



REVIEW

# Perspectives for improving the evaluation and access of therapies for rare lