*** Condition that once diagnosed does never revert to healthy status because of permanent irreversible changes, and currently there is no SOC for the known or unknown etiological cause or able to reverse the condition.
6.	***Predictability*** ***A:*** Predictable clinical course ***B:*** Highly variable clinical course	***A:*** The change in health status along time is well described and any change in the known natural history is unexpected, or reflects treatment activity. ***B:*** Any change in health status along time is possible and there is no prior expectation as regards to the degree or speed of health deterioration or

	Terms	DEFINITION
		on the frequency/intensity of flares
7.	***Diagnostic criteria*** (non exclusive) ***A:*** Based on chromosome or genetic diagnosis ***B:*** Based on pathology, physiology microbiology or biochemical measures ***C:*** Physiological and clinical criteria ***D:*** Syndromical diagnosis	The condition is defined by ***A:*** A well described and characterised condition specific chromosomal or genetic abnormality. ***B:*** A well described pathology, microbiology or biochemical finding or findings which is univocally condition especific ***C:*** A set of findings that includes measures of physiology and at least one clinical sign o symptom, of which at least one is almost condition specific. ***D:*** A combination of findings that may include measures as in A or B or C but is mainly based on clinical signs o symptoms which are not condition specific if standing alone
8.	***Disease subgroups*** ***A:*** Differential prognosis ***B:*** Differential response to treatment	For a given condition, a clinical o biochemical or genetic parameter, or groups of parameters (I ex: clinical staging) allows to predict ***A:*** The clinical course (speed or type of progression) of the condition. ***B:*** The magnitude of the response to treatment
9.	***Target organ***	Body system or organ whose function is impaired by the condition, either directly or by its indirect consequences. (detail up to 3 terms from close list – System-Organ class according to MedDRA)
10.	***Rarity*** (non exclusive categories) ***A:*** Incidence rate ***B:*** Prevalence	May be a number, a range or unknown ***A:*** Number of new cases per population at risk in a given time period ***B:*** Proportion of cases in a given population at a given time

Table 4. Dictionary: Clinical characteristics of the condition

7.2.1.2. Treatments

The treatment block described the main concepts to take into account in rare condition therapeutic approaches, and its main role in the selection of the best design for a clinical trial.

It is key to know if there is any standard of care for a rare condition studied, since it will determine the acceptability and type of control in the study. Whether the treatment goal is curative, disease modifying or only symptomatic will condition temporal follow-up and the type of measurements. If the treatment works, the duration of the effect and the impact of the discontinuation of the drug on the condition are two relevant points to value when choosing a clinical design. Whether the intervention may be reintroduced after interruption is relevant for applicability of challenge-rechallenge methods, such as those using randomised withdrawal.

	Terms	DEFINITION
11.	***Standard of care (SOC)***	Treatment alternative *(with regulatory authorisation) (with published supportive data)* for which it is recognised that has a degree of influence on the signs or symptoms of the condition or a delaying or halting effect on the clinical course, of magnitude enough as to justify that is routinely offered to subjects with the condition.
12.	***Effect of treatment withdrawal on condition*** *(non exclusive categories)* ***A:*** Impairment due to delayed treatment initiation ***B:*** Impairment due to periods without treatment ***C:*** Effect on prognosis unknown	The fact of exposing the subject to a SOC has an impact on the condition ***A:*** A late start of a SOC has a permanent effect on patient prognosis. ***B:*** The temporary deprivation of a SOC has a permanent effect on patient prognosis. ***C:*** Unknown, either because the symptoms of the condition return but the impact on long term is unknown, or because it has not been studied
13.	***Feasibility of re-challenge*** ***A:*** Re-exposure unfeasible ***B:*** Re-exposure feasible	The fact of exposing the subject to a SOC has an impact on the feasibility of future re-challenges ***A:*** The administration of the SOC or a given treatment precludes future re-challenge to the same treatment. ***B:*** The temporary deprivation of a SOC or administration of a given treatment does not adversely affect the condition nor the expected efficacy or safety on treatment reintroduction.
14.	***Treatment approach*** ***A:*** Intended to modify the course of the disease ***B:*** Curative ***C:*** Symptomatic	***A:*** A therapeutic intervention aimed to delay or halt the progression of the clinical course of the condition, with or without reversion to pre-diseased status. ***B:*** A therapeutic intervention aimed to correct the known or unknown etiological cause of the condition. ***C:*** A therapeutic intervention aimed to improve or reduce the clinical signs and symptoms of the condition, with no substantial influence on progression or cause.
15.	***Duration of effect*** ***A:*** Short lasting effect ***B:*** Long lasting effect	***A:*** The effect reverts when treatment administration is stopped or plasma concentrations decrease, so that the signs or symptoms of the disease reappear. ***B:*** The effect is either irreversible or persists for a substantial period of time after the complete disappearance of the product from the body

Table 5. Dictionary: Treatments

7.2.1.3. Endpoints and variables

The type and the validity of endpoints were described according to a number of characteristics, including the classical description of types of variables (dichotomic, categorical, continuous, time to event, etc) and whther they were direct or indirect measurements of benefit. a finalist or hard primary endpoint is usually considered as the backbone of evidence for clinical practice guidelines, but is not always well defined for certain conditons, and in general requires higher sample sizes. In the context of

rare disorders for a given clinical endpoint recruitment of a sufficient number of patients is difficult and/or demonstration of this endpoint would sometimes take an unreasonable length of time. Intermediate or surrogate endpoints are often available, sometimes used as main end-points and often considered important for stratifying risk and determining treatment strategy in clinical practice. We distinguished single clinically relevant endpoints, either simple or composite, and multiple endpoints, either in the same domain or in different domains reflecting affectation of several dimensions of the health and wellbeing. Multiplicity of assessments will determine sample size requirements, the net effect of an intervention and the presence of bias of competing risk. The robustness of the variable was approached, although assuming that the concept would have certain degree subjectivity regardless of fixed definitions.

	Term	DEFINITION
16.	***Time to measurable effect*** ***A:*** Rapid onset ***B:*** Long term onset ***C:*** Early markers of treatment failure	The effect of the treatment appears and is measurable in a period: ***A:*** Short (days, weeks) or shorter than the duration of the estimated recruitment period. ***B:*** Long (months or years) or longer than the duration of the estimated recruitment period ***C:*** An intermediate end-point allows reaching conclusions on the lack of efficacy of a tested intervention before completing the full course of treatment.
17.	***Type of endpoint*** ***A:*** Dichotomic ***B:*** Continuous ***C:*** Ordinal ***D:*** Time to one event ***E:*** Number of events in a period of time	***A:*** Only two options for a single outcome ***B:*** Numerical value - all possible intermediate values ***C:*** Numerical value – only some discrete values ***D:*** The untreated condition invariably progresses to a clinically relevant (*irreversible*) situation (may be e.g.: death or blindness or deafness or serious motor disability). ***E:*** The condition produces repeated adverse events which are clearly limited in time, and the number of such events reflects relevantly the clinical status of the subject.

	Term	DEFINITION
18.	***Strength (validity?) of end-point*** *(non exclusive categories)* ***A:*** Direct clinical outcome ***B:*** Valid surrogate clinical endpoint ***C:*** Raw surrogate clinical end-point ***D:*** Valid biomarker ***E:*** Raw biomarker	***A:*** The end-point measures the final treatment goal ***B:*** A clinical or physiological parameter has demonstrated a correlation with relevant clinical changes or outcomes of the condition that is sensitive to changes and treatment effect. ***C:*** A clinical or physiological parameter has shown correlation with clinical status of the condition but whether it changes with condition improvement due to treatment is unknown. ***D:*** Changes on a biological parameter allows consistently predicting the treatment effect on the final clinical outcome; the intermediate measure may substitute for a clinical endpoint. ***E:*** Changes on a biological parameter relate to the clinical status of the condition but whether it changes with condition improvement due to treatment is unknown.
19.	***Robustness of end-point*** ***A:*** Main endpoint is an objective measure with no possible bias ***B:*** Main end-point is a measurable item subject to bias ***C:*** Main end-point is a subjective endpoint reported by investigator ***D:*** Main endpoint is a patient reported outcome	Susceptibility to bias and/or inter-observer variability of measures ***A:*** The outcome measure is not subject to inter-observer variability nor bias ***B:*** The outcome measure may be subject to different degrees of inter-observer variability or bias ***C:*** The outcome measure is a subjective judgement made by the investigator ***D:*** The outcome measure is collected and reported by the subject with the condition
20.	***Multiplicity of assessments*** ***A:*** Single clinically relevant end-point 1: Simple endpoint 2: Composite end-point ***B:*** Multiple endpoints in same domain ***C:*** Multiple assessment domains	***A:*** There is one single end-point that is able to summarise the condition status 1: The assessment reflects only one parameter or measure 2: The assessment reflects the combination of a number of parameters or measures ***B:*** There are several valid variables measuring different aspects of a single domain of disease ***C:*** There are several domains of the subject clinical status that have to be considered to assess the disease status

Table 6. Dictionary: Endpoints and variables

7.2.1.4. Feasibility of recruitment

Patient registries and databases constitute important instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. Recruitment of patients with rare conditions to participate in a clinical trial is not always easy. Prevalence was assumed to be related with a low speed of newly diagnosed patients' recruitment in a clinical trial, but existence of registries was assumed to have the opposite effect if prevalent patients were the target population

to be studied. The speed of recruitment is relevant to apply methods that use information as acquired, such as sequential or adaptive designs.

Besides of feasibility, registries are a source of information on the natural course of the diseases and thus a relevant source of data to build appropriate designs. Registries of patients with orphan conditions may be a useful tool to facilitate study feasibility, and registries of patients treated with orphan drugs are particularly relevant as they allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, especially when marketing authorization is granted at a time when evidence is still limited.

	Term	**DEFINITION**
21.	***Registry*** *(non exclusive categories)* ***A:*** Disease registry ***B:*** Treatment registry ***C:*** National registry ***D:*** Multinational registry	A database with clinical information from a substantial number of patients *(often with exhaustive intention)*, who: ***A:*** Share a same medical condition ***B:*** Receive a same active principle for a condition or number of conditions. ***C:*** Gathering information on subjects from a single country ***D:*** Gathering information on subjects from several countries (i e: European, American, Asian, Global...)
22.	***Expected accrual time*** ***A:*** Short accrual time ***B:*** Long accrual time	Estimated length of the period of time required to recruit the required number of patients into a study; this is related with the incidence and/or prevalence of the condition, as well as on the easiness of identifying potentially eligible patients through a number of systems; i ex: registries, patient organizations or specialised medical sites. ***A:*** Condition for which the time to main end-point in a given patient exceeds *(by several times)* the expected accrual time for the clinical trial. ***B:*** Condition for which the time to main end-point in a given patient is *(several times)* shorter than the expected accrual time for the clinical trial.
23.	***Source of recruitment*** *(non exclusive)* ***A:*** Incident cases ***B:*** Prevalent cases	Condition for which the eligible population for a clinical trial will be mostly at the expense of: ***A:*** Newly diagnosed subjects. ***B:*** Subjects already diagnosed in the past.

Table 7. Dictionary: Feasibility of recruitment

7.2.1.5. Knowledge of condition

This block refers to the degree of knowledge of the given condition. Not only related to the physiopathology, but also data estimated in previous studies or experiences,

predictive preclinical models of the disease or medical conditions with analogous mechanisms. It will determine to carry out a clinical trial using previous information that is added to the one obtained, such as Bayesian methods, or the feasibility of using external controls to compare with the small sample size of orphan conditions.

	Terms	DEFINITION
24.	***Degree of knowledge on the condition****(non-exclusive categories)* ***A:*** Known physiopathology ***B:*** Predictive preclinical models of the disease ***C:*** Previous data on event / response rate or variance available ***D:*** Available data in medical conditions with analogous mechanisms ***E:*** No previous data available for modelling purposes	***A:*** Data exists on the molecular mechanisms *(suppressed, altered or over-expressed)* in diseased subjects which are causally related to the clinical signs and symptoms of the condition ***B:*** An *(experimentally induced)* animal disease or condition exists which resembles closely the human clinical pathology, for which clinical improvements induced by treatments correlate with the likelihood of improvements in diseased subjects. ***C:*** Data allowing to estimate the value and variance of a main end-point is available ***D:*** A condition sharing similar physiopathology to other known conditions for whose data exists on molecular mechanisms, clinical course, clinical end-points, biomarkers and /or effective therapeutic interventions. ***E:*** No previous information on the values nor variance of efficacy end-points is available allowing to model for study design purposes

Table 8. Dictionary: Knowledge of condition

7.2.1.6. Standard of care, therapeutic approaches and impact on prognosis

This block complements the one referred to treatment with the possibility of further disaggregating the variable of standard of care, specifying if genetic treatment is a possible approach, since theoretiacallly this fact may limit the reaplicability of treatment, on one side, but also will determine the type of end-points for efficacy and safety. In the case of having an available standard of care, identifying if the available treatment may potentially return the subject to its basal state or is aimed to treat the symptoms will determine the acceptability of control groups, the type of endpoints and follow-up, as well as crossing-over strategies.

	Terms	DEFINITON
25.	***Gene therapy possible***	A: Yes B: No
26.	***Standard of care aimed to treat cause available***	A: Yes, and very effective B: Yes, but poorly effective C: No directed to cause, but only symptomatic, if any
27.	***Standard of care returns subject to normal status***	A: Yes B: No

Table 9. Dictionary: Additional variables on standard of care

7.3. Dictionary training phase

A sample of orphan diseases was selected among those proposed by each investigator, with the aim to represent many independent and unrelated clinical situations in terms of physiopathology and clinical features. The diseases included in the model were not intended to be exhaustive, but diverse enough to be useful to discriminate representative groups of clinical characteristics with relevance to study design. Seventeen different diseases were initially proposed to apply the qualitative variables of the dictionary.

A database with all the variables of the dictionary was created with the aim of introducing the result of each one of the dichotomous variables described above. The initial selected diseases were distributed between the investigators, so that each one was analyzed by two different investigators. The results of the 76 variables of the dictionary for the chosen diseases were introduced in the database and then confronted and discussed for discrepancies until consensus. A peer review procedure with intervention of a third investigator was applied in case of persistent discrepancies.

It was observed after confronting opinions between investigators that some of the characteristics from the dictionary were not represented when applying the seventeen initially selected diseases. It was also found that there were diseases that could be

described in more than one way, depending on the therapeutic objective sought, and thus the intended treatment indication, so the interpretation could be totally different depending on the studied feature of the disease. For example, it was the case of Multiple Sclerosis disease. One of the investigators applied the dictionary on the basis of the acute treatment of flares, and a second investigator applied it on the basis of progressive neurological impairment. The result of applying the dictionary according to each chosen clinical condition was totally different. To solve these discrepancies it was necessary to change the concept that was used until that moment.

Applying the dicctionary to rare diseases was too little concise and it made us think that we should specify more in the concept of disease. So, after several discussions and the exposure of different points of view, we decided that it was necessary to focus more on medical conditions, rather than in general diseases. With this change of concept the discrepancies between investigators related to the application of the variables, were significantly reduced.

This led to increasing by 10 the number of conditions evaluated to confirm that discrepancies between investigators had decreased. The concept of disease was changed to medical condition, and differences in interpretation disappeared. A final list of 27 conditions was agreed, representing 24 different diseases, of which 3 had two different separate conditions (Table 9).

Described diseases
1. Toxic megacolon
2. Alport syndrome
3. Angelman syndrome / Prader Willy syndrome
4. Fragile X syndrome

Described diseases
5. Ventilator associated pneumonia caused by Pseudomonas aeruginosa
6. Pulmonary arterial Hypertension
7. Huntington Disease (HD)
8. Cystic Fibrosis (CF)
9. Guillain-Barré syndrome
10. Amyotrophic lateral sclerosis (ALS)
11. Haemophilia
12. Burkitt lymphoma
13. Pompe disease (Glycogen storage disease type II) Early Onset
14. Pompe disease (Glycogen storage disease type II) Late Onset
15. Hereditary angioedema – acute treatment of flares
16. Renal Cell carcinoma
17. Adenocarcinoma of the pancreas
18. Nocturnal Paroxismal Hemoglobinuria
19. Acute Lymphocytic Leukemia
20. Chronic Myeloid Leukemia
21. Phenylketonuria (PKU)
22. Lennox–Gastaut syndrome
23. Cryopyrin – associated periodic syndromes CAPS/FCAS/MWS
24. NOMID (Cryopyrin – associated periodic syndromes: neonatal onset)
25. Multiple sclerosis – Acute treatment of flares
26. Multiple sclerosis – Progressive neurological impairment
27. Hereditary angioedema – prevention of flares

Table 10. List of conditions used as models for the unsupervised analysis

The 27 medical conditions were valued for all the qualitative variables independently by 2 investigators working at different sites. Investigators used an electronic case report form and referred to the variable dictionary in order to identify if each of the terms on clinical characteristics was present or absent in each disease.

Groups of diseases were distributed so that 5 investigators participated in the assessments, with no fixed pairs of investigators working on the same condition, so that one criterion or pair of criteria did not systematically prevail over others, ensuring a high degree of consensus and reproducibility. The medical conditions were qualified keeping in mind that the main objective was to group methods and designs of clinical studies applicable to the assessment of efficacy and safety in that condition, and not epidemiological classification or medical management.

After confrontation of both entries for each disease, discrepancies were discussed in joint meetings until consensus. In the event that discrepancies still remained, a third investigator, external to the core team of 5, concurred. The final consensus data set was used as test model for the MCA analysis.

7.4. MCA as unsupervised analysis and proposal for clustering

An MCA analysis was conducted on the database of clinical characteristics and conditions. MCA is a non-supervised method for a multivariate description of qualitative variables that shares the same objective as other descriptive factorial methods, such as Principal Component Analysis: without the use of any dependent variable, this analysis reduces the number of dimensions by means of the relationship between categories of several qualitative (dichotomics) variables and each new dimension explains a proportion of inertia (variability) from total.

The analysis calculates the Chi-Square distance between data characteristics, with the aim of defining new factors than represent new orthogonal dimensions. These new dimensions can be used to represent supplementary variables not included in the

analysis, but added to the results in order to check their association with the active variables in a multidimensional space. In our case, these supplementary variables were the name of rare disease and the aim was to form comprensible clusters with them[79-82]. The MCA analysis provided coordinates for each condition in a multiple-axes dimension system generated.

Since the data suggested that more than 4 dimensions provided little additional explanation to data in terms of inertia (variability explained by a dimension), the system was described finally by 4 dimensions.

A first approach of clustering was proposed based on the coordinates and supported by graphs.

This preliminary cluster proposal was further refined by the assessment of the actual coincidences between conditions for the leading characteristics of the relevant dimension determining their joint grouping, and the checking of the plausibility of methodological, clinical and regulatory current treatment for each group of conditions.

7.5. Testing cluster phase

The 125 orphan medical conditions were classified into the clusters identified in the previous steps in order to test if the proposed groups were wide enough and able to cover most of the regulatory conditions for which orphan medicinal products have been assessed in Europe up to now. These medical conditions were all the authorized indications for the orphan medicinal products for which an EMA regulatory opinion was available. Two separate investigators assessed each condition, in pairs different from the previous ones, and the panel was widened by including additional

investigators not involved in the previous exercise. The results were summarized and checked for inter-subject consistency and to test the fitness of the groups to cover most of the potential regulatory conditions for orphan medicinal products, and also to refine group definitions based on the investigator's feedback.

7.6. Clinical Advisory Board

Finally, since the expertise covered by the team was limited to clinical pharmacology/ pharmacy, statistics, epidemiology, methodology and regulation, the validation process of the clustering included a meeting with clinical specialists (Table 10) with recognised experites in the field of orphan diseases, in order to know their opinion towards the proposed classification and to get insights on potential weaknesses of the approach.

Specialist name	*Clinical Area and Hospital workplace*
Assumpta Caixàs	Endocrinology (Hospital Taulí of Sabadell)
Raquel Corripio	Paediatrics' Endocrinology (Hospital Taulí of Sabadell)
Jordi Esteve	Haematology (Hospital Clínic of Barcelona)
Pere Gascón	Oncology (Hospital Clínic of Barcelona)
Manuel Ramos	Internal Medicine (autoimmune diseases) (Hospital Clínic of Barcelona)
Mireia del Toro	Paediatrics' Neurology (Hospital Vall d'Hebrón of Barcelona)

Table 11. Panel of experts: name and clinical area

A session was held with the panel of clinical advisors where they were presened the objectives of the interaction, namely to gather inpout on their perception of the frailties of methods aimed to obtain evidence on efficacy for orphan drugs, how this may impact regulatory decision making and clinical practice, and to provide insights on the clustering approach proposed by the ASTERIX group.

They were presented the methodology by which the clustering was proposed, and the clustering itself. A short discussion followed the presentation.

Then they were given a brief exercise asking them to validate a listing of already classified conditions amongst the different clusters; the listing included 83 conditons – they were ased to answer only those whith wic they were familiar. After the exercise, they were asked to coment on whether the clustering was fitting the definitions and if such approach was useful to think on the methods to be applicable.

Finally, In order to collect their opinion, a questionnaire was developed referring to different aspects of the project, inclusding general questions on their perception on the current regulatory process, on the need to accelerate the processes involving commercialization of new treatments for orphan diseases, and some more specific, such as the use of a new classification and their relationship with new design methodologies, among others.

The document used during the meeting is included as Annex 2.

Their opinions were given as score from 0 (completely disagree) to 10 (totally agree). These were summarised and tabulated.

8. RESULTS

8.1. Identification of dimensions

The MCA analysis was conducted on the database of clinical characteristics and conditions with the aim of defining dimensions to form clusters. Those dimensions were determined by the confluence between the selected conditions and the clinical characteristics of the dictionary.

The initial MCA exploration suggested that most of data variability was explained by 32 of the 76 variables introduced in the database. The remaining variables were overlapping information on these 32 explanatory variables, offering small additional explanation of the dataset relationships and not contributing to further definition of dimensions, so that these were excluded from the model.

The output identified 4 data dimensions that explained 63.12% of variability according to Greenacre method[82]. These 4 dimensions were the axes along whose the different conditions were best discriminated. Considering additional dimensions did not improve the interpretation of data, nor improved the graphic representation of clinical conditions.

The numerical values of the distance of each condition to the each dimension axis ("DimN" parameter, N standing for the number of the dimension from 1 to 4) were used to graphic representation of data and to propose clustering of conditions sharing close values in dimensions. The relative weight of each variable within a dimension was proportional to the absolute value in the “Dim” parameter.

The next table shows the coordinates calculated for each condition relative to each dimension (Table 11). Results are sorted by "best dimension" (dimension with higher absolute value)

Label	Dim1	Dim2	Dim3	Dim4	Best
Acute condition: Yes	1.185	0.192	0.169	-0.150	1
Acute condition: No	-0.592	-0.096	-0.084	0.075	1
Life threatening condition: No	-0.632	-0.074	-0.276	0.199	1
Life threatening condition: Yes	0.587	0.069	0.256	-0.185	1
Very rapid or fulminating progression: No	-0.313	-0.089	-0.162	0.112	1
Very rapid or fulminating progression: Yes	1.376	0.393	0.712	-0.495	1
Differential response to treatment: No	-0.424	0.245	-0.168	-0.187	1
Differential response to treatment: Yes	0.616	-0.356	0.244	0.272	1
Dichotomic: No	-0.466	0.233	0.093	0.046	1
Dichotomic: Yes	0.791	-0.396	-0.159	-0.078	1
Continuous: No	0.606	-0.083	-0.152	0.326	1
Continuous: Yes	-0.882	0.120	0.222	-0.474	1
Prevalent cases: No	1.191	-0.191	-0.036	-0.002	1
Prevalent cases: Yes	-0.502	0.081	0.015	0.001	1
Etiological SOC: No	-1.141	-0.510	0.246	-0.601	1
SOC returns to normal: No	-0.527	-0.137	0.059	0.127	1
SOC returns to normal: Yes	1.251	0.325	-0.139	-0.301	1
Neonatal: No	-0.008	0.260	-0.016	-0.127	2
Neonatal: Yes	0.048	-1.495	0.094	0.731	2
Childhood: No	0.237	0.428	-0.070	0.025	2
Childhood: Yes	-0.562	-1.017	0.166	-0.059	2
Predictable clinical course: No	-0.746	0.791	0.299	-0.595	2
Predictable clinical course: Yes	0.314	-0.333	-0.126	0.251	2
Ordinal: No	0.089	-0.316	-0.152	-0.196	2
Ordinal: Yes	-0.312	1.108	0.531	0.687	2
Single clinically relevant Simple endpoint: No	-0.193	0.317	-0.203	-0.076	2
Single clinically relevant Simple endpoint: Yes	0.458	-0.752	0.481	0.181	2
Multiple endpoints in same domain: No	0.065	-0.351	0.280	-0.022	2
Multiple endpoints in same domain: Yes	-0.154	0.834	-0.665	0.053	2
Multiple assessment domains: No	0.353	0.329	-0.139	-0.113	2
Multiple assessment domains: Yes	-0.600	-0.560	0.236	0.191	2
Previous data on response rate / variance available: No	-0.249	-0.499	-0.389	-0.336	2
Previous data on response rate/ variance available: Yes	0.312	0.624	0.486	0.420	2
Gene-therapy: No	0.471	0.579	0.016	0.092	2
Gene-therapy: Yes	-0.507	-0.623	-0.017	-0.099	2
Intermittent condition: No	0.197	-0.368	-0.375	-0.058	3
Intermittent condition: Yes	-0.335	0.625	0.638	0.098	3
Impairment due to delayed treatment initiation: No	-0.777	0.125	0.756	-0.366	3
Impairment due to delayed treatment initiation: Yes	0.457	-0.074	-0.444	0.215	3
Impairment due to periods without treatment: No	0.287	-0.244	0.405	-0.347	3
Impairment due to periods without treatment: Yes	-0.418	0.354	-0.589	0.504	3
Rapid onset: No	-0.656	0.192	-0.431	0.016	3
Rapid onset: Yes	0.386	-0.113	0.253	-0.009	3
Direct clinical outcome: No	-0.073	-0.029	-0.500	-0.285	3
Direct clinical outcome: Yes	0.078	0.031	0.538	0.306	3
Long accrual time: No	-0.484	-0.014	-0.430	0.326	3

Label	Dim1	Dim2	Dim3	Dim4	Best
Long accrual time: Yes	0.522	0.015	0.463	-0.351	3
Incident cases: No	-0.552	0.094	0.520	0.319	3
Incident cases: Yes	0.594	-0.101	-0.560	-0.344	3
Etiological SOC: Good	0.588	0.456	-0.591	-0.138	3
Etiological SOC: Poor	-0.069	-0.224	0.479	0.412	3
Differential prognosis: No	-0.662	0.038	-0.416	-0.595	4
Differential prognosis: Yes	0.331	-0.019	0.208	0.297	4
Time to one event: No	-0.503	0.362	-0.160	-0.315	4
Time to one event: Yes	0.541	-0.389	0.172	0.339	4
Number of events in a period of time: No	0.073	-0.122	-0.013	-0.137	4
Number of events in a period of time: Yes	-0.918	1.526	0.164	1.716	4
Valid surrogate clinical endpoint: No	-0.340	-0.099	0.021	-0.284	4
Valid surrogate clinical endpoint: Yes	0.679	0.198	-0.041	0.568	4
Main endpoint objective measure: No	-0.249	-0.025	0.446	-0.433	4
Main endpoint objective measure: Yes	0.268	0.027	-0.481	0.467	4
Single clinically relevant Composite end-point: No	-0.119	-0.100	-0.043	0.105	4
Single clinically relevant Composite end-point: Yes	0.954	0.796	0.347	-0.839	4
Short accrual time: No	0.653	0.091	-0.038	-0.493	4
Short accrual time: Yes	-0.606	-0.085	0.036	0.458	4

*highest absolute value for any "Dim"

Table 12. Results of MCA: 4 selected dimensions and relative weigh of the 32 variables included in the model

According to the variables determining each of the 4 dimensions, an exercise of inference was done to identify the characteristics that better described the dimension expressed, in order to interpret clinically the potential clusters defined along the dimensions. The results are summarised in the table below (Table 12).

Dimension	Dominating characteristic	Dominating variables in the dimension
Dim1	Adverse acute prognosis Type of main end-point	Acute condition Life threatening condition Very rapid or fulminating progression Rapid onset Dichotomic Continuous Ordinal Time to one event Number of events in a period of time No etiological standard of care available Standard of care returns to normal

Dimension	Dominating characteristic	Dominating variables in the dimension
Dim2	Paediatric age Multidimensional efficacy assessments Knowledge of disease	Intermittent condition Neonatal Childhood Predictable clinical course Multiple endpoints in same domain Multiple assessment domains Previous data on event / response rate or variance available Gene therapy possible
Dim3	Hard end-point Long accrual time	Direct clinical outcome Main endpoint is an objective measure with no possible bias Single clinically relevant end-point 1: Simple endpoint Multiple endpoints in same domain Multiple assessment domains Long accrual time Etiologic standard of care - good results
Dim4	Subgroups Relapsing diseases Composite variables Short accrual time Time to one event	Differential prognosis Differential response to treatment Time to one event Number of events in a period of time Valid surrogate clinical endpoint Single clinically relevant end-point 2: Composite end-point Short accrual time Incident cases

Table 13. Summary of the characteristics determining each dimension

8.2. Interpretation of MCA clustering of conditions

Analysing the entire set of data, the dimensions were defined based using the descriptive variables defined in the dictionary as explanatory of the relationships between conditions. Placement of each condition (supplementary variables) on the axes, by displaying the numerical values of the distance of each condition to each of the 4 axis (coordinates) are included in the tables below, sorted by highest value in dimension 1, 2, 3, 4 (Tables 13-16). This summary of coordinates and the graphical representation were used to obtain an initial clustering. The text colours used in the first column of the tables signal the proposed clustering of conditions.

Disease	Dim 1	Dim 2	Dim 3	Dim 4	Best 1	Best 2
Multiple Esclerosis -Chronic Treatment	-1.328	1.525	1.061	1.293	2	1
Fragile X Syndrome	-1.312	-0.902	0.051	-0.665	1	2
Angelman Syndrome / Prader Willy Syndrome	-1.306	-0.963	0.069	-0.989	1	4
Huntington Disease	-1.203	-0.320	-0.226	-1.169	1	4
Lennox-Gastaut Syndrome	-1.087	1.004	1.021	-0.233	1	3
Pompe Disease - Late Onset	-0.973	0.382	-1.731	-0.382	3	1
Nocturnal Paroxysmal Hemoglobinuria	-0.910	1.494	-0.591	-0.294	2	1
Alport Syndrome	-0.799	-1.371	0.316	0.049	2	1
Hereditary Angioedema - Prevention of Flares	-0.752	0.111	1.143	-1.356	4	3
Haemophilia	-0.508	1.528	-0.733	2.139	4	2
Cystic Fibrosis	-0.448	-1.575	0.009	1.373	2	4
Amiotrophic Lateral Sclerosis	-0.352	0.405	-0.136	2.221	4	2
Phenylketonuria	-0.150	-1.250	-0.980	-0.343	2	3
Chronic Myeloid Leukemia	-0.143	0.408	-2.404	-0.307	3	2
Cryopyrin-Associated Periodic Sds CAPS/FCAS/MWS	-0.087	-1.113	1.109	-0.339	2	3
CAPS-NOMID	0.096	-1.192	1.613	1.217	3	4
Multiple Sclerosis - Acute Treatment of Flares	0.122	1.611	2.305	-1.121	3	2
Hereditary Angioedema - Acute Treatment of Flares	0.160	0.523	-0.591	-1.499	4	3
Pulmonary Arterial Hypertension	0.441	-0.418	-0.518	0.639	4	3
Pompe Disease - Early Onset	0.692	-1.962	-0.266	0.677	2	1
Acute Lymphocytic Leukemia	0.860	0.394	-1.482	-0.557	3	1
Renal Cell Carcinoma	0.950	0.758	0.041	1.171	4	1
Burkitt Lymphoma	1.282	0.571	-0.333	-0.173	1	2
Guillain-Barré Syndrome	1.392	0.168	0.095	-0.398	1	4
Toxic Megacolon	1.655	0.040	0.261	-0.420	1	4
Adenocarcinoma of the Pancreas	1.829	-0.238	0.678	0.307	1	3
Ventilator Associated Pneumonia by Pseudomonas	1.880	0.383	0.219	-0.840	1	4

Table 14. Numerical values for supplementary variable (name of disease) from results of clinical conditions in each dimension, sorted by dimension 1.

Disease	Dim 1	Dim 2	Dim 3	Dim 4	Best 1	Best 2
Pompe Disease - Early Onset	0.692	-1.962	-0.266	0.677	2	1
Cystic Fibrosis	-0.448	-1.575	0.009	1.373	2	4
Alport Syndrome	-0.799	-1.371	0.316	0.049	2	1
Phenylketonuria	-0.150	-1.250	-0.980	-0.343	2	3
CAPS-NOMID	0.096	-1.192	1.613	1.217	3	4
Cryopyrin-Associated Periodic Sds CAPS/FCAS/MWS	-0.087	-1.113	1.109	-0.339	2	3
Angelman Syndrome / Prader Willy Syndrome	-1.306	-0.963	0.069	-0.989	1	4
Fragile X Syndrome	-1.312	-0.902	0.051	-0.665	1	2
Pulmonary Arterial Hypertension	0.441	-0.418	-0.518	0.639	4	3
Huntington Disease	-1.203	-0.320	-0.226	-1.169	1	4
Adenocarcinoma of the Pancreas	1.829	-0.238	0.678	0.307	1	3
Toxic Megacolon	1.655	0.040	0.261	-0.420	1	4
Hereditary Angioedema - Prevention of Flares	-0.752	0.111	1.143	-1.356	4	3
Guillain-Barré Syndrome	1.392	0.168	0.095	-0.398	1	4

Disease	Dim 1	Dim 2	Dim 3	Dim 4	Best 1	Best 2
Pompe Disease - Late Onset	-0.973	0.382	-1.731	-0.382	3	1
Ventilator Associated Pneumonia by Pseudomonas	1.880	0.383	0.219	-0.840	1	4
Acute Lymphocytic Leukemia	0.860	0.394	-1.482	-0.557	3	1
Amiotrophic Lateral Sclerosis	-0.352	0.405	-0.136	2.221	4	2
Chronic Myeloid Leukemia	-0.143	0.408	-2.404	-0.307	3	2
Hereditary Angioedema - Acute Treatment of Flares	0.160	0.523	-0.591	-1.499	4	3
Burkitt Lymphoma	1.282	0.571	-0.333	-0.173	1	2
Renal Cell Carcinoma	0.950	0.758	0.041	1.171	4	1
Lennox-Gastaut Syndrome	-1.087	1.004	1.021	-0.233	1	3
Nocturnal Paroxysmal Hemoglobinuria	-0.910	1.494	-0.591	-0.294	2	1
Multiple Esclerosis -Chronic Treatment	-1.328	1.525	1.061	1.293	2	1
Haemophilia	-0.508	1.528	-0.733	2.139	4	2
Multiple Sclerosis - Acute Treatment of Flares	0.122	1.611	2.305	-1.121	3	2

Table 15. Numerical values for conditions in each dimension, sorted by dimension 2

Disease	Dim 1	Dim 2	Dim 3	Dim 4	Best 1	Best 2
Chronic Myeloid Leukemia	-0.143	0.408	-2.404	-0.307	3	2
Pompe Disease - Late Onset	-0.973	0.382	-1.731	-0.382	3	1
Acute Lymphocytic Leukemia	0.860	0.394	-1.482	-0.557	3	1
Phenylketonuria	-0.150	-1.250	-0.980	-0.343	2	3
Haemophilia	-0.508	1.528	-0.733	2.139	4	2
Nocturnal Paroxysmal Hemoglobinuria	-0.910	1.494	-0.591	-0.294	2	1
Hereditary Angioedema - Acute Treatment of Flares	0.160	0.523	-0.591	-1.499	4	3
Pulmonary Arterial Hypertension	0.441	-0.418	-0.518	0.639	4	3
Burkitt Lymphoma	1.282	0.571	-0.333	-0.173	1	2
Pompe Disease - Early Onset	0.692	-1.962	-0.266	0.677	2	1
Huntington Disease	-1.203	-0.320	-0.226	-1.169	1	4
Amiotrophic Lateral Sclerosis	-0.352	0.405	-0.136	2.221	4	2
Cystic Fibrosis	-0.448	-1.575	0.009	1.373	2	4
Renal Cell Carcinoma	0.950	0.758	0.041	1.171	4	1
Fragile X Syndrome	-1.312	-0.902	0.051	-0.665	1	2
Angelman Syndrome / Prader Willy Syndrome	-1.306	-0.963	0.069	-0.989	1	4
Guillain-Barré Syndrome	1.392	0.168	0.095	-0.398	1	4
Ventilator Associated Pneumonia by Pseudomonas	1.880	0.383	0.219	-0.840	1	4
Toxic Megacolon	1.655	0.040	0.261	-0.420	1	4
Alport Syndrome	-0.799	-1.371	0.316	0.049	2	1
Adenocarcinoma of the Pancreas	1.829	-0.238	0.678	0.307	1	3
Lennox-Gastaut Syndrome	-1.087	1.004	1.021	-0.233	1	3
Multiple Esclerosis -Chronic Treatment	-1.328	1.525	1.061	1.293	2	1
Cryopyrin-Associated Periodic Sds CAPS/FCAS/MWS	-0.087	-1.113	1.109	-0.339	2	3
Hereditary Angioedema - Prevention of Flares	-0.752	0.111	1.143	-1.356	4	3
CAPS-NOMID	0.096	-1.192	1.613	1.217	3	4
Multiple Sclerosis - Acute Treatment of Flares	0.122	1.611	2.305	-1.121	3	2

Table 16. Numerical values for conditions in each dimension, sorted by dimension 3

Disease	Dim 1	Dim 2	Dim 3	Dim 4	Best 1	Best 2
Hereditary Angioedema - Acute Treatment of Flares	0.160	0.523	-0.591	-1.499	4	3
Hereditary Angioedema - Prevention of Flares	-0.752	0.111	1.143	-1.356	4	3
Huntington Disease	-1.203	-0.320	-0.226	-1.169	1	4
Multiple Sclerosis - Acute Treatment of Flares	0.122	1.611	2.305	-1.121	3	2
Angelman Syndrome / Prader Willy Syndrome	-1.306	-0.963	0.069	-0.989	1	4
Ventilator Associated Pneumonia by Pseudomonas	1.880	0.383	0.219	-0.840	1	4
Fragile X Syndrome	-1.312	-0.902	0.051	-0.665	1	2
Acute Lymphocytic Leukemia	0.860	0.394	-1.482	-0.557	3	1
Toxic Megacolon	1.655	0.040	0.261	-0.420	1	4
Guillain-Barré Syndrome	1.392	0.168	0.095	-0.398	1	4
Pompe Disease - Late Onset	-0.973	0.382	-1.731	-0.382	3	1
Phenylketonuria	-0.150	-1.250	-0.980	-0.343	2	3
Cryopyrin-Associated Periodic Sds CAPS/FCAS/MWS	-0.087	-1.113	1.109	-0.339	2	3
Chronic Myeloid Leukemia	-0.143	0.408	-2.404	-0.307	3	2
Nocturnal Paroxysmal Hemoglobinuria	-0.910	1.494	-0.591	-0.294	2	1
Lennox-Gastaut Syndrome	-1.087	1.004	1.021	-0.233	1	3
Burkitt Lymphoma	1.282	0.571	-0.333	-0.173	1	2
Alport Syndrome	-0.799	-1.371	0.316	0.049	2	1
Adenocarcinoma of the Pancreas	1.829	-0.238	0.678	0.307	1	3
Pulmonary Arterial Hypertension	0.441	-0.418	-0.518	0.639	4	3
Pompe Disease - Early Onset	0.692	-1.962	-0.266	0.677	2	1
Renal Cell Carcinoma	0.950	0.758	0.041	1.171	4	1
CAPS-NOMID	0.096	-1.192	1.613	1.217	3	4
Multiple Esclerosis -Chronic Treatment	-1.328	1.525	1.061	1.293	2	1
Cystic Fibrosis	-0.448	-1.575	0.009	1.373	2	4
Haemophilia	-0.508	1.528	-0.733	2.139	4	2
Amiotrophic Lateral Sclerosis	-0.352	0.405	-0.136	2.221	4	2

Table 17. Numerical values for conditions in each dimension, sorted by dimension 4

The next six figures represent bubble-plotting of coordinates for each of the conditions by pairs of dimensions in bidimensional graphics: dimensions 1 vs 2 (Figure 12), 1 vs 3 (Figure 13), 1 vs 4 (Figure 14), 2 vs 3 (Figure 15), 2 vs 4 (Figure 16) and 3 vs 4 (Figure 17). The latter (3 vs 4) did not contribute to further grouping. Conditions that were identified as having similar coordinates in two-dimensional graphs were marked with colour codes, and colours were maintained across graphs for the ease of visualizing consistency of grouping; these are the same codes used in the first column of tables 13 to 16 (I ex: red conditions were grouped based on positive values in dimension 1, yellow conditions on negative values for dimension 1 and 2, and brown conditions were those with positive values for dimension 2 and 4) (Figures 12-17).

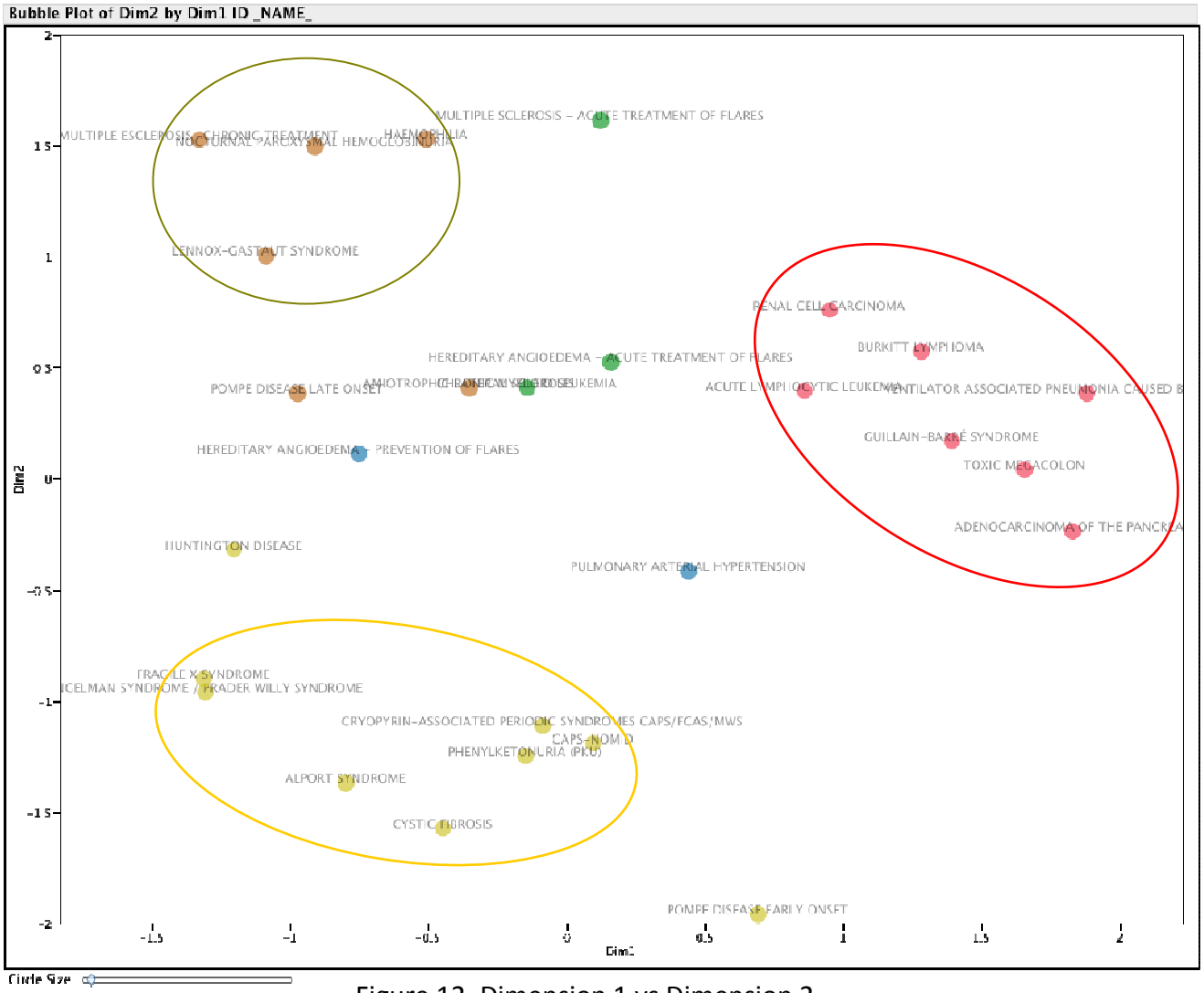


Figure 12. Dimension 1 vs Dimension 2

Figure 13. Dimension 1 vs dimension 3

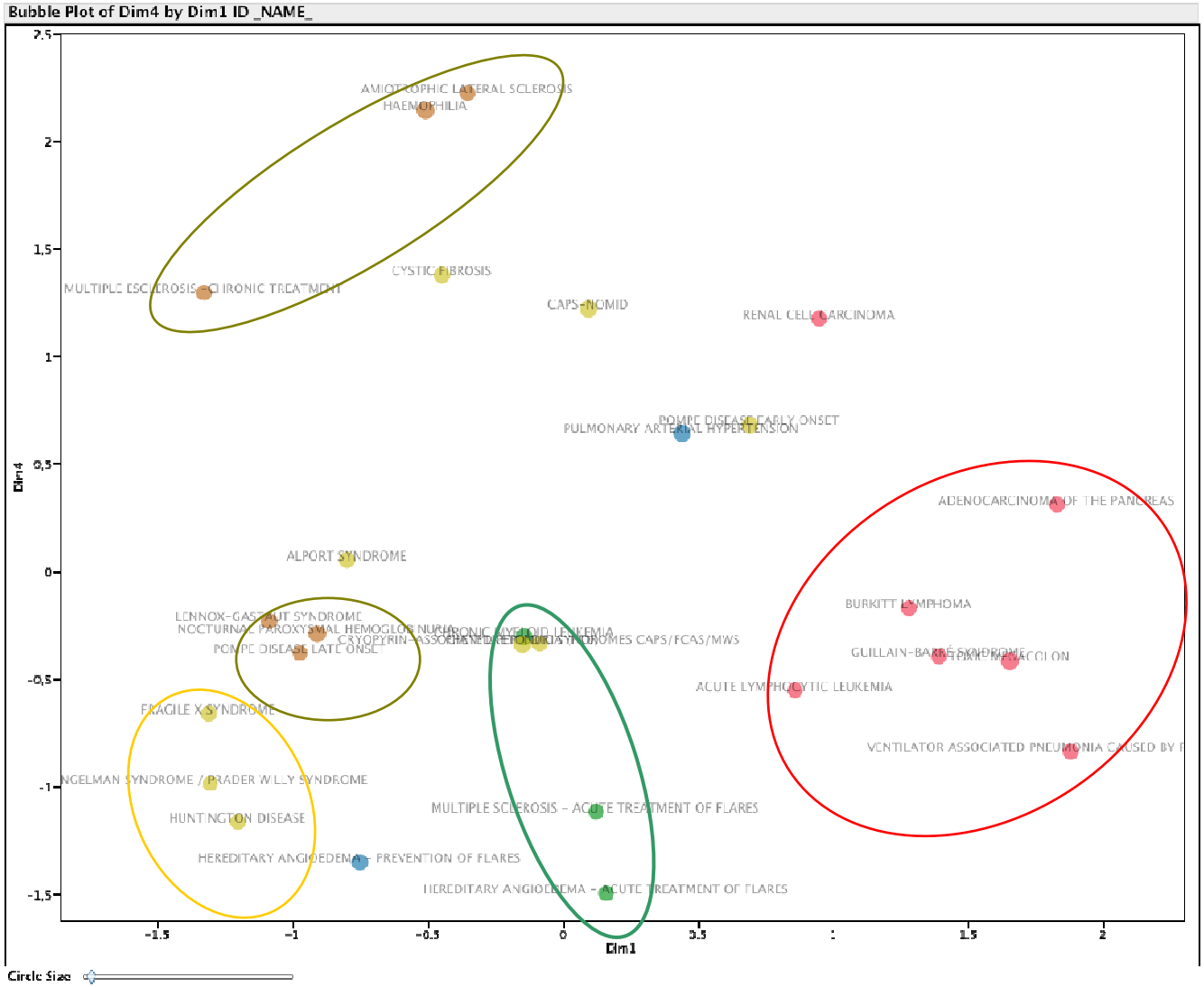


Figure 14. Dimension 1 vs dimension 4

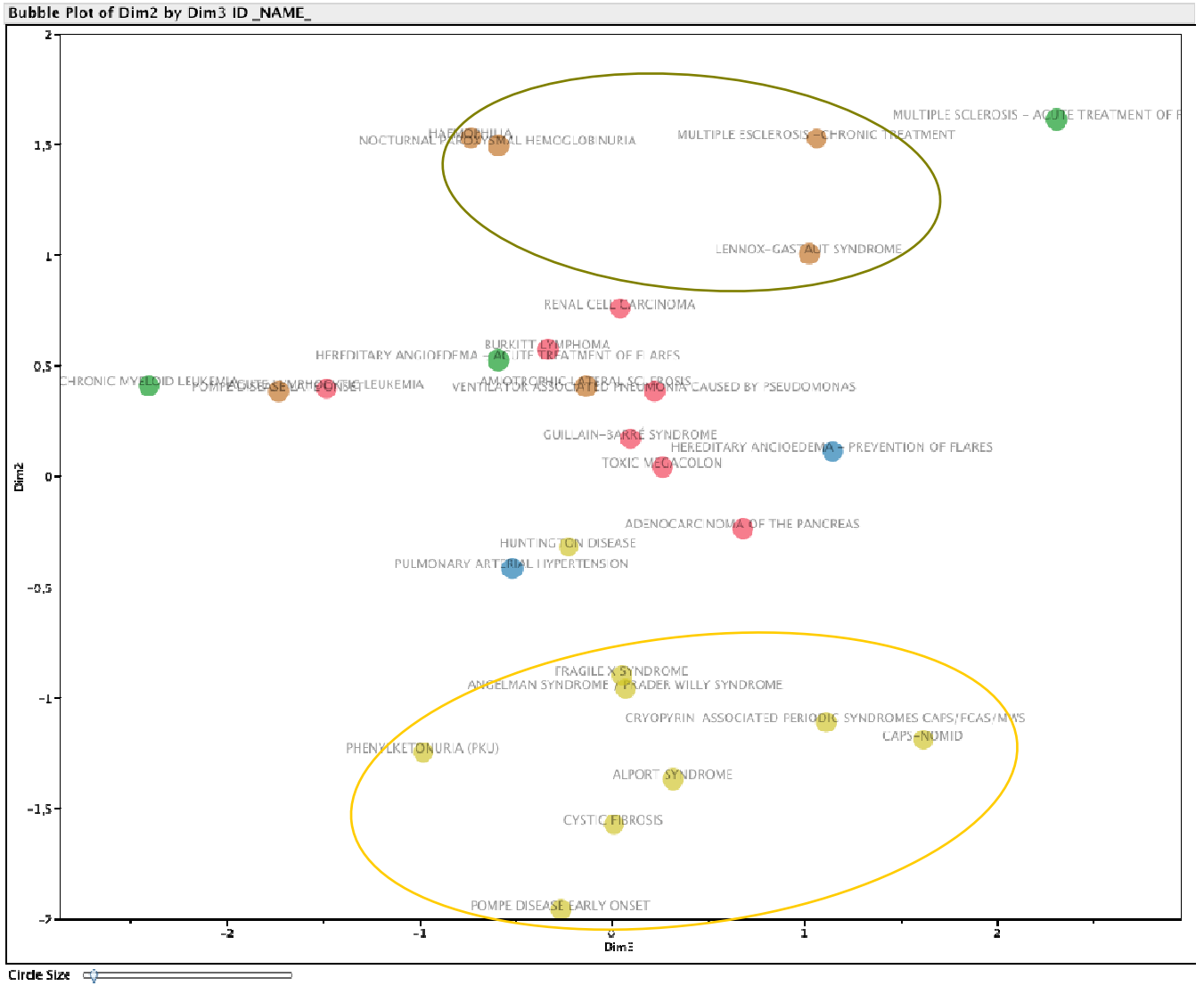


Figure 15. Dimension 2 vs dimension 3

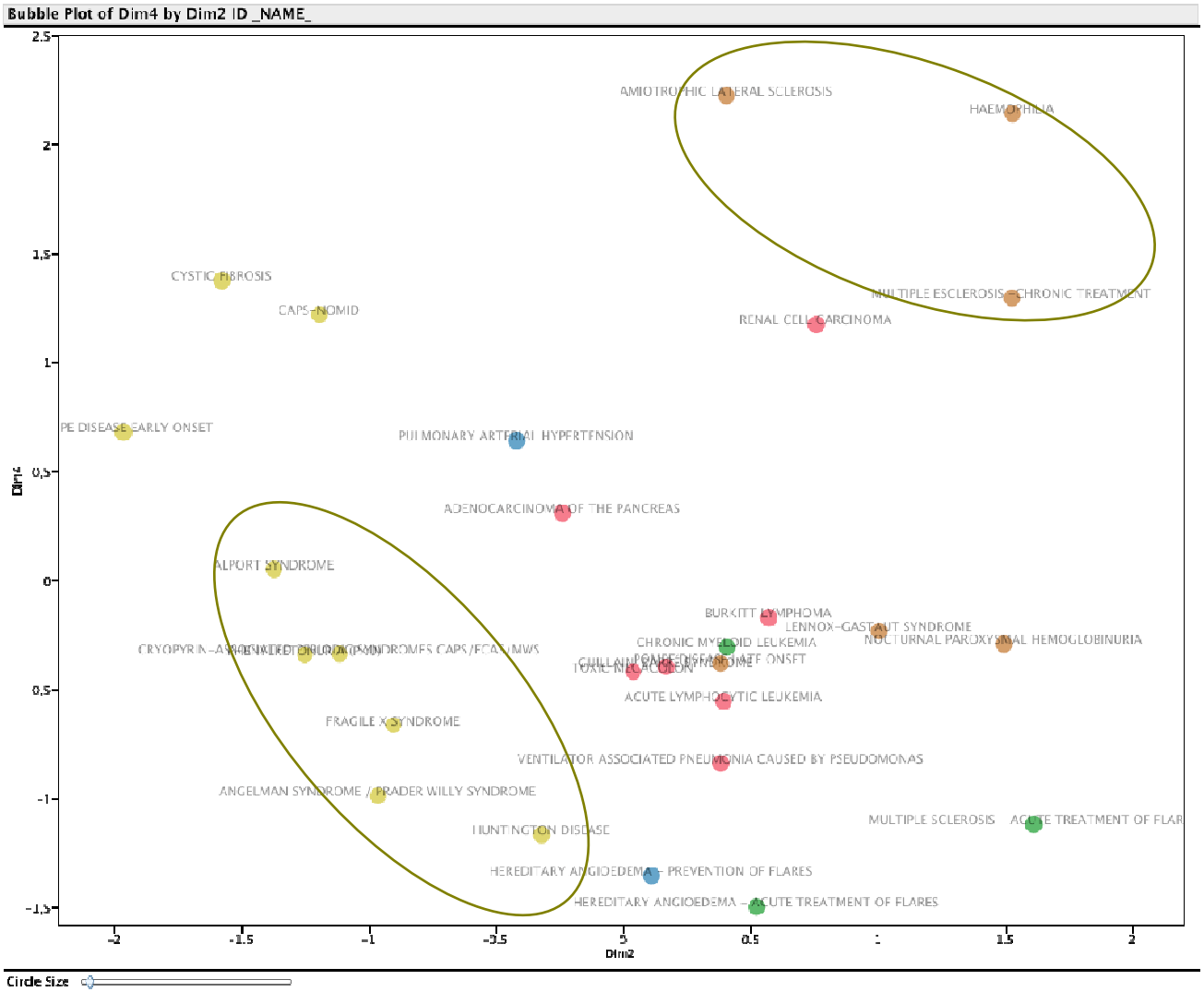


Figure 16. Dimension 2 vs dimension 4

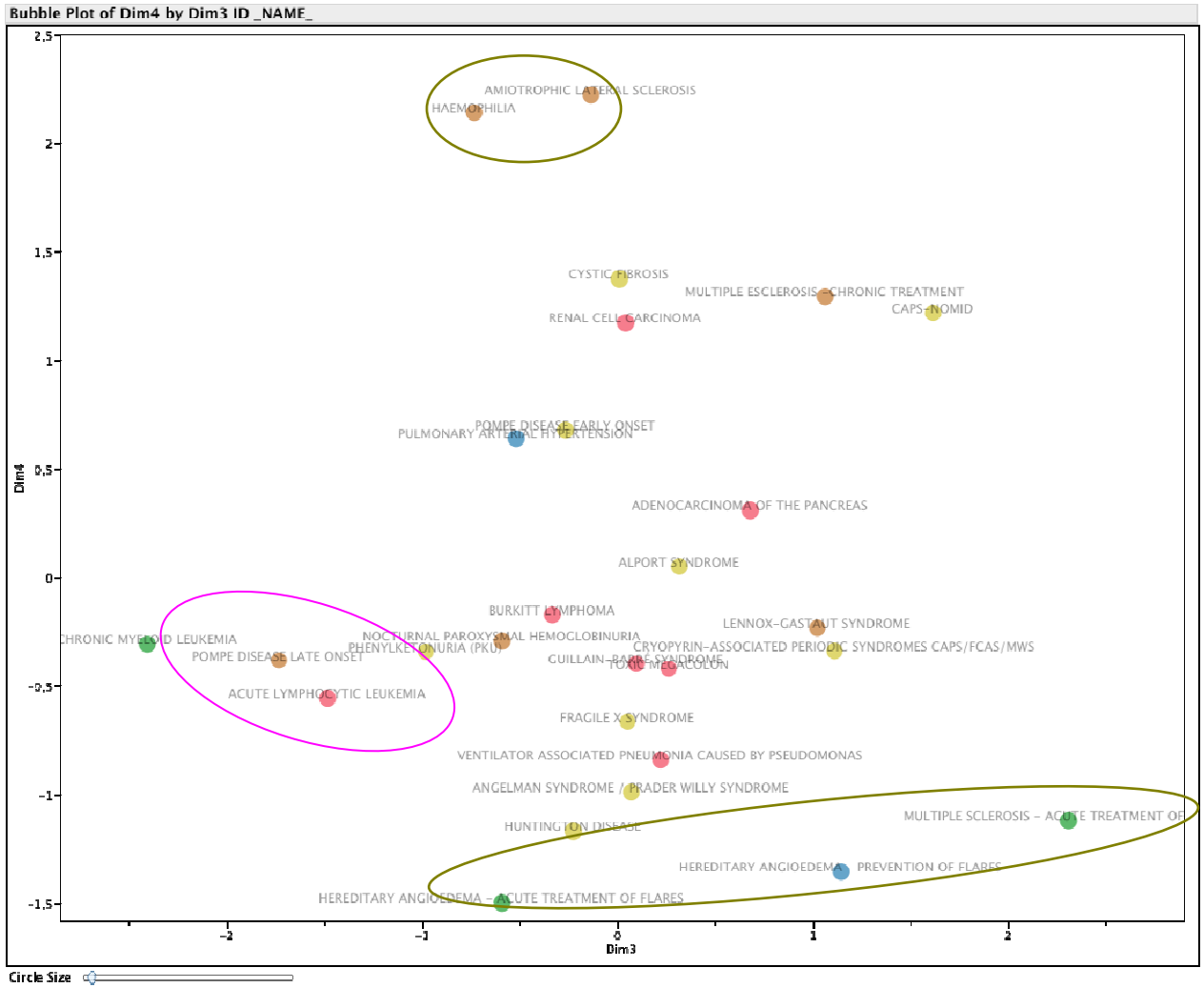


Figure 17. Dimension 3 vs dimension 4

8.3. Clustering proposal

After the inspection of the numeric values for coordinates (Table 13-16) and plots (Figures 12-17), a preliminary grouping of rare conditions used were identified (Table 17).

Based on dimension	Diseases discriminated
1	VAP Guillain-Barré syndrome Toxic Megacolon Adenocarcinoma of the pancreas Renal adenocarcinoma Burkitt lymphoma Acute lymphocytic leukemia
2	X Fragile syndrome Angelman/ Prader Willy syndromes Alport Syndrome Cryopirin associated periodic syndromes Phenylketyonuria Cystic Fibrosis CAPS-NOMID Pompe disease (early onset) Huntington disease
3	Hemophilia Multiple sclerosis – Progressive neurological impairment Nocturnal Paroxysmal Hemoglobinuria Lennox-Gastaut Syndrome Pompe disease (adult onset)
4	Multiple Sclerosis – acute treatment of flares Hereditary angioedema – acute treatment of flares Chronic myeloid Leukemia
Not clustered	Pulmonary hypertension Hereditary angioedema - prevention of flares Amiotrophic Lateral Sclerosis

Table 18. Preliminary grouping of diseases

A first set of 5 clusters was proposed on the basis on the coordinates and graphics:

- Acute conditions with poor prognosis
- Chronic (pediatric) conditions with multidimensional impairment
- Recurrent chronic conditions (progressive and not progressive)

- Conditions with clear-cut episodes (single or recurrent)
- Chronic staged conditions

The last cluster (staged conditions) was not derived from bubble-plots, but proposed to fit non-clustered conditions that did not show extreme values in the working dimensions, since they shared many characteristics of other conditions depending on the evolutive phase of the disease. However, they shared as a common feature that stages were clearcut along the progression of the disease, with different severities that conditioned changes in the applicability of methods, but the overall approach to their study was similar.

The different conditions were then preliminary classified according to the proposed clusters (Table 18). Some conditions were proposed to be in a cluster regardless of the bubble-plot, these are marked in italics. The table was used as the basis-case to start the consensus process.

Group description	Diseases included
1: Conditions with clear-cut episodes	
a. Single event	Chronic myelocytic leukemia Acute lymphoblastic leukemia
b. Repeated events	Hereditary angioedema – acute treatment of flares Multiple sclerosis – acute treatment of flares Cryopirin associated periodic syndromes *CAPS- NOMID*
2: Recurrent chronic diseases	
A. Progressive	Amiotrophic Lateral Sclerosis Multiple sclerosis – Progressive neurological impairment Nocturnal Paroxismal Hemoglobinuria *Huntington disease?*
B. Non progressive	Hemophilia Lennox-Gastaut Syndrome *Prevention of flares in hereditary angioedema*

Group description	Diseases included
3: Acute diseases with poor prognosis	VAP Guillain-Barré syndrome Toxic Megacolon Adenocarcinoma of the pancreas Renal adenocarcinoma Burkitt lymphoma *Early onset Pompe disease*
4: Chronic (pediatric) conditions with multidimensional impairment	Cystic Fibrosis X Fragile syndrome Alport Syndrome Angelman / Prader Willy syndromes Phenylketyonuria *Late onset Pompe disease* *CAPS- NOMID?*
5: *Chronic staged disease?*	Pulmonary Hypertension *Huntington disease* *Cystic fibrosis*

Table 19. Preliminary grouping of conditions

In subsequent sessions, iterative discussions were done by the investigators in the team from the methodological, clinical and regulatory perspectives, where the basis-case derived from the MCA was used as a starting point to discuss on clusters.

The clusters were reviewed and tested using different conditions as examples, to check fitness with the working definitions of each cluster and their methodological implications. A clustering with defintions was proposed (Figure 18).

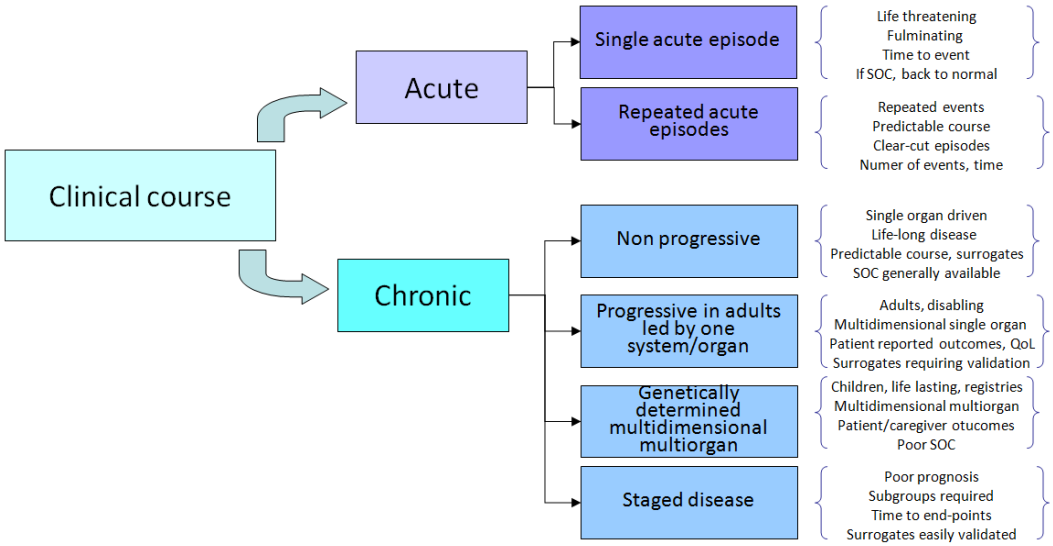
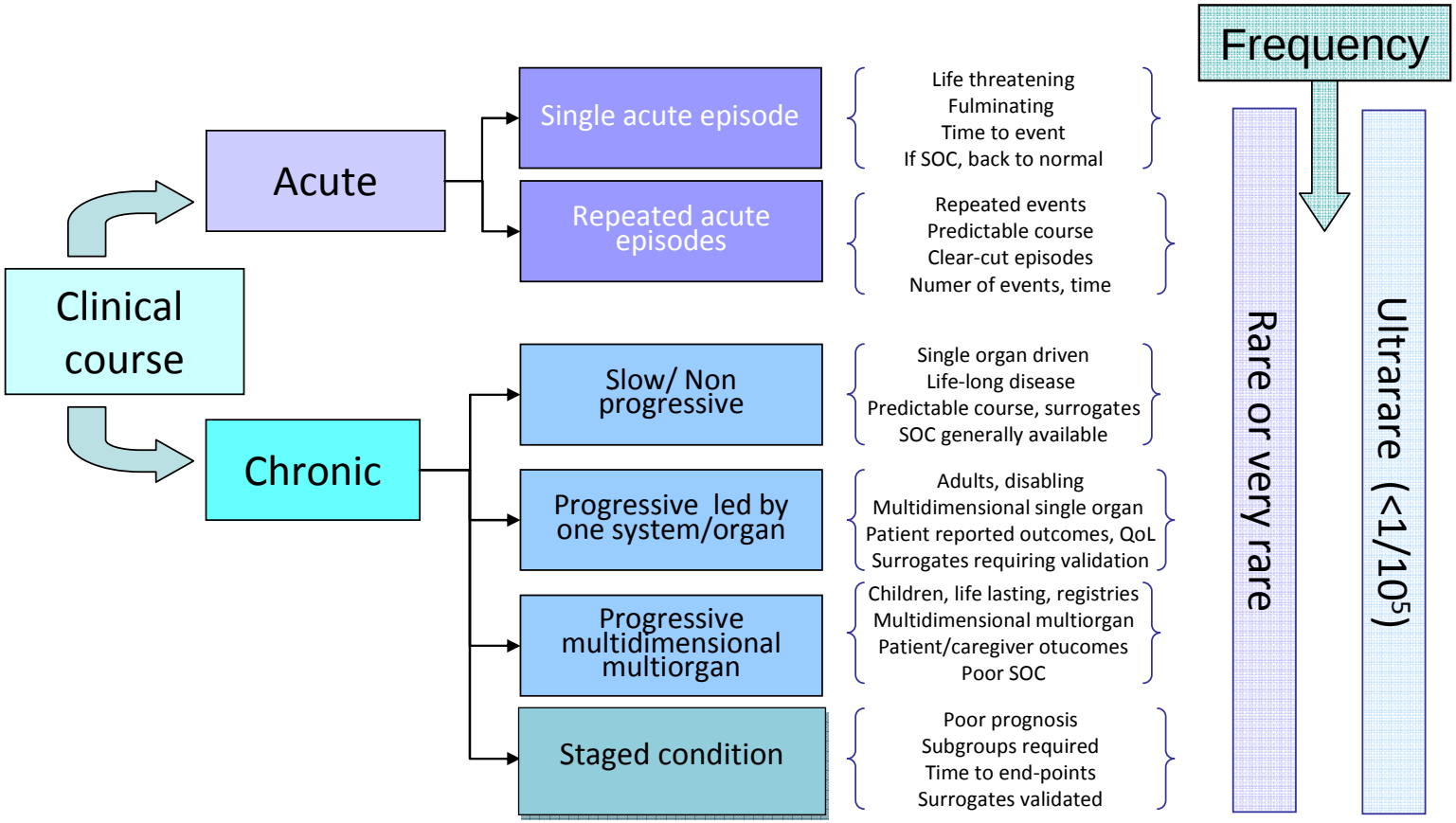


Figure 18. Preliminary proposed clustering

Then, the prevalence of the conditions (ultrarare conditions vs others) was included as a descriptor within each cluster, since it was regarded as a relevant characteristic from the methodological perspective despite it was not a discriminant characteristic in the MCA. Actually, the prevalence could be either rare or ultrarare independently from the clinical features or the pathophysiology of the condition, so that the clinical descriptors were unable to catch this factor to explain differences across conditions.

This led to the final proposal of the clustering (Figure 19, next page).

Figure 19. Final grouping of conditions



The final clustering of conditions was tested by two different investigators using the conditions for which orphan medicinal products had been issued an opinion by the EMA until December 2014 (Annex 3).

The results showed that all the conditions could be classified to at least one of the clusters (Figure 20).

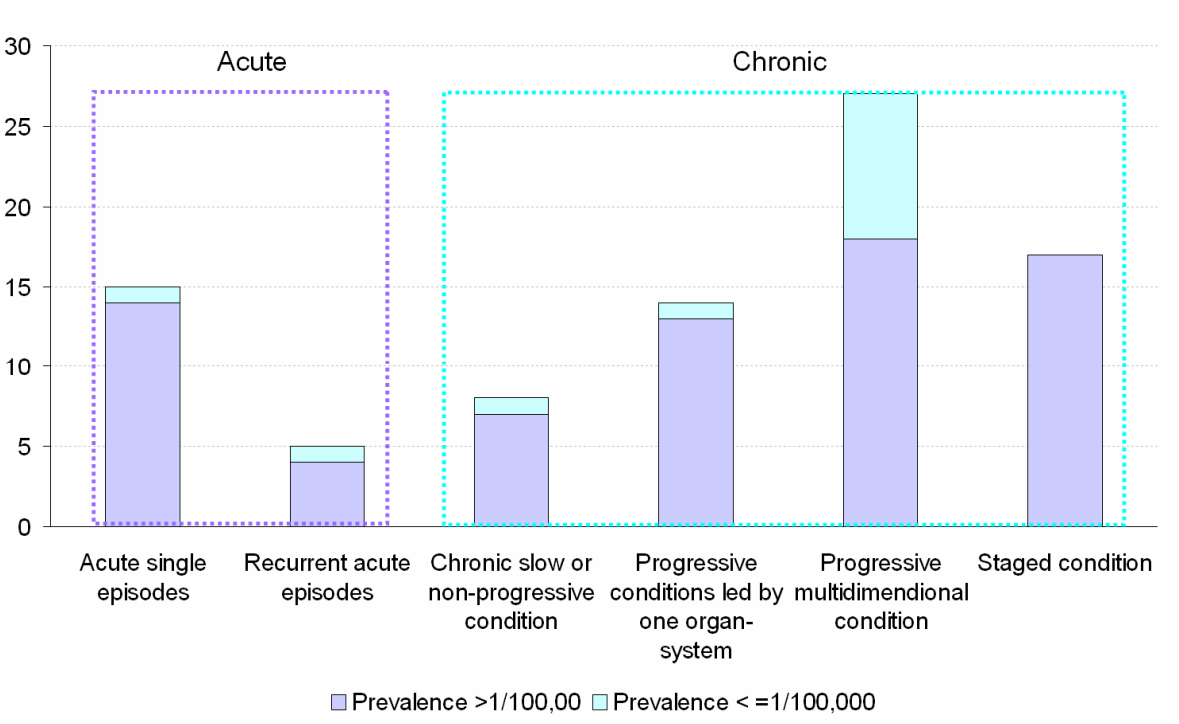


Figure 20. Testing of clustering with EMA authorised OMP up to Dec 2014

There were some medical conditions that could fit in more than one cluster depending on the treatment goals or intended indications; yet, all could be classified, and thus it was condiered that the clustering was collecting most plausible scenarios for drugs currently handled by regulators.

There was consistency between investigators for the grouping of conditions. The feedback obtained during this validation was used to further refine the final wording defining each category.

8.4. Inference of methodological homogeneity within clusters

The process to carry out the methodological inferences to the different established clusters implied a first step of listing the variables that had a high discriminative value for each cluster, and a second step to make detailed descriptions of these determinants in relation to aspects required to define clinical study designs. This was done in order to test the validity of the proposed clusters to their main purpose; i e: issuing common recommendations on product development for a given group of conditions.

The characteristics of the conditions determining designs were then systematised for each cluster, and the potential designs fitting the study of treatments intended for the type of conditions included within a group were proposed as shown in the following table (Table 20).

Sample conditions were incuded for ease of reference.

Table 20. Description of clusters and implicatons for study design

Cluster	Description	Implications	Examples
(1) Single acute episode	Incident cases with single acute episode, with rapid onset and rapid endpoint. Well-known and predictable course in absence of treatment, often serious or life-threatening. Recovery generally returns to baseline health status with or without sequels. Generally led by one organ/system that then derives into multiorganic impairment. Comparison must consider whether there is an effective SOC. Add-on designs. Generally single hard objective and clinically relevant end-point, often dichotomic.	Studies with longer recruitment than follow-up for a given subject, thus application of sequential and adaptive methods may optimise the trial size. Time to event may be applied. If SOC available, then placebo could be applicable in parallel, add-on designs with non-inferiority or superiority objective. Single hard objective end-point may allow unblinded designs. Lack of SOC may ease recruitment, but comparisons against placebo generally not acceptable unless add-on designs to e.g. best supportive care. Placebo may be used for limited time in non life-threatening conditions. For disease without SOC or trials in patients who have exhausted all SOC options, controls may be historical, external or even uncontrolled trials assessing change from baseline or superiority to substantiated expectations may be justified. Rescue strategies generally required during patient follow-up.	Ventilator associated pneumonia caused by *Pseudomonas aeruginosa* Guillain-Barré syndrome Toxic Megacolon Progressive Multifocal Leukoencephalopathy Idiopathic acute eosinophilic pneumonia Familial acute necrotizing encephalopathy

Cluster	Description	Implications	Examples
(2) Repeated acute episodes	Prevalent subjects who suffer clear-cut repeated episodes separated by relatively healthy periods. The condition has a well known predictable clinical course, with repeated clinical episodes led by one organ/system, which are generally due to a single biological or physiological abnormality which -if severe or immunological- may derive into multiorganic impairment. Baseline status may deteriorate slowly along years due to repeated episodes. Generally there are clinically relevant time-related end-points, measuring the underlying activity of the abnormality through number of episodes by time. If the condition is mild, variables may be based on patient reported outcomes. If the condition is serious, then dichotomic clinical end-points can be used.	Generally two different indications: treatment of acute episodes and prevention of new episodes. If condition is returning to normal after acute episode, start-stop designs (withdrawal, cross-over and intrasubject comparison) may be applicable for both indications. For treatment of acute episodes, variables generally include remission of the episode (dichotomic), time to remission of the episode (time to event) or intensity of the episode. For prevention of the episodes, variables generally rely on number of episodes per time. Longitudinal designs with repeated measurements may be applied. Response may be based on clinical assessments supported by lab/biological/imaging data. Multiple assessments are generally feasible. Use of placebo generally limited in time for non life-threatening conditions or when lack of prognostic consequences for periods without treatment. Rescue plan needed (either for placebo or for experimental treatment)	Cryopirin associated periodic syndromes Long term prevention of acute attacks of hereditary angioedema Multiple sclerosis – treatment of flares Nocturnal Paroxismal Hemoglobinuria Alternating hemiplegia Acute intermitent porphyria

Cluster	Description	Implications	Examples
(3) Chronic non-progressive	The condition is life-long and affects mainly a single system/organ, with constitutive activity due to deficiency or impairment of function and a predictable well-known clinical course. May be adult or both pediatric and adult. In general, it does not rapidly deteriorate the subject function or life-expectancy with current standard of care, which is generally available but not always evidence based. However, if SOC is not optimal, further deterioration may occur in years. Prevalence is higher than incidence, and often there are available surrogates which measure the underlying defect or deficiency directly.	Recruitment may be more rapid than subject follow-up, potentially limiting the role for sequential designs and some adaptions. Start – stop based methods (crossover, withdrawal) may be applicable. Intrasubject comparisons generally feasible. Double blind would be generally required, and because SOC is generally available, designs would generally be add-on, unless treatments share mechanism of action – then direct comparison may be required with non-inferiority approach. Surrogates would generally be available and often easily validated. Safety requirements must be widely assessed due to chronicity and relative mildness of conditions with current SOC.	Hemophilia (maintenance) Short bowel syndrome (maintenance) Charcot-Marie-Tooth type 2B2 Growth delay due to ILGF-1 deficiency Lennox-Gastaut Syndrome Chronic Lymphocytic Leukemia- early stage

Cluster	Description	Implications	Examples
(4) Chronic progressive led by one system-organ	Initial impairment of one system/organ, which may or not involve others along time Clinical course is longer than acute conditions, usually year(s). Progressively reducing life quality and/or quantity of life, typically subjects are seriously disabled due to disease. Current standard of care is generally symptomatic or supportive, but not curative. Variables are often relying on patient reported outcomes, and patient perceptions on the disease; disability and QoL may be relevant for decision-making.	Due to progression, start stop methods and intrasubject comparison generally not feasible. Parallel trials needed when heterogeneity or poor predictability of clinical course are present, with add-on to SOC. Enrichment designs may reduce heterogeneity. Disease assessment often highly dependent on patient inputs, with (time to change in) function(s) and QoL being key components of the efficacy measures; multiple end-points usually in the same domain may be acceptable/required. Often using surrogates that allow early (interim) results used for decision making. Some adaptions can be applied along the trial. When severe, classical parallel sequential designs with long term comparison may not be applicable, unless early rescue / crossing over. Patient input on clinical relevance required. High willingness to accept trials even if SOC available. Unbalanced randomization may be useful. Thorough safety requirements may be delayed if substantial effect is observed	Amyotrophic Lateral Sclerosis Multiple Sclerosis - Progressive neurological impairment Retinitis pigmentosa Hemoglobinuria Huntington disease Aceruloplasminemia Fibrodysplasia ossificans progressiva

Cluster	Description	Implications	Examples
(5) Chronic progressive multidimensional	Life-lasting diseases, often inherited starting as paediatric and, if mild or available SOC, affecting (young) adults. Often SOC is poor or not available. Highly variable clinical course, with impact in multiple system/organs, requiring multidimensional assessment and endpoints relying on subjective assessments from caregivers/patients on clinical or functional status and QoL. Previous data on event/response rate or variance is often available for current SOC. Prevalent cases much more frequent than incident cases. If not rapidly life-threatening, prospective registries often feasible and available If inherited, known physiopathology allowing development of targeted therapies and options for genetic approaches.	Prevalent cases in paediatric population may be identified from registries, speeding recruitment. Parallel designs will be generally needed, due to progression and intersubject variability. Enrichment /stratification may be useful to control heterogeneity. Previous information on the clinical course can be suitable for bayesian approaches and planning of adaptions. Designs generally add-on to supportive SOC;reluctance to placebo may occur because of paediatric population, concern on progression and lack of effective SOC. Unbalanced randomisation, delayed start and early escape/crossing-over may be useful to limit placebo exposure and cover ethical concerns. Multiple variables applicable to cover the multidimensional nature. Function and quality of life would generally be regarded as key assessments, including patient/ caregiver's input on reported outcomes and clinical relevance. Surrogates may be useful for early (interim) decision-making, and may be validated along clinical development. For gene-therapy trials, generally a single chance is possible by subject, so that early participation preclude future options.	Treatment of cystic fibrosis (gain of function of chloride channels) X Fragile syndrome Alport Syndrome Angelman / Prader Willy syndromes Glucogenosis Pheniketonuria Progeria

Cluster	Description	Implications	Examples
(6) Staged conditions	The condition initially is mild/limited to one system/organ and then progresses/expands impairment into other system/organs, with clearly defined clinical stages which cannot be studied together. Conditions are not age-specific. Different severities or extensions of disease have different prognosis and treatment approaches; disease extension is a key variable, either time dependent or not. For those neoplastic, imaging is preferred method for staging; haematological conditions also assess tumour burden, and non-malignant conditions generally measure subject function. Quality of life relevant for all. Outcomes are generally referred to progression, stagnation or reversal of the condition, with time in each stage as a relevant measure of disease. Complete healing may be possible, but requires long term confirmation. If reversal is not feasible, late stages have poor (fatal) prognosis.	Prevalent diseases with subjects identified at any stage. Registries available for slow progressive conditions, or subjects diagnosed in early stage. Well documented case series on natural course available for many conditions favouring bayesian approaches and allowing external/historical controls for ultrarare/poor prognosis. Long follow-up is required. Stage determines both design (through stratification of pre-defined subgroups) and variables (main variable being different in each stage); a variable may be change of status. Enrichment designs may use biomarkers selecting potential respondes. Multidimensional and multiple objective measurable end-points would be acceptable in milder conditions; if progression is rapid hard end-points may be accessible. Ofen survval designs. Repeated measurements applicable along follow-up. High willingness to accept trials even if SOC available; when poor prognosis, methods to limit placebo exposure required to cover ethical concerns. Unbalanced randomization may be useful. Safety requirements may be less stringent or delayed if progression is rapid and severe, but should consider impact on QoL.	Pulmonary Hypertension Liver cancer Hematological cancers Familial melanoma Osteosarcoma Angiosarcoma Anaplastic thyroid carcinoma Hepatoblastoma

Furhter, the suitability of some of the general methodological approaches that could be most suitably applied to each of the clusters proposed was explored (Table 21).

	Single acute episodes	Repeated acute episodes	Non progressive	Progressive led by one system/organ	Multi-dimensional multiorgan	Staged conditions
Adaptions	X	(X) (some if slow recruitment)	X	(X) (some if slow recruitment)	(X) (some if slow recruitment)	X
Sequential approaches	X			X		X
Bayesian	X	(X) (if estable)	X	X	X	X
Multiple endpoints		X	X		X	(X) (if low severity)
Enrichment		X	(X) (BMK)	(X) (BMK, severity)	(X) (BMK, genotyping)	X (BMK)
Intra- subject comparison (cross-over)		(X) (if estable)	X		(X) (if no irreversible damage)	
Challenge-dechallenge-rechallenge		(X) (if estable)	X		(X) (if no irreversible damage)	
External /historical controls	(X) (if poor prognosis)			(X) (if poor prognosis)	(X) (if poor prognosis)	(X) (if low heterogeneity)
Longitudinal designs: repeated measures		X	X	X	X	
Delayed start		X	X	(X) (if no irreversible damage)	(X) (if no irreversible damage)	
Early scape / rescue		X		X	X	X

Table 21. General approaches aplicable to each cluster

8.5. Clinical Advisory Board

The results of the surveys given to members of the clinical board were collected and summarised.

In general, clinicians agreed on the fact that current methods in clinical esearch have room for improvement in the research of rare conditions, and that this represents a hurdle at the time of regulatoy assessment so that a certain degree of subjectivity is present in regulatory assessments.

They were strongly in agreement with the fact that there is room for a more structured approach and that would help to the access to new treatments urgently needed, although did not foresee this would strongly impact on financial decision making.

They strongly agreed on the soundness of the approach to the ASTERIX project as a whole, and to the proposed clustering in particular, and considered it would be useful to guide methodological decision for industry and regulators, also to investigators and health technology assessment, but to a lower extent; they were more neutral on the role of the clustering to improve uptaking of patient's opinion into research.

After testing the classified conditons, they considered that the clustering was collecting most situations, and did not consider that there were substantial missing situations within the cluster.

The results of the questionnaire are summarised below (Table 22).

	Mean (SD)	(Min-Max)
Regarding clinical research and development		
Current methods in clinical research allow to obtain reliable information on the efficacy of new treatments aimed to treat non-orphan diseases	7.7 (0.5)	[7-8]
Current methods in clinical research allow to obtain reliable information on the efficacy of new treatments aimed to treat orphan diseases	3.7 (0.5)	[3-4]
Regarding the process of drug authorisation		
When referred to non-orphan drugs, the evaluation and authorization processes are finally based on certain degree of case by case subjectivity	4.3 (2.3)	[1-7]
When referred to orphan drugs, the evaluation and authorization processes are finally based on certain degree of case by case subjectivity	8.7 (0.8)	[7-9]
The evaluation and authorization of orphan drugs could benefit from a structured approach	8.3 (1.4)	[6-10]
An structured approach to the evaluation and authorization of orphan drugs could ease patient access to new treatments	8.3 (1.4)	[6-10]
Predictability of which are the requirements of regulatory bodies to authorise commercialization of orphan drugs would accelerate the patient access to new treatments	7.8 (1.6)	[5-9]
Regarding the ASTERIX clinical and regulatory project:		
The overall approach of the ASTERIX clinical and regulatory project, ie: the development of grouped regulatory guidance on methodology and evaluation of orphan drugs		
Is scientifically sound	8 (0.9)	[7-9]
May represent innovation in clinical research of rare diseases	8.3 (0.8)	[7-9]
May contribute to improve the clinical research of rare diseases	8.3 (0.8)	[7-9]
May be useful to regulators	8.3 (0.8)	[7-9]
May be useful to industry	8.3 (0.8)	[7-9]
May be useful to investigators	7.8 (1.2)	[6-9]
May be useful to identify aspects of research where input from patient organizations is necessary	7 (1.7)	[5-9]
Regarding the proposed ASTERIX classification of diseases		
The approach for the development of the ASTERIX classification is scientifically sound	7.7 (0.5)	[7-8]
Grouping diseases sharing characteristics allowing similar methodological approaches may be a useful tool to:		
Increase predictability of the regulatory assessment of orphan drugs	7.5 (1)	[6-9]
Guide clinical development of orphan drugs	8 (1.4)	[5-9]
Facilitate decisions on marketing authorisation	7.3 (1.5)	[7-8]
Facilitate decisions on pricing and reimbursement	6 (1.8)	[4-9]
Facilitate actual patient access to new treatments	6.7 (1.9)	[4-9]
Evaluation of health technologies, funding and reimbursement by health care system	6.5 (1.6)	[4-8]
Most types of orphan diseases or indications can be represented in the groups proposed by the ASTERIX classification	7.7 (7.5)	[5-9]
Some types of diseases or key concepts in the proposed approach for ASTERIX classification are missing	5.5 (2.3)	[2-9]

Table 22. Results of the Clinical Board survey

9. DISCUSSION

Methodologies aimed to increase efficiency of clinical studies in small populations have been only scarcely applied to the clinical development of OMP. The lack of references and guidance may explain reluctance to alternative methodologies, but specific guidance is impractical due to the huge number of existing orphan conditions. We propose a systematic approach for grouping medical conditions based on their methodological requirements which could be useful to allow generalisation of recommendations to types of conditions, rather than to single disease models. The clustering of medical conditions is based on their methodological requirements, with the aim to provide a framework for guidance on treatment development and regulatory decision making on OMP.

To that purpose, a dictionary was built on characteristics which were considered to be relevant to decide study design and to regulatory decision making, and a number of sample conditions were described in detail for these characteristics. The resulting database served to prepare a base-case of clustering, obtained through unsupervised analysis using MCA. The base-case was refined validated from a clinical and regulatory perspective so that 6 groups of conditions are finally proposed, which share characteristics that are determinant to the applicability of similar methodologies to their study. A total of 125 medical indications with positive opinions issued by the EMA on OMP applications has been systematised into these 6 groups. The result of the MCA and the post-validation by clinical and regulatory experts is the proposed of a new

clustering of conditions based on their methodological requirements as a framework for guidance on treatment development and regulatory decision making on OMP.

9.1. Regulation and development process for Orphan Drugs

The EU legislation determines that market access to new drugs requires the same level of evidence regardless of whether they are intended for rare or highly prevalent diseases. However, all rare diseases have in common the difficulties of conducting clinical trials in small populations[29,83]. Despite there are methodologies aimed to increase efficiency of clinical studies in small populations, these have been scarcely applied to the clinical development on OMP. Also, regulatory risk derived from uncertainty on the acceptability of new methodologies as the basis to conclude on new product efficacy makes sponsors and industries reluctant to apply such methods. Thus, the EU legislation requires substantial efforts to companies that should conduct pivotal trials to gather evidence on the product efficacy and safety (Regulation (EC) No 141/2000), and such requirements can be difficult to accomplish due to the characteristics and low prevalence of rare diseases which hinder the performance of clinical trials with sufficient statistical power[1].

Amongst the obstacles to research in rare diseases, some are difficult to solve (i ex: scarcity of experts, basic research projects and small niche of market for industrial products), but others may be improved by specific policies (such as funding opportunities, fostering of networks and regulatory incentives and innovative access systems)[16]. Amongst these, accelerated approval is a reasonable option as long as it does no translate in a low level of efficacy and/or safety of new products that would be ethically unacceptable, especially because of the vulnerability of minories. An

intermediate point must be found where systems to enhance efficiency of trials to conclude robustly on risk/benefit of new treatments may play a key role.

Conventional parallel group randomized controlled trials, which randomly allocate participants to one of two or more treatment groups, are not always feasible in rare conditions. On one hand the sample size of trials in orphan conditions is generally lower compared to the sample size of trials aimed to demonstrate clinical efficacy in prevalent conditions, often exceeding the recruitment feasibility due to availability of these patients. Because of that, orphan drugs are frequently studied using less and smaller trials, thus aiming for lower approval standards in terms of amount and strength of evidence, taking in consideration that they are designed for small populations in which organization of controlled trials is difficult[67,84]

In fact, recent experience suggests that orphan drugs are often approved with more limited premarket testing than that carried out for non-orphan drugs, and consequently uncertainties at the time of approval cannot discard that patients are exposed to more risk and less certain efficacy. It is true that patients with rare diseases feel the need to accelerate the approval time and may be willing to accept the risk of uncertainty of therapeutic results in return for the hope of effective treatment, but such approach should never compromise the safety of those treatments[29].

A number of publications alert on the potential risks of accelerated approval procedures. Limitations of safety information for orphan drugs could be a result of various factors that do not apply to conventional studies, such as the limited number of patients in clinical trials that can not be overcome because of the low prevalence of such diseases, the quality of the underpowered clinical trials and consequences of

special approval procedures. Clinical experience of an orphan drug at the time of marketing may thus be fairly limited, with the result that knowledge on the safety profile may be less than that used for common diseases[85].

Several studies have been conducted to describe the profile of the drugs with the highest number of safety-related regulatory actions.

Giezen et al. found that the probability of first regulatory action, including written communications to healthcare professionals and black-box warnings in the US and EU, was up to 29% in 10 years after approval for biological drugs, including orphan biological. They concluded that the nature of safety problems identified after approval for biologicals was often related to their immunomodulatory effect (infections), and for these type of drugs exhaustive monitoring was recommended [86].

Lasser et al. also found that the probability of a black-box warning or withdrawal due to a safety reason was up 9% for molecular entities after 6 years after approval, concluding that the safety of new agents cannot be known with certainly until a drug has been on the market for many years [87].

Specifically for orphan drugs, Heemstra et al. did a study to determine the frequency and nature of safety-related regulatory actions in the US and EU. They examined public available data from regulatory authorities on orphan drugs approved between January 2000 and December 2007 in both US and EU. They looked for nature, frequency and timing of safety-related regulatory actions, defined as safety withdrawals, black-box warnings or written communications from healthcare professionals to the FDA or EMA. 95 orphan drugs were approved during the studied period (75 in the US, 44 in the EU, and 24 in both regions). Of these 95 drugs, 10 received a safety-related regulatory

action: no safety withdrawals, 4 black-box warnings and 12 written communications from professionals. They noticed that the overall probability for obtaining a first safety-related regulatory action for orphan drugs was 3.5% after 3 years of follow-up and 20.3% after 8 years of following-up, and that drugs approved by accelerated approvals, oncological products and products for gastrointestinal and metabolism indications had a higher risk for a safety-related regulatory action[88].

Contrarily, there also are studies that defend that the accelerated approval procedures are not related to a greater number of safety regulatory actions for orphan drugs or drugs for common diseases, and therefore no differences exist in safety post-marketing between both types of drugs.

In 2011 Arnardottir et al. compared approval procedures between exceptional, conditional and standard procedures, and the frequency and timing of a first safety regulatory action, highlighting the relationship between safety risk and exceptionally approved drugs in Europe. It was a retrospective cohort study of new drugs approved in Europe during ten years (1999/2009). The results of this study showed a total of 289 new drugs approved where 46 (16,4%) were approved under exceptional condition or conditional procedures; from these 7 (15%) drugs received some type of safety regulatory action. These results were similar to those with standard procedure approval (243 drugs), of which 33 (14%) received safety regulatory actions. The conclusion was that that early drug approval does not increase the risk of serious safety issues [89].

All these publications, anyway, comment that conventional trials in rare conditions are not always feasible to demonstrate efficiency and security with the same level of

evidence that trials for common diseases. Clinical trials need to apply atypical designs, or underpowered trials with a difficult interpretation, but often there are no possible alternatives[29,83].

Although study methodologies especially suited to increase efficiency in small samples have been proposed for decades, and are being developed, their application to the clinical development of new OMP has been traditionally limited, in grand part due to the regulatory reluctance to rely on evidences obtained through alternative rather than conventional approaches [90, 91].

9.2. Non-conventional designs for clinical trials in rare conditions

Clinical trials for orphan diseases need to show the same level of evidence than clinical trials carried out by common diseases, but often this is not always feasible with "conventional" methods because the overall population is finite. A number of innovative statistical methods have been developed in the last decades aimed to efficiently deal with the assessment of evidence in small populations. There are studies that summarize the evidence provided for the approval of new drugs in the recent years by the EMA or FDA and others that compare different type of studies between drugs for rare diseases and for common diseases. Most of them are addressed to anticancer drugs.

Apolone G et al. summarised the different types of studies and endpoints used by the EMA over 10 years (January 1995- December 2004) to approve new anticancer drugs through the centralized procedure, and discussed the application of the current regulations. Information about empirical evidence supporting the approval of anticancer drugs was retrieved from the European Public Assessment Report (EPAR).

They collected several information, including the design of the pivotal trials (randomised comparative (phase III), randomised non comparative (phase II) and single-arm trial), and the primary and secondary end points supporting the approval (survival, time to progression or response rate). They determined that phase III randomised comparative trials were generally required for marketing anticancer drugs authorizations. One controlled trial with statistical and clinical relevant results was the minimum required by the agencies, however, instead of replicate confirmatory experiments generally requested for prevalent conditions. They described 14 anticancer drugs for 27 different indications, and generally a drug was approved on the basis of results from phase II and phase III studies. In one case only, approval was granted without empirical data, on the basis of a bibliographic review of non-clinical and clinical data. Drugs were approved on the basis of phase II studies only in exceptional cases, and phase III comparative trial generally was required. Despite the recommendations in the current EMA guidance documents, the approval of new anticancer agents sometimes was based on small single arm trials that do not allow an acceptable toxicity and safety profiling [92].

Similarly, three years ago the Clinical Cancer Research published a study addressed to characterized rare cancer trial designs that served as the basis for orphan drugs aimed to oncological conditions during 1987 and 2011 by the *FDA*. They indicated that, of 99 trials that supported the approvals of 45 drugs for 68 rare cancer indications, only one third of these trials were randomised, and 63% of approvals were based on a single trial. Also, 69% of the approvals were based on a surrogate variable (objective response rate) as a primary outcome for the study. Drugs that were granted

accelerated approval appeared more likely to be associated with post marketing safety findings, relative to drugs approved under the regular approval[93].

Also Tsimberidou et al. reviewed the long term safety and efficacy of anticancer drugs from 1973 through 2006. They determined that many cancer drugs have been approved in US by the FDA on the basis surrogate endpoints, and often without a randomized trial. They found that 68 oncology drugs were approved, 31 of them without a randomized trial, mainly using uncontrolled single arm designs, and that objective response was the most common endpoint for approval. Yet, several drugs have been later demonstrated to be good treatments in clinical terms, and none demonstrated safety concerns, despite lack of control and randomized comparisons at the time of approval. However, one product authorization was later rescinded because of lack of demonstration of benefit on overall survival. They comment that the experience to date with accelerated approval strategies, which may or may not include a randomized trial, suggests that this approach for the identification of useful new therapies is valid, and that it is meant to reduce the time required to make a new therapy available to patients with life-threatening illnesses. While the accelerated approval process is concentrated on eliminating procedural delays, the authors suggest that favorable long-term experience with several drugs approved without a randomized trial using a comparator arm with standard therapy, supportive care, or placebo, supports that also a reduced requirement of data for approval in certain circumstances could be acceptable [94].

Finally, Kesselheim et al. compared the type of pivotal trials to treat cancer between orphan and non-orphan drugs approved by the FDA from 2004 to 2010, with the

objective of looking for differences between them. They included 15 orphan drugs and 12 non orphan drugs approved to treat 14 different categories of cancer. The FDA approvals for the 27 drugs were based on 38 pivotal trials, of which 23 were done to support orphan drugs and 15 were conducted for non-orphan drugs. There also were 19 supportive trials. They found that the pivotal trials supporting the approval of orphan drugs were significantly less likely to be randomized, and an adequate blinding was less common that in the pivotal trials of non-orphan drugs (double blind 4% vs. 33%). Patient outcomes also differed between orphan and non orphan drugs most pivotal trials of orphan drugs used a surrogate measure of disease response as the primary trial endpoint (68% vs 27%), while pivotal trials for non-orphan drugs most commonly used a measure of disease progression; survival was evaluated les often in trials for orphan than for non-orphan drugs (8% vs 27%)[67].

A number of innovative statistical methods have been developed in the last decades aimed to efficiently deal with the assessment of evidence in small populations, as a potential solution to the fact that orphan medicinal products cannot the use of classical methods (randomized, double-blind, parallel well powered trials) allowing valid comparisons with controls.

Literature shows examples of methodological differences between orphan drugs and those that are not aimed to treat orphan diseases. But the use of alternative designs suitable to small populations, which theoretically are particularly suitable to increase efficiency of trials in rare diseases, seems to be limited by lack of general knowledge, and by regulatory reluctance. New methods have been paradoxically applied mostly in highly prevalent diseases, where conventional standards are fully feasible, because

new methods may reduce substantially the overall costs of large trials. The reason for such paradox may be related to the need of a minimum population exposure for safety assessment. While alternative methods would likely be efficient in efficacy demonstration, the regulatory assessment of safety would still require larger populations than efficacy. In prevalent conditins, the minimum size of the safety database is easily reached and exceeded due to need of large samples for efficacy assessment – increasing efficiency with alternative designs does not compromise the achievement of a sufficient safety database. The opposite occurs with orphan conditions: since more efficient and smaller trials often lead to smaller pre-marketing safety populations, conventional trials with wider sample sizes reduce uncertainty in benefit-risk assessment, allow more confident decision making and have been logically preferred to new designs by regulators.

Another obstacle to wider use of alternative designs in OMP is the lack of information about the non-conventional designs, so one one side developers do not feel confident due to lack of experience, and regulators are not familiar to their performance and key aspects for evaluation. So, it is necessary not only to encourage developers to use alternative methodologies, but also encourage regulators to accept them as an alternative to achieve good results for this type of drugs. Considering that alternative methodologies may ease the obtention of robust evidence to spport new treatments, there is a need for tools to developers and regulators to promote research and development in OMP, and subsequently encourage the commercialization of new orphan drugs.

9.3. Absence of specific development guidelines for rare diseases

The number of diseases which have a low prevalence in general population is huge, and thus almost each new OMP development faces a regulatory scenario where there is a lack of previous references and specific guidances on how to conduct a regulatory development. While a number of general statements on methodological approaches to small populations are valid for all, a single guidance document reveals to be too wide to deal with the huge diversity of medical conditions.

The specific Guideline on Clinical Trials in Small Populations. CHMP/EWP/83561/2005[73], includes methodological recommendations delivered by the EMA for small populations in early two-thousands is impractical due to lack of specificity applicable to the huge number of orphan conditions. This guideline provides a general background but does not help to determine which design could be acceptable from a regulatory perspective for a given rare condition.

However, it is not feasible either to develop specific guidance for each rare disease, since the estimated number of entities ranges from 6000 to 8000[23] and many different clinical features characterize each disease.

On the other hand, while there are few rare diseases that have specific guidance for their development issued by the EMA such as the case of pulmonary arterial hypertension[95], cystic fibrosis (CF)[96], Duchenne and Becker muscular dystrophy[97] or amyotrophic lateral sclerosis[98], all correspond to conditions that, while orphan, are chronic, relatively frequent, and have been quite active in the search and development of new treatments, making it sensible to issue specific guidance. Thus, the development of such documents has been reactive, and actually the ability to

propectively issuing additional guidance aimed to cover areas with few or no available products undergoing regulatory assessment is limited, and the task impractical.

Besides, some of these guidelines give general clinical development recommendations, but taking CF as an example, there are different clinical conditions within the disease which require different designs for their study, and that may require different methodological approaches to develop a non-conventional clinical trial.

In recent years, a number of proposals have been published on algorithms and recommendations to choose the ideal design for a trial for a given condition with small available population[74,75,76].

Cornu et al. [75] and Gupta et al. [74] summarized in their publications some novel designs methods in clinical trials and provide examples of applications for rare diseases.

Besides those examples, Cornu et al. proposed an algorithm for the choice of an appropriate trial design in the development of orphan drugs depending on the reversibility of the outcome, the speed of response, the need to minimise time on placeo, if active control is given at end of study, and whether intra-patient control can be applied (Figure 21)

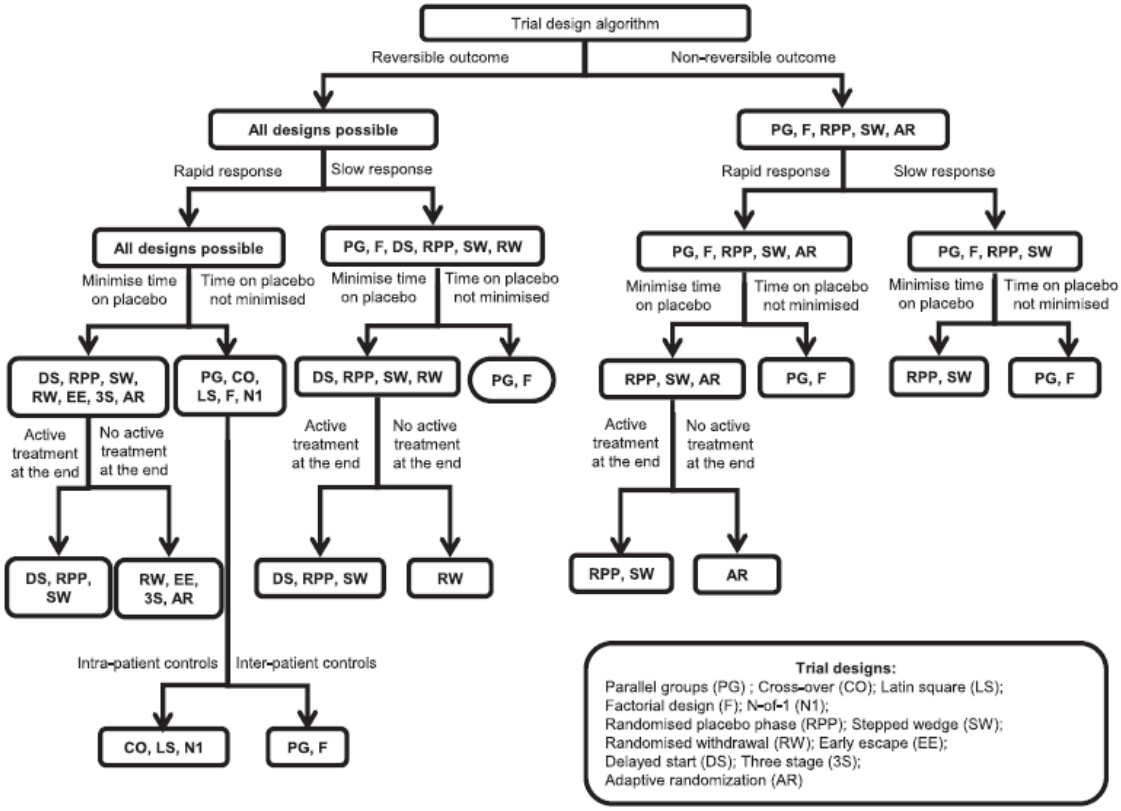


Figure 21. Algorithm for chosing best design by Cornu et al (2013). Taken from Cornu et al. [75]

Gupta et al. also provided a framework for selecting a clinical trial methodology among those described in their review as new approaches for studies of rare diseases, based on a number of determinants including duration of effect, stability of clinical course, time between inclusion and outcome as compared to recruitment time, difficulties of retention of patients, availability of the required sample size and prior level of confidence in the effect of treatment (Figure 22).

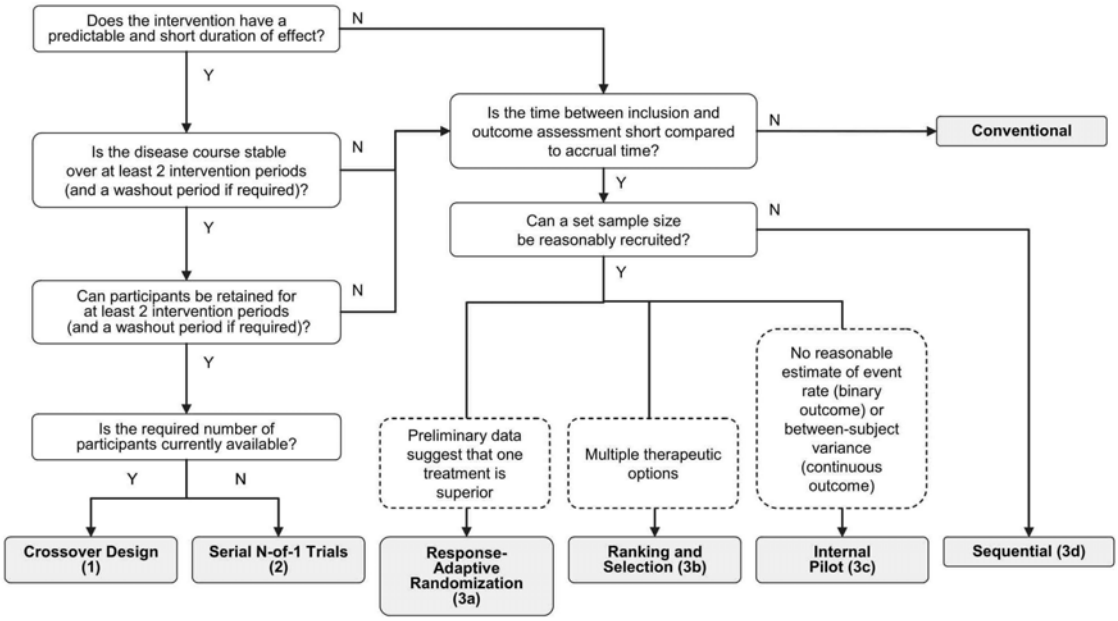


Figure 22. Algorithm for chosing best design by Gupta et al (2011). Taken from Gupta et al. [74]

Both proposed a number of items that are used to sequential decision on the most suitable methods for a given study; they agree on the importance of the duration of clinical effect, required follow-up versus accrual time and feasibility of intra-subject comparison (estability of conditions and ability to retain sujects long enough), but suggest decision based on other items that differ amongst both proposals, such as the need to minimise time on placebo, if active control is given at end of study, anticipated sample sizes and prior level of confidence in the effect of treatment.

Nony et al.[76] rather than an algoritm for decision making proposed an overall approach to modelling and simulation as a means to ensure best use of prior information to refine best possible design, which may apply to situations where there is already some available information, but does not give specific directions according to clinical characteristics.

Our clustering proposal is similar in that many determinants for single trial decision are the same or closely related to Gupta's and Cornu's proposals, such as clinical course of conditions, ratio of time to outcome vs time required for recruitment and ability to use intrasubject comparisons. However, the inclusion of additional clinical conditionants such as those related to clinical presentation and course, number or organs involved, type of outcomes and the severity of the conditions substantially differs from these exercises. I ex: the inclusion of clinical factors as a cluster determinant for the choice of endpoints is a major contribution, intended to foster the use of new methods based on multiple endpoints for multidimensional conditions, and in situations where underpowered trials may improve the robustness of their conclusions by multiple measurements. Considerations on the actual frequency of the condition can modulate decisions on the size of the safety database and ability to conduct risk/benefit assessments.

Also, our proposal differs in its intention being to generalize recommendations to the whole process of development and regulatory assessment applicable to groups of conditions, rather than to achieve single trial best choices[74,75,76]. In this sense, the regulatory focus of the clustering is mainly practical and aimed to ease clinically oriented communication.

9.4. Methodological approach

Many approaches could have been applied to the exercise of grouping rare diseases. In general a combination of data analysis and expert consensus is generally regarded as a reasonable approach[90].

Our main objective was to simplify the regulatory framework to allow specific but yet affordable guidance, and because of that, our aim was not to classify diseases from a clinical, etiological nor pathogenic point of view, but to obtain a methodologically driven grouping of conditions.

Since we anticipated that this grouping could not be obvious, we chose to approach the process avoiding a subjective first scenario, and instead we used a data driven proposal base-case obtained through unsupervised methods. An exploratory MCA analysis of a database containing detailed methodological descriptions of characteristics relevant for the choice of design and statistical methods of diverse rare conditions was our means to create such base-case. This was regarded as a wide approach that could yield general results, allowing that apparently completely medically unrelated diseases could be grouped according to whether they shared the applicability of similar methodologies for their study, with no subjective a priori clinical obvious conditioning or biases.

Since this first result required interpretation and refinement, an iterative process of consensus was applied afterwards, until a satisfactory grouping was agreed. Formal consensus methods, like Delphi method[100], Nominal Group Technique [101], RAND/UCLA Appropriateness Method[102], or others, are well established ways to reach agreement on criteria for diagnosing diseases, identify prognosis and risk factors, to develop ideas for exploratory research or to propose therapeutic guidance. In general, these methods organize subjective judgments to synthesize them with the available evidence, and to that purpose use an initial problem, case or scenario, which serves to gather opinion from expert panels in an iterative process until consensus is reached.

However, consensus methods are strongly led by the contents of the initial problem, depend heavily on panel composition, expertise and background, and may conclude obvious results, iterating current knowledge and beliefs[103].

Alternative approaches may be less dependent on previous assumptions, like network systems analysis, which identify nodes or determinants of behaviour [104], or MCA methods[79,82], which unsupervised analyse groupings of data, and may be of use when new perspectives are desired without conditioning by previous premises. MCA has been extensively used for classification and identification of profiles in medical research[90], and its application as a starting point for reaching consensus has been reported before as a tool used to define risk factors for clinical events [105], and clinical prognosis[106]. Therefore, we considered MCA particularly useful to provide initially independent from expert opinion scenario to be used during the consensus process.

We approximate the exercise trying to avoid preconceived ideas, but with a qualitative approach; so we mixed two approaches, one to create the initial base-case scenario from non-supervised analysis by the MCA, and from this initial stage, we had a consensus iterative approach working with regulators, methodologists and clinical investigators. The result was the free identification of similarities amongst different conditions from a methodological point of view, and a posterior refinement of clustering of conditions for which similar and relatively specific guidance may be regarded as a reasonable approach from regulatory and clinical grounds. The approach was later validated with a board of physicians with recognised expertise in the treatment and research of treatments for orphan conditons, who assessed not only

the overall approach and sensibility of the process to obtain the proposal, but also the logics, consistency and applicability of the proposed clusters.

9.5. Appropriateness of the clustering

A systematic approach to grouping medical conditions based on their methodological requirements may be useful to allow generalisation of recommendations to type's conditions, rather than to single disease models. We propose a limited number of clusters for rare conditions that might allow the choice of methods to develop new OMPs, so that six different groups of conditions are proposed. Two clusters are referred to acute conditions, distinguishing single from repeated episodes, and four to chronic conditions, distinguishing estable from progressive conditions, those affecting one organ from those affecting several organs, and those with different stages. The leading determinant characteristicsincluded the clinical course, determining mostly the type and setting of control groups and applicability of methods applying acquired information in an ongoing basis; the specificity of the impairment, determining the type and number of variables that may be required or used for efficacy assessment; the severity of the impairment, determining the type and source of efficacy information and type and duration of internal/external control groups; the homogeneity of the condition, determining assessments based on extent of disease, suitability of enrichment methods and need for subgroups; and availability of standard of care and reversibility of the condition, determining sequence of designs, amongst others.

Unexpectedly, the prevalence of conditions did not show to be a main grouping determinant in the MCA, likely because all types of diseases and clusters may have

examples of ultrarare versus non-ultrarare conditions, regardless of their clinical characteristics. Contrarily, some of the previously described characteristics are strong determinants of the applicability of designs. However, since availability of subjects is key at the time to assess other regulatory aspects of the clinical development of treatments[73], frequency was included in the final proposal as a subtype within each cluster, since it will be still a key determinant of applicability of certain methods that may still require relevant sample sizes, i ex: group-sequential analyses.

It is not surprising that some of the characteristics that Cornu[75] and Gupta[74] include in their proposals to select the optimal design are similar to the ones determinant of our clustering, such as the required follow-up versus accrual time, and factors related to difficulties of participation or retention of patients or the duration of clinical effect of the treatment (which we distinguish as symptomatic or curative). Others, in change, such as anticipated sample sizes and prior level of confidence in the effect of treatment are not determinant in our model, although some considerations to a good knowledge of the natural history are included when discussing control groups setting and types.

We have described in detail the type of conditions included in each of the clusters, and the methodological implications of the characteristics that determine each characteristic.

The potential benefits of the application of the proposed clustering include both the increase and the decrease of the number of regulatory and clinical scenarios, respectively, so that general recommendations for 6 groups may be more specific and thus predictable than a single general description, but affordable as opposed to

hundreds or even thousands of condition-specific documents. While still general, the clustering may provide a framework for reference in which the development of different methods and design proposals may be better communicated.

9.6. Limitations

We have found a number of limitations in our work.

Considering the general approach to the proposal of clustering, it could be regarded that the number of studied conditions used for creating the initial MCA scenario was small. Also, the fact that these were chosen arbitrarily by the investigative team, and based on a list of conditions with approved orphan medicinal products, may be regarded as vulnerable to bias.

However, the iteration in the process allowed enriching the sample by adding conditions which were considered as not being yet represented, in order to increase the diversity of the sample, including some conditions for which no authorised product was available. We cannot discard that there may have been lack of representation of diseases, or types of diseases, especially since the actual number of rare conditions is about thousands[23]. Also, the validation of the clustering by classifying all authorised products the EMA until December 2014 showed that the clustering is thorough and able to cover most of the situations with regulatory relevance up to now.

Besides, the fact that the problem conditions used were mostly identified amongst those with an authorized orphan medicinal products by the EMA might represent a bias, favoring to represent diseases with certain characteristics allowing easier development than others for whose there are no authorized products. As said, some of

the initial examples chosen for the MCA were conditions with no available authorised OMP. Also, considering that the objective of the clustering was focused on the need to have available regulatory reference for future development of standards and proposals, the choice of the conditions for building the base-case and the validation of the final clusterig may support ours as a sensible and pragmatic choice.

Another potential limitation is the fact that the MCA procedure does not output traditional statistical measures such as p-values and test statistics, and thus, subjectivity is applied in the interpretation of results provided by MCA on the graphical displays or maps given by any two factors.

This is not a major issue considering that the MCA was used to obtain a base-case for further discussion, and results were interpreted by consensus in an expert panel setting. The main goal of the MCA was to avoid pre-existing beliefs guiding an obvious clustering based on routine thinking at the time of methodological advice to researchers, based on pharmacological reasoning, clinical diagnosis thinking or usual sequence of regulatory assessment. Unlike other procedures, in unsupervised methods there are not any preconditions (such as multivariate normality and linearity) except a rectangular data matrix with nonnegative entries[107], thus MCA was considered suitable for our purpose. The non-supervised analysis was an exploratory exercise used only to serve as the basis for the posterior inference consensus process.

Further, the process of discussion and validation took into account the potential flaws of the initial clusters, actually expanding the number of proposed categories to enable fitting of conditions which were not properly clustered through numeric analysis. There is yet a possibility that the proposed clustering will, in use, be unable to fit some

conditions; however, it may be improved in future revisions and include new categories if required.

Another potential limitation of the consensus process may be related to the fact that the investigators in the team included regulators, methodologists, pharmacologists and pharmacists, and counted with the contribution of a panel of clinical specialists in different medical areas where orphan diseases are prevalent pathologies. While the team included 10 people and no more than 2 were from the same department or institution, the academic filiation was mostly Universitat Autònoma de Barcelona or Universitat de Barcelona. Despite having members working at the Spanish Agency of Medicines and at the European Medicines Agency, having members of the CHMP and the Scientific Advice Working Party of European Medicines Agency, investigators working at three different hospitals (Parc Taulí, Hospital Clinic de Barcelona, Hospital de la Santa Creu i Sant Pau) and at a research institute of primary care (Institut d'Invesgació en Atenció Primària Jordi Gol), the fact is that all but 2 members were based in Barcelona. Whether not including international experts in the core team proposing the clustering may limit the value and generalizability of the work may be questioned, even though the international expertise in regulation and statistics of 5 of the members is undisputed. The fact that the team was not working in the same department nor used to collaborate in other projects ensured the diversity of opinions; actually, the need of several rounds of discussion for most of the steps reflected that discussions were rich and collecting many divergent opinions.

Besides of the diversity, the work was part of a multinational project, and was pesened at different stages to the rest of working packages, for discussion and input. The advice

and opinions from mainly the teams based in Utrech (lead Dr Roes), in Hannover (lead Dr Koch) and Vienna (Dr Posch) were received at different time points and contributed to enrich the proposal.

Our proposal differs from other medical or clinical classifications of diseases as used by the World Health Organization (WHO) with the International Classification of Diseases[108], Orphanet Disease classification [23] or the Online Mendelian Inheritance in Man[109,110] in that our proposed clusters agglutinate rare clinical conditions, instead of rare diseases.

While clinical classifications are aimed, amongst other uses, to guide diagnosis and treatment, our clustering is aimed to provide practical references to the design of the clinical development of new treatments for rare conditions, with the final objective to obtain a regulatory marketing authorisation opinion. Because of that, the same rare disease may present several clinical settings, representing separate conditions that may be fitted in separate clusters. Using the example of the CF, several situations such as acute exacerbation, colonization of airway by pseudomonas, restoration of normal channel function or modification of clinical course by improving channel function differ not only in their treatment approach, but also in clinical outcomes and methodological approaches when a clinical trial could be postulated. Here we show some conditions for the same rare disease and the cluster proposed where best fit:

- Treatment of *Pseudomonas aeruginosa* acute lung infection --> **Cluster 1: Acute clinical course, single episode**
- Treatment of lung colonization by *Pseudomonas aeruginosa* (to avoid re-infections) --> **Cluster 2: Acute clinical course, relapsing**

- Induction of Pluripotent fibroblasts cells genetically modified to express full functioning channels to be transplantated in lungs--> **Cluster 4: Chronic progressive single-organ**
- Treatment of cystic fibrosis by improving overall chloride channel function (multi-systemic improvement)--> **Cluster 5: Chronic multidimensional**

Although we cannot group CF in a single cluster, the resulting multiple classification of CF is sound because each condition differ in the clinical outcomes, the length of follow-up, the therapeutic approach to standard of care and acceptability of controls, and the overall study design possibilities.

Regarding the validation, another potential limitation was the choice of rare diseases that we selected to validate our proposed clustering. We applied the results of the MCA to 125 OMP positive opinions issued by the EMA, as derived from the European Public Assessment Reports (EPAR) identified in the EMA webpage. The fact that all the selected diseases had a positive opinion could represent a bias, so that all the conditions included were more suitable to be developed and thus the lack in the validation of conditions without any OMP approved, or with OMP applications rejected, could made it incomplete. If conditions without OMP are not included in the clusters and also more difficult to study, the utility of the clustering to provide guidance could be hampered. Should that be the case, as already said the clustering may be improved in future revisions and include new categories if required.

9.7. Future applications of the proposed clustering

The cluster is now being applicated within the ASTERIX project as a tool to generalise the applicability of the new methods that are being developed by statisticians in other working packages. Also, as a reference framework to describe the current regulatory standard requirements for authorisation of new OMP in Europe, and finally, to ease the issue of specific recommendations on applicability of alternative and/or new methods to the study of OMP for types of conditions with certain characteristics.

Our clustering proposal is intended to improve the communication and dissemination of complex statistical approaches by providing a clear seting in whose these may provide a methodological improvement [111].

Future applications of our classification also include the grouped description of the regulatory criteria or requirements for the authorisation of OMP in Europe.

The availability of a systematized summary of the current requirements, and the description of potentially applicable methods to each group, may allow to detect opportunities for testing and validation of alternative methodologies and designs to the development of similar conditions, and thus may ease the path towards the issue of more detailed guidance on how to develop OMP in each type of condition, improving predictability of outcomes, incentive research of new treatments and, in definitive, easing the access of patients to new treatments in neglected medical situations with huge medical needs.

10. CONCLUSIONS

- A new grouping of orphan and / or rare conditions is proposed, resulting of linking the characteristics of the medical condition with the requirements of applicability of the experimental methods and different research designs and methods for its study.
- To that purpose, a clinical and methodological dictionary has been built including a set of 76 characteristics that describe the different clinical traits of medical conditions that determine the applicability of designs or methodologies to the study of medical conditions.
- A process of consensus was done where a base-case grouping not led by previous assumptions was created through an unsupervised analysis of a database including detailed descriptions according to the clinical and methodological dictionary of a sample of diverse and heterogeneous rare medical conditions, using plotting of coordinates for conditions on 4 descriptive dimensions for clustering, and by interpretation of the variables determining the dimensions for refinement and creation of categories.
- After the consensus process six groups of medical conditions were identified:

    (1) Conditions with single acute episode
    (2) Conditions with repeated acute episodes
    (3) Chronic non-progressive conditions
    (4) Chronic progressive conditions led by one system-organ
    (5) Chronic progressive multidimensional conditions
    (6) Staged conditions

- The methodological approaches generally applicable to each one of the clusters were analysed and described.
- The proposed groups share similar characteristics and methodological approaches to their study, and are able to describe most regulatory situations where similar research methodologies can be applied.
- The availability of a systematized grouping of rare conditions based on methodological requirements may allow to detect opportunities for testing and validation of alternative methodologies and designs to the development of similar conditions, and thus may ease the path towards the issue of more detailed guidance on how to develop OMP in each type of condition, improving predictability of outcomes, incentivation of research and, eventually, easing the access of patients to new treatments in neglected medical situations with huge medical needs.

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12. Index of Figures

13. Index of Tables

14. Annexes

14.1. Annex 1. Dictionary of variables

	Term	Definition	Sample condition / treatment/ variable...	Potential use
CLINICAL CHARACTERISTICS OF THE CONDITION				
1.	***Temporal scope of condition*** ***A:*** Chronic condition ***B:*** Acute condition	***A:*** Condition with long-term (years, decades) clinical course. ***B:*** Condition with short-term (days, months) clinical course.	***A:*** Congenital enzyme deficiencies Haemophilia, HTP, CAPS, Systemic sclerosis, Sd Angelman, Pompe disease ***B:*** Ventilator Associated Pneumonia Renal cancer, Sd Guillain Barre	Feasibility of finalist end-points Recruitment based on incident or prevalent cases Feasibility of sequential/adaptive approaches
2.	***Clinical course*** ***A:*** Constant course ***B:*** Intermittent condition	***A:*** Regular or homogeneous impairment along the temporal scope of condition; separate episodes can not be distinguished ***B:*** Condition whit clear-cut worsening episodes or flares	***A:*** Sd Angelman, Cancer ***B:*** CAPS, Angioedema, PNH	Feasibility of start-stop designs Feasibility of end-point based on number of flares

	Term	Definition	Sample condition / treatment/ variable...	Potential use
3.	***Seriousness*** ***A:*** Life threatening condition ***B:*** Debilitating condition ***C:*** Mild significant condition	***A:*** With current SOC the condition progresses to either death or requirement of vital support, which is clinically more relevant than the burden of disease. ***B:*** With current SOC the condition progresses to serious disability, organ substitution or transplant, which is clinically more relevant than the threaten to life it represents. ***C:*** The condition does not seriously compromise the patient life or function, but may derive into life-threatening or debilitating condition if untreated.	***A:*** Cancer, Systemic sclerosis ***B:*** CAPS, Sd Alport, Sd Angelman, Huntington disease, Multiple sclerosis ***C:*** Hemophilia	Feasibility of survival end-points, death as an end-point Feasibility of sequential/adaptive approaches Prevalence vs incidence as a source of cases for study. Urgency of finding treatments; willingness of patients to try new alternatives and easiness of recruitment
4.	***Speed of progression*** ***A:*** Stable clinical course ***B:*** Progressive condition ***1:*** Very rapid or fulminating progression ***2:*** Rapidly progressive condition ***3:*** Slow progression	***A:*** Condition that does not increase in severity along time; does not exclude conditions with flares that return to baseline once resolved. ***B:*** Condition that once diagnosed does not revert to healthy status and progresses, either steadily or due to subsequent flares that do not revert to pre-flare status ***1:*** Condition that progresses towards maximum deterioration in a period up to 12 weeks ***2:*** Condition that progresses towards clinical deterioration in a period longer than 12 weeks but shorter than 36 months ***3:*** Condition that progresses towards clinical deterioration in a period longer than 36 months	***A:*** Haemophilia, angioedema ***B:*** Cancer, ALS, MS, Duchenne ***1:*** Toxic megacolon. Sd Guillain Barre ***2:*** Cancer, ALS ***3:*** Duchenne, Huntington disease, Cystic fibrosis	Feasibility of start-stop designs Feasibility of finalist end-points Feasibility of sequential/adaptive approaches Recruitment based on incident or prevalent cases
5.	***Reversibility*** ***A:*** Reversible condition ***B:*** Irreversible condition	***A:*** Self limited condition *(that may revert or reverts to pre-disease status)* either due to natural history or after SOC. ***B:*** Condition that once diagnosed does never revert to healthy status because of permanent irreversible changes, and currently there is no SOC for the known or unknown etiological cause or able to reverse the condition.	***A:*** Sd Guillain Barre ***B:*** Haemophilia, HTP, CAPS, PNH, cystic fibrosis,	Feasibility of finalist end-points Willingness of patients to try new alternatives, easiness of recruitment

	Term	Definition	Sample condition / treatment/ variable...	Potential use
6.	***Predictability*** ***A:*** Predictable clinical course ***B:*** Highly variable clinical course	***A:*** The change in health status along time is well described and any change in the known natural history is unexpected, or reflects treatment activity. ***B:*** Any change in health status along time is possible and there is no prior expectation as regards to the degree or speed of health deterioration or on the frequency/intensity of flares	***A:*** Haemophilia, HTP, CAPS, cancer, hematologic malignancies ***B:*** ALS, Huntington disease, metabolic diseases, genetic inherited defects.	Feasibility of external controls Feasibility of Bayesian approaches Feasibility of start-stop designs
7.	***Diagnostic criteria*** (non exclusive) ***A:*** Based on chromosome or genetic diagnosis ***B:*** Based on pathology, physiology microbiology or biochemical measures ***C:*** Physiological and clinical criteria ***D:*** Syndromical diagnosis	The condition is defined by ***A:*** A well described and characterised condition specific chromosomal or genetic abnormality. ***B:*** A well described pathology, microbiology or biochemical finding or findings which is univocally condition especific ***C:*** A set of findings that includes measures of physiology and at least one clinical sign o symptom, of which at least one is almost condition specific. ***D:*** A combination of findings that may include measures as in A or B or C but is mainly based on clinical signs o symptoms which are not condition specific if standing alone	***A:*** Alport Syndrome ***B:*** Cancer, haemophilia ***C:*** VAP, LES ***D:*** Undetermined colitis	Degree of heterogeneity of population when criteria are ambiguous or variable in time Reliability of previous data and registries when criteria are ambiguous or variable in time
8.	***Disease subgroups*** ***A:*** Differential prognosis ***B:*** Differential response to treatment	For a given condition, a clinical o biochemical or genetic parameter, or groups of parameters (I ex: clinical staging) allows to predict ***A:*** The clinical course (speed or type of progression) of the condition. ***B:*** The magnitude of the response to treatment	***A:*** HTP (stage), CAPS (age of start) , Multiple sclerosis (clinical course) , cancer (TNM) ***B:*** Pompe disease (neonatal with cardiomyopathy)	Heterogeneity of population Need for stratification Different SOC according to subgroups Feasibility of enrichment designs

	Term	Definition	Sample condition / treatment/ variable...	Potential use
9.	***Target organ***	Body system or organ whose function is impaired by the condition, either directly or by its indirect consequences. (detail up to 3 terms from close list – System-Organ class according to MedDRA)	Blood -> haemophilia, PNH Lung: HTP Solid organ: Renal cancer Skin: Pemphigo CNS: Guillain-Barré, MS, ALS Systemic, body as a whole: CAPS	Type of variables determined by the criticality of the organ affected and availability of objective measures of organ function or impairment
10.	***Rarity*** (non exclusive categories) ***A:*** Incidence rate ***B:*** Prevalence	May be a number, a range or unknown ***A:*** Number of new cases per population at risk in a given time period ***B:*** Proportion of cases in a given population at a given time		Determines the speed of accrual Determines the possibility of a disease registry
TREATMENTS				
11.	***Standard of care (SOC)***	Treatment alternative *(with regulatory authorisation) (with published supportive data)* for which it is recognised that has a degree of influence on the signs or symptoms of the condition or a delaying or halting effect on the clinical course, of magnitude enough as to justify that is routinely offered to subjects with the condition.	Haemophilia → coagulation factors HTP → sildenafil, bosentan, tadalafil... CAPS → anakinra, canakinumab... Renal cancer → everolimus, sorafenib... PNH → eculizumab Pompe disease → recombinant alpha glucosidase	Determines -Feasibility of negative controls / requirement of add-on / limited period off-treatment -Magnitude of the expected effect -Availability of naive patients -Willingness of patients to enrol

	Term	Definition	Sample condition / treatment/ variable...	Potential use
12.	***Effect of treatment withdrawal on condition*** *(non exclusive categories)* ***A:*** Impairment due to delayed treatment initiation ***B:*** Impairment due to periods without treatment ***C:*** Effect on prognosis unknown	The fact of exposing the subject to a SOC has an impact on the condition ***A:*** A late start of a SOC has a permanent effect on patient prognosis. ***B:*** The temporary deprivation of a SOC has a permanent effect on patient prognosis. ***C:*** Unknown, either because the symptoms of the condition return but the impact on long term is unknown, or because it has not been studied	***A:*** Chemotherapy for oncology, HTP, Renal cancer ***B:*** Vasoactive treatment for pulmonary hypertension ***C:*** Muckle Wells	Feasibility of negative controls / requirement of add-on / limited period off-treatment Feasibility of start-stop designs
13.	***Feasibility of re-challenge*** ***A:*** Re-exposure unfeasible ***B:*** Re-exposure feasible	The fact of exposing the subject to a SOC has an impact on the feasibility of future re-challenges ***A:*** The administration of the SOC or a given treatment precludes future re-challenge to the same treatment. ***B:*** The temporary deprivation of a SOC or administration of a given treatment does not adversely affect the condition nor the expected efficacy or safety on treatment reintroduction.	***A:*** Genetic treatment of enzyme deficiencies ***B:*** Steroids for inflammatory diseases? Haemophilia	Feasibility of negative controls / requirement of add-on / limited period off-treatment Feasibility of start-stop designs / adaptive designs Willingness of patients to enrol If re-exposure unfeasible, may be difficult to find/ enrol naive patients
14.	***Treatment approach*** ***A:*** Intended to modify the course of the disease ***B:*** Curative ***C:*** Symptomatic	***A:*** A therapeutic intervention aimed to delay or halt the progression of the clinical course of the condition, with or without reversion to pre-diseased status. ***B:*** A therapeutic intervention aimed to correct the known or unknown etiological cause of the condition. ***C:*** A therapeutic intervention aimed to improve or reduce the clinical signs and symptoms of the condition, with no substantial influence on progression or cause.	***A:*** Cardiac surgery for arterial transposition. Vasoactive treatment for pulmonary hypertension. Neoadjuvant chemotherapy in cancer. ***B:*** Genetic therapy for St Filippo ***C:*** Coagulation factor supplementation for haemophilia, antibodies for IL-1beta or IL-1R for CAPS, Vasoactive treatment HTP	Feasibility of start-stop designs

	Term	Definition	Sample condition / treatment/ variable...	Potential use
15.	***Duration of effect*** ***A:*** Short lasting effect ***B:*** Long lasting effect	***A:*** The effect reverts when treatment administration is stopped or plasma concentrations decrease, so that the signs or symptoms of the disease reappear. ***B:*** The effect is either irreversible or persists for a substantial period of time after the complete disappearance of the product from the body	***A:*** Haemophilia, CAPS ***B:*** Gene therapy for St Filippo, antibiotic treatment of VAP	Feasibility of start-stop designs Willingness of patients to enrol
	END-POINTS AND VARIABLES			
16.	***Time to measurable effect*** ***A:*** Rapid onset ***B:*** Long term onset ***C:*** Early markers of treatment failure	The effect of the treatment appears and is measurable in a period: ***A:*** Short (days, weeks) or shorter than the duration of the estimated recruitment period. ***B:*** Long (months or years) or longer than the duration of the estimated recruitment period ***C:*** An intermediate end-point allows reaching conclusions on the lack of efficacy of a tested intervention before completing the full course of treatment.	***A:*** Extubation in VAP (antibiotics) ***B:*** Progression to dementia ***C:*** On-treatment tumour progression.	Feasibility of start-stop designs /sequential designs/ adaptive designs
17.	***Type of endpoint*** ***A:*** Dichotomic ***B:*** Continuous ***C:*** Ordinal ***D:*** Time to one event ***E:*** Number of events in a period of time	***A:*** Only two options for a single outcome ***B:*** Numerical value - all possible intermediate values ***C:*** Numerical value – only some discrete values ***D:*** The untreated condition invariably progresses to a clinically relevant (*irreversible*) situation (may be e.g.: death or blindness or deafness or serious motor disability). ***E:*** The condition produces repeated adverse events which are clearly limited in time, and the number of such events reflects relevantly the clinical status of the subject.	***A:*** Death ***B:*** Pain, quality of life, glomerular filtration ***C:*** Stage renal failure ***D:*** Time to death, full dependence, dialysis, deafness , conversion to dementia ***E:*** Number of flares	Feasibility of sequential designs (dichotomic) /survival designs (time to) Sensitivity of the tests (continuous variables)

	Term	Definition	Sample condition / treatment/ variable...	Potential use
18.	***Strength (validity?) of end-point*** *(non exclusive categories)* ***A:*** Direct clinical outcome ***B:*** Valid surrogate clinical endpoint ***C:*** Raw surrogate clinical end-point ***D:*** Valid biomarker ***E:*** Raw biomarker	***A:*** The end-point measures the final treatment goal ***B:*** A clinical or physiological parameter has demonstrated a correlation with relevant clinical changes or outcomes of the condition that is sensitive to changes and treatment effect. ***C:*** A clinical or physiological parameter has shown correlation with clinical status of the condition but whether it changes with condition improvement due to treatment is unknown. ***D:*** Changes on a biological parameter allows consistently to predict the treatment effect on the final clinical outcome; the intermediate measure may substitute for a clinical endpoint. ***E:*** Changes on a biological parameter relate to the clinical status of the condition but whether it changes with condition improvement due to treatment is unknown.	***A:*** Death, deafness, blindness, disability, requirement for mechanical ventilation ***B:*** Glomerular filtration rate – renal function, audiometry ***C:*** Pulmonary arterial pressure, investigator global assessment ***D:*** Levels of coagulation factor in serum, expression of philadelphia chromosome ***E:*** PCR in rheumatoid arthritis	Degree of evidence that can be concluded from the studies / strength of conclusions on the results Requirement for a wide safety / risk assessment to allow for precise understanding of the clinical benefit
19.	***Robustness of end-point*** ***A:*** Main endpoint is an objective measure with no possible bias ***B:*** Main end-point is a measurable item subject to bias ***C:*** Main end-point is a subjective endpoint reported by investigator ***D:*** Main endpoint is a patient reported outcome	Susceptibility to bias and/or inter-observer variability of measures ***A:*** The outcome measure is not subject to inter-observer variability nor bias ***B:*** The outcome measure may be subject to different degrees of inter-observer variability or bias ***C:*** The outcome measure is a subjective judgement made by the investigator ***D:*** The outcome measure is collected and reported by the subject with the condition	***A:*** Death, laboratory measures ***B:*** Cognitive testing, tumour size, pathology, endoscopy scoring ***C:*** Clinical ratings and scores, IGA ***D:*** Pain, fatigue, symptom score, quality of life	Requirement for blinding / assessment by third parties Suitability for multiple assessments Degree of evidence that can be concluded from the studies / strength of conclusions on the results The inclusion of patient measured assessments approaches the study of the individual as a whole.

	Term	Definition	Sample condition / treatment/ variable...	Potential use
20.	***Multiplicity of assessments*** ***A:*** Single clinically relevant end-point 1: Simple endpoint 2: Composite end-point ***B:*** Multiple endpoints in same domain ***C:*** Multiple assessment domains	***A:*** There is one single end-point that is able to summarise the condition status 1: The assessment reflects only one parameter or measure 2: The assessment reflects the combination of a number of parameters or measures ***B:*** There are several valid variables measuring different aspects of a single domain of disease ***C:*** There are several domains of the subject clinical status that have to be considered to assess the disease status	***A1:*** Death ***A2:*** Composite of transplantation + dialysis+death ***B:*** mean pain severity, maximum intensity of pain, time free of pain, need of rescue ***C:*** Symptom scores + Functional scores + imaging + biomarkers + Quality of life	Suitability for multiple sources of evidence and applicability of consistency testing across results Multidimensional assessment of the subject; study of the individual as a whole.
	FEASIBILITY OF RECRUITMENT			
21.	***Registry*** *(non exclusive categories)* ***A:*** Disease registry ***B:*** Treatment registry ***C:*** National registry ***D:*** Multinational registry	A database with clinical information from a substantial number of patients *(often with exhaustive intention)*, who: ***A:*** Share a same medical condition ***B:*** Receive a same active principle for a condition or number of conditions. ***C:*** Gathering information on subjects from a single country ***D:*** Gathering information on subjects from several countries (i e: European, American, Asian, Global...)		Feasibility of external controls Feasibility of bayesian approaches Recruitment based on incident or prevalent cases Feasibility of multinational trials Feasibility of registry based trials

	Term	Definition	Sample condition / treatment/ variable...	Potential use
22.	***Expected accrual time*** ***A:*** Short accrual time ***B:*** Long accrual time	Estimated length of the period of time required to recruit the required number of patients into a study; this is related with the incidence and/or prevalence of the condition, as well as on the easiness of identifying potentially eligible patients through a number of systems; i ex: registries, patient organizations or specialised medical sites. ***A:*** Condition for which the time to main end-point in a given patient exceeds *(by several times)* the expected accrual time for the clinical trial. ***B:*** Condition for which the time to main end-point in a given patient is *(several times)* shorter than the expected accrual time for the clinical trial.	***A:*** Ventilator associated pneumonia ***B:*** Cystic fibrosis, haemophilia,	Feasibility of sequential designs/ adaptive designs
23.	***Source of recruitment*** *(non exclusive)* ***A:*** Incident cases ***B:*** Prevalent cases	Condition for which the eligible population for a clinical trial will be mostly at the expense of: ***A:*** Newly diagnosed subjects. ***B:*** Subjects already diagnosed in the past.	***A:*** Ventilator associated pneumonia ***B:*** Cystic fibrosis, haemophilia, HTP, CAPS,	Determines the speed of accrual Determines the possibility of a disease registry

	Term	Definition	Sample condition / treatment/ variable...	Potential use
KNOWLEDGE OF THE CONDITION				
24.	***Degree of knowledge on the condition****(non-exclusive categories)* ***A:*** Known physiopathology ***B:*** Predictive preclinical models of the disease ***C:*** Previous data on event / response rate or variance available ***D:*** Available data in medical conditions with analogous mechanisms ***E:*** No previous data available for modelling purposes	***A:*** Data exists on the molecular mechanisms *(suppressed, altered or over-expressed)* in diseased subjects which are causally related to the clinical signs and symptoms of the condition ***B:*** An *(experimentally induced)* animal disease or condition exists which resembles closely the human clinical pathology, for which clinical improvements induced by treatments correlate with the likelihood of improvements in diseased subjects. ***C:*** Data allowing to estimate the value and variance of a main end-point is available ***D:*** A condition sharing similar physiopathology to other known conditions for whose data exists on molecular mechanisms, clinical course, clinical end-points, biomarkers and /or effective therapeutic interventions. ***E:*** No previous information on the values nor variance of efficacy end-points is available allowing to model for study design purposes	***A:*** Haemophilia, Pompe disease, CAPS ***B:*** Pulmonary hypertension, CAPS, tumours ***C:*** CAPS, ALS (aggressive form), pulmonary hypertension, VAP, tumours ***D:*** Different types of haemophilia, Different types of arthritis, leukemias *E:* Ultrarare diseases with no SOC.	Feasibility of external controls Feasibility of Bayesian approaches
ADDITIONAL VARIABLES ON STANDARD OF CARE AND THERAPEUTIC APPROACHES TO CONDITION				
25.	***Gene therapy possible***	A: Yes B: No	A: Pompe disease B: Lennox-Gastaut	Potential cure of underlying defect; single test per patient
26.	***Standard of care aimed to treat cause available***	A: Yes, and very effective B: Yes, but poorly effective C: No directed to cause, but only symptomatic, if any	A: VAP B: Adenocarcinoma of the pancreas C: Lennox-Gastaut	Acceptability and type of controls, need for add-on designs, potential carry-over impairing cross-over

	Term	Definition	Sample condition / treatment/ variable...	Potential use
27.	***Standard of care returns subject to normal status***	A: Yes B: No	A: VAP, acute lymphoblastic leukaemia B: Cystic fibrosis	Single observation per patient vs longitudinal follow-up, repeated measuring and potential cross-over.

14.2. Annex 2. Document used to validate the clustering with the clinical advisory board

Work package 5 - Clinical Advisory Board

Subject: Input on classification of diseases

Version 1	12th January 2015

Internal use only – do not distribute

Advances in Small Trials dEsign for Regulatory Innovation and eXcellence: Work Package 5

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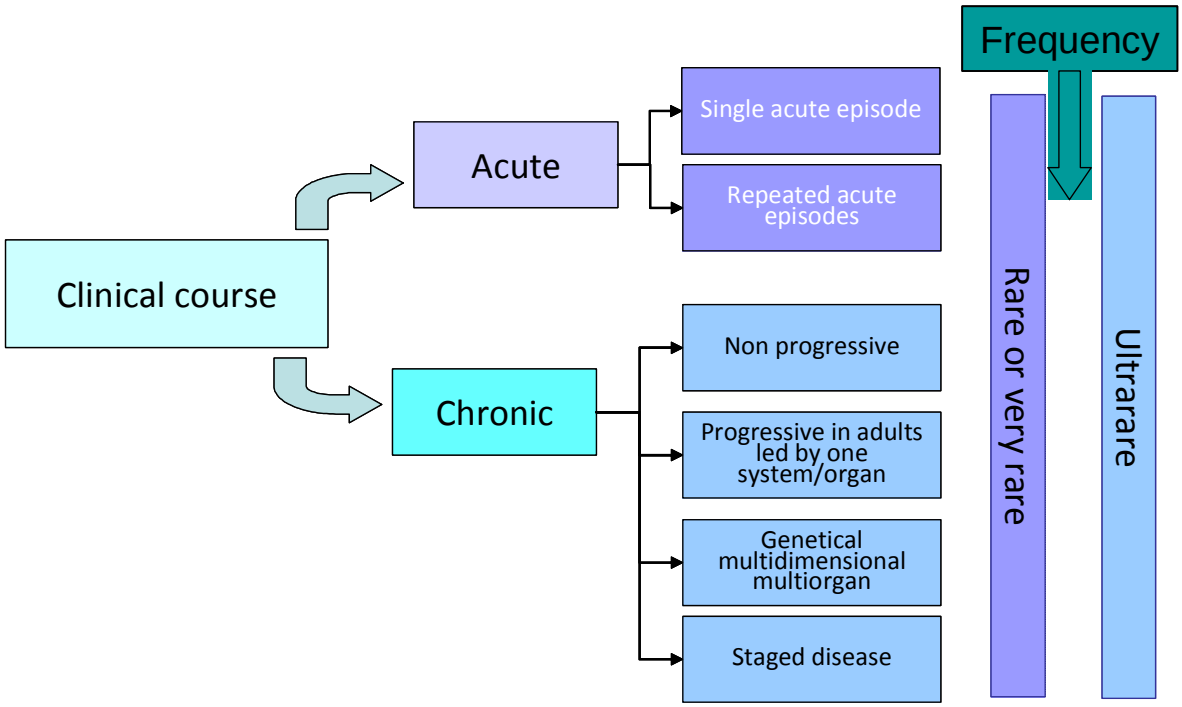
Classification of conditions for which EMA has issued an opinion with available European Public Assessment Report on a medicinal product with Orphan Designation.

Methods:

The classification used is that of rare diseases based on clinical features which determine applicability of investigative designs and methods to their study, as proposed by WP5.



Each condition has been classified by 2 different investigators and reviewed in a final pannel discussion.

Source of data:

European Public Assessment Reports for medicinal products with Orphan Designation

Thank you very much for sharing your opinion on the following topics.

Regarding clinical research and development

Current methods in clinical research allow to obtain reliable information on the efficacy of new treatments aimed to treat non-orphan diseases

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Current methods in clinical research allow to obtain reliable information on the efficacy of new treatments aimed to treat orphan diseases

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Regarding the process of drug authorisation

When referred to non-orphan drugs, the evaluation and authorization processes are finally based on certain degree of case by case subjectivity

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

When referred to orphan drugs, the evaluation and authorization processes are finally based on certain degree of case by case subjectivity

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

The evaluation and authorization of orphan drugs could benefit from a structured approach

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

An structured approach to the evaluation and authorization of orphan drugs could ease patient access to new treatments

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Predictability of which are the requirements of regulatory bodies to authorise commercialization of orphan drugs would accelerate the patient access to new treatments

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Regarding the process of drug funding

Decisions on funding and reimbursement by health care system are often divergent from opinions reflected in regulatory decisions

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Evaluation of health technologies and decisions on funding and reimbursement by health care system are difficult mainly due to heterogeneity of clinical evidences

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Evaluation of health technologies and decisions on funding and reimbursement by health care system are difficult mainly due to the potential impact on budget, rather than clinical evidences

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Decisions on funding and reimbursement by health care system are finally based on certain degree of case by case subjectivity

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

The development of grouped regulatory guidance on methodology of research of orphan drugs could ease decisions on funding and reimbursement by health care system

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Regarding the ASTERIX clinical and regulatory project

The overall approach of the ASTERIX clinical and regulatory project, ie: the development of grouped regulatory guidance on methodology and evaluation of orphan drugs

Is scientifically sound

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

May represent innovation in clinical research of rare diseases

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

May contribute to improve the clinical research of rare diseases

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

May be useful to regulators

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

May be useful to industry

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

May be useful to investigators

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

May be useful to identify aspects of research where input from patient organizations is necessary

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Regarding the proposed ASTERIX classification of diseases

The approach for the development of the ASTERIX classification is scientifically sound

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Grouping diseases sharing characteristics allowing similar methodological approaches may be a useful tool to:

Increase predictability of the regulatory assessment of orphan drugs

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Guide clinical development of orphan drugs

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Facilitate decisions on marketing authorisation

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Facilitate decisions on pricing and reimbursement

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Facilitate actual patient access to new treatments

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Evaluation of health technologies, funding and reimbursement by health care system

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Most types of orphan diseases or indications can be represented in the groups proposed by the ASTERIX classification

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Some types of diseases or key concepts in the proposed approach for ASTERIX classification are missing

Totally disagree	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Totally agree*

Please comment:

Thank you very much for sharing your opinion on the following proposed classification for conditions included in EMA -EPAR regarding products with orphan registration

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
cardiovascular	Patent Ductus Arteriosus	Single acute episode	no	Yes ☐ No ☐	
digestive	Inborn errors of primary bile acid synthesis responsive to treatment with cholic acid	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
digestive	Inborn errors of primary bile acid synthesis	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
digestive	Short bowel syndrome	Non progressive	no	Yes ☐ No ☐	
digestive	Hepatic veno-occlusive disease	Progressive led by one system /organ	no	Yes ☐ No ☐	
digestive	Malignant gastrointestinal stromal tumours	Staged disease	yes	Yes ☐ No ☐	
digestive	High-grade dysplasia in Barrett's Esophagus	Staged disease	no	Yes ☐ No ☐	
digestive	Familial Adenomatous Polyposis (FAP)	Staged disease	no	Yes ☐ No ☐	
endocrinology	Acromegaly	Multidimensional /multiple organ	no	Yes ☐ No ☐	
endocrinology	Primary insulin-like growth factor-1 deficiency due to molecular or genetic defects	Multidimensional /multiple organ	no	Yes ☐ No ☐	
endocrinology	Cushing's disease	Non progressive	yes	Yes ☐ No ☐	

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
endocrinology	Adrenal insufficiency	Non progressive	no	Yes ☐ No ☐	
haematology	Essential thrombocythaemia	Non progressive	no	Yes ☐ No ☐	
haematology	Chronic idiopathic myelofibrosis	Progressive led by one system /organ	yes	Yes ☐ No ☐	
haematology	Myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia	Progressive led by one system /organ	yes	Yes ☐ No ☐	
haematology	Idiopathic thrombocytopenic purpura	Progressive led by one system /organ	no	Yes ☐ No ☐	
haematology	Iron overload requiring chelation therapy	Progressive led by one system /organ	no	Yes ☐ No ☐	
haematology	Sickle cell syndrome	Progressive led by one system /organ	no	Yes ☐ No ☐	
haematology	Atypical haemolytic uremic syndrome	Repeated acute episode	yes	Yes ☐ No ☐	
haematology	Anaplastic large cell lymphoma	Single acute episode	yes	Yes ☐ No ☐	
haematology	Acute myeloid leukaemia	Single acute episode	no	Yes ☐ No ☐	
haematology	Acute promyelocytic leukaemia (APL)	Single acute episode	no	Yes ☐ No ☐	
haematology	Conditioning treatment prior to haematopoietic progenitor cell transplantation	Single acute episode	no	Yes ☐ No ☐	
haematology	Treatment to mobilize progenitor cells prior to stem cell transplantation	Single acute episode	no	Yes ☐ No ☐	

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
haematology	Conditioning treatment prior to haematopoietic progenitor cell transplantation	Single acute episode	no	Yes ☐ No ☐	
haematology	Acute lymphoblastic leukaemia	Single acute episode	no	Yes ☐ No ☐	
haematology	Mantle cell lymphoma	Staged disease	yes	Yes ☐ No ☐	
haematology	Indolent non-Hodgkin's lymphoma	Staged disease	no	Yes ☐ No ☐	
haematology	Chronic myeloid leukaemia	Staged disease	no	Yes ☐ No ☐	
haematology	Chronic lymphocytic leukaemia	Staged disease	no	Yes ☐ No ☐	
haematology	Multiple myeloma	Staged disease	no	Yes ☐ No ☐	
haematology	Myelodysplastic syndromes	Staged disease	no	Yes ☐ No ☐	
haematology	Hodgkin lymphoma	Staged disease	no	Yes ☐ No ☐	
haematology	Myelodysplastic/myeloproliferative diseases	Staged disease	no	Yes ☐ No ☐	
inflammatory	Paroxysmal nocturnal haemoglobinuria	Progressive led by one system /organ	yes	Yes ☐ No ☐	
inflammatory	Systemic sclerosis (scleroderma)	Progressive led by one system /organ	no	Yes ☐ No ☐	
inflammatory	Chronic eosinophilic leukaemia and the hypereosinophilic syndrome	Progressive led by one system /organ	no	Yes ☐ No ☐	

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
inflammatory	Cryopirin-associated periodic syndromes (Familial Cold Urticaria Syndrome (FCUS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous Articular Syndrome (CINCA))	Repeated acute episode	yes	Yes ☐ No ☐	
inflammatory	Angioedema	Repeated acute episode	no	Yes ☐ No ☐	
metabolic	Propionic acidaemia	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	MN-acetylglutamate synthetase (NAGS) deficiency	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Gaucher disease	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Methylmalonic acidaemia	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Treatment of Mucopolysaccharidosis type I	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Mucopolysaccharidosis VI (MPS VI) or Maroteaux-Lamy Syndrome	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Mucopolysaccharidosis, type II (Hunter syndrome)	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Niemann-Pick disease, type C	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Isovaleric acidaemia	Multidimensional /multiple organ	yes	Yes ☐ No ☐	

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
metabolic	Cystinosis	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Fabry disease	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Glycogen Storage Disease type II (Pompe's disease)	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Tyrosinaemia type I	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Homocystinuria	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
metabolic	Hyperphenylalaninemia	Multidimensional /multiple organ	no	Yes ☐ No ☐	
metabolic	Lipoprotein lipase deficiency	Non progressive	yes	Yes ☐ No ☐	
neurological	Wilson's disease	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
neurological	Familial amyloid polyneuropathy	Multidimensional /multiple organ	yes	Yes ☐ No ☐	
neurological	Tuberous sclerosis	Multidimensional /multiple organ	no	Yes ☐ No ☐	
neurological	Lambert-Eaton myasthenic syndrome	Non progressive	yes	Yes ☐ No ☐	
neurological	Narcolepsy	Non progressive	no	Yes ☐ No ☐	
neurological	Severe myoclonic epilepsy in infancy	Repeated acute episode	yes	Yes ☐ No ☐	

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
neurological	Lennox-Gastaut syndrome	Repeated acute episode	no	Yes ☐ No ☐	
neurological	Chronic pain requiring intraspinal analgesia	Single acute episode	no	Yes ☐ No ☐	
oncology	Adrenal cortical carcinoma	Staged disease	yes	Yes ☐ No ☐	
oncology	Soft tissue sarcoma	Staged disease	yes	Yes ☐ No ☐	
oncology	Dermatofibrosarcoma protuberans	Staged disease	no	Yes ☐ No ☐	
oncology	Hepatocellular carcinoma	Staged disease	no	Yes ☐ No ☐	
oncology	Osteosarcoma	Staged disease	no	Yes ☐ No ☐	
oncology	Renal cell carcinoma	Staged disease	no	Yes ☐ No ☐	
oncology	Ovarian cancer	Staged disease	no	Yes ☐ No ☐	
oncology	Renal cell carcinoma	Staged disease	no	Yes ☐ No ☐	
other	Partial deep dermal and full thickness burns	Single acute episode	no	Yes ☐ No ☐	
other	Anthracycline extravasations	Single acute episode	no	Yes ☐ No ☐	
other	Intra-operative photodynamic diagnosis of residual glioma	Staged disease	no	Yes ☐ No ☐	

Broad therapeutic group	Designated orphan indication in EPAR	Proposed classification	Ultrarare	Agree?	Comments
respiratory	Cystic fibrosis	Multidimensional /multiple organ	no	Yes ☐ No ☐	
respiratory	Gram negative bacterial lung infection in cystic fibrosis	Repeated acute episode	no	Yes ☐ No ☐	
respiratory	Primary apnoea of premature newborns	Repeated acute episode	no	Yes ☐ No ☐	
respiratory	Pseudomonas aeruginosa lung infection in cystic fibrosis	Repeated acute episode	no	Yes ☐ No ☐	
respiratory	Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Staged disease	no	Yes ☐ No ☐	
respiratory	Pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension	Staged disease	no	Yes ☐ No ☐	
respiratory	Primary and of the following forms of secondary pulmonary hypertension: connective tissue disease pulmonary hypertension, drug-induced pulmonary hypertension, portopulmonary hypertension, pulmonary hypertension associated with congenital heart disease	Staged disease	no	Yes ☐ No ☐	
respiratory	Idiopathic pulmonary fibrosis	Staged disease	no	Yes ☐ No ☐	
respiratory	Pulmonary arterial hypertension	Staged disease	no	Yes ☐ No ☐	

14.3. Annex 3. Application of clustering to indications in EPARs

Orphan Medical Condition	Main cluster	Secondary cluster	Frequency
1. Acromegaly	Progressive multidimendional		Rare
2. Acute Lymphoblastic Leukaemia	Acute single episodes	Progressive led by one organ-system	Rare
3. Acute Myeloid Leukaemia	Acute single episodes		Rare
4. Adrenal Cortical Carcinoma	Staged		Rare
5. Adrenal Insufficiency	Chronic slow or non-progressive		Rare
6. Anaplastic Large Cell Lymphoma	Staged		Rare
7. Angioedema	Acute single episodes	Recurrent acute episodes	Rare
8. Anthracycline Extravasations	Acute single episodes		Ultrarare
9. Atypical Haemolytic Uremic Syndrome	Progressive multidimendional	Recurrent acute episodes	Rare
10. Castleman's Disease	Progressive multidimendional		Rare
11. Chronic Eosinophilic Leukaemia /Hypereosinophilic Syndrome	Progressive led by one organ-system		Rare
12. Chronic Idiopathic /secondary Myelofibrosis	Progressive led by one organ-system		Rare
13. Chronic Iron Overload Requiring Chelation	Chronic slow or non-progressive		Rare
14. Chronic Lymphocytic Leukaemia	Staged	Progressive led by one organ-system	Rare
15. Chronic Myeloid Leukaemia	Progressive led by one organ-system	Staged	Rare
16. Chronic Pain	Chronic slow or non-progressive		Rare
17. Conditioning For Stem Cell Transplantation	Acute single episodes		Rare
18. Cryopirin-Associated Periodic Syndromes	Recurrent acute episodes		Ultrarare
19. Cushing’s Syndrome	Acute single episodes	Progressive led by one organ-system	Rare

Orphan Medical Condition	Main cluster	Secondary cluster	Frequency
20. Cushing's Disease	Acute single episodes	Progressive led by one organ-system	Rare
21. Cystic Fibrosis: Lung Infection	Recurrent acute episodes	Progressive led by one organ-system	Rare
22. Cystic Fibrosis: Receptor Estabilization	Progressive multidimendional		Rare
23. Cystic Fibrosis: Symptomatic	Progressive multidimendional		Rare
24. Cystinosis	Progressive multidimendional		Rare
25. Dermatofibrosarcoma Protuberans	Progressive led by one organ-system		Rare
26. Duchenne Muscular Dystrophy	Progressive multidimendional		Rare
27. Dysplasia In Barrett's Esophagus	Staged		Rare
28. Erythropoietic Protoporphyria	Progressive multidimendional		Rare
29. Essential Thrombocythaemia	Chronic slow or non-progressive		Rare
30. Fabry Disease	Progressive multidimendional		Ultrarare
31. Familial Adenomatous Polyposis	Staged		Rare
32. Familial Amyloid Polyneuropathy	Progressive multidimendional		Rare
33. Follicular / Papillary Thyroid Cancer	Staged		Rare
34. Gastric Cancer	Staged		Rare
35. Gaucher Disease	Progressive multidimendional		Rare
36. Glycogen Storage Disease Type II	Progressive multidimendional		Rare
37. Haematopoietic Cell Transplantation	Acute single episodes		Rare
38. Hairy Cell Leukaemia	Staged		Rare
39. Hepatic Veno-Occlusive Disease	Acute single episodes	Progressive led by one organ-system	Rare
40. Hepatocellular Carcinoma	Progressive led by one organ-system		Rare
41. Hodgkin Lymphoma	Staged		Rare
42. Homocystinuria	Progressive multidimendional		Rare
43. Hyperphenylalaninemia	Progressive multidimendional		Rare

Orphan Medical Condition	Main cluster	Secondary cluster	Frequency
44. Idiopathic Pulmonary Fibrosis	Staged		Rare
45. Idiopathic Thrombocytopenic Purpura	Acute single episodes	Progressive led by one organ-system	Rare
46. Inborn Errors Of Primary Bile Acid Synthesis	Progressive multidimendional		Ultrarare
47. Intra-Operative Diagnosis Of Residual Glioma	Acute single episodes		Rare
48. Isovaleric Acidaemia	Progressive multidimendional		Ultrarare
49. Lambert-Eaton Myasthenic Syndrome	Chronic slow or non-progressive	Acute single episodes	Rare
50. Lennox-Gastaut Syndrome	Recurrent acute episodes		Rare
51. Lipoprotein Lipase Deficiency	Chronic slow or non-progressive		Ultrarare
52. Malignant Gastrointestinal Stromal Tumours	Progressive led by one organ-system	Staged	Ultrarare
53. Mantle Cell Lymphoma	Staged	Progressive led by one organ-system	Rare
54. Medullary Thyroid Carcinoma	Staged		Rare
55. Methylmalonic Acidaemia	Progressive multidimendional		Ultrarare
56. Mucopolysaccharidosis Type I	Progressive multidimendional		Ultrarare
57. Mucopolysaccharidosis Type II	Progressive multidimendional		Ultrarare
58. Mucopolysaccharidosis Type IVA	Progressive multidimendional		Rare
59. Mucopolysaccharidosis Type VI	Progressive multidimendional		Ultrarare
60. Multiple Myeloma	Progressive led by one organ-system	Staged	Rare
61. Myelodysplastic Syndromes	Staged		Rare
62. Myelodysplastic/Myeloproliferative Diseases	Progressive led by one organ-system		Rare
63. N-Acetylglutamate Synthetase Deficiency	Progressive multidimendional		Ultrarare
64. Narcolepsy	Recurrent acute episodes	Chronic slow or non-progressive	Rare
65. Niemann-Pick Disease, Type C	Progressive multidimendional		Rare
66. Osteosarcoma	Staged		Rare
67. Ovarian Cancer	Staged		Rare

Orphan Medical Condition	Main cluster	Secondary cluster	Frequency
68. Paroxysmal Nocturnal Haemoglobinuria	Progressive led by one organ-system		Rare
69. Patent Ductus Arteriosus	Acute single episodes		Rare
70. Primary Apnoea Of Premature Newborns	Acute single episodes		Rare
71. Primary Insulin-Like Growth Factor-1 Deficiency	Chronic slow or non-progressive		Rare
72. Propionic Acidaemia	Progressive multidimendional		Ultrarare
73. Pulmonary Arterial Hypertension	Staged	Progressive led by one organ-system	Rare
74. Renal Cell Carcinoma	Staged	Progressive led by one organ-system	Rare
75. Severe Myoclonic Epilepsy In Infancy	Recurrent acute episodes		Rare
76. Severe Skin Burns	Acute single episodes		Rare
77. Short Bowel Syndrome	Chronic slow or non-progressive		Rare
78. Sickle Cell Syndrome	Progressive led by one organ-system	Recurrent acute episodes	Rare
79. Soft Tissue Sarcoma	Progressive led by one organ-system		Rare
80. Systemic Sclerosis (Scleroderma)	Progressive multidimendional		Rare
81. Tuberculosis	Acute single episodes		Rare
82. Tuberous Sclerosis - AML	Progressive multidimendional		Rare
83. Tuberous Sclerosis - SEGA	Progressive multidimendional		Rare
84. Tyrosinaemia Type I	Progressive led by one organ-system		Rare
85. Wilson's Disease	Progressive led by one organ-system		Rare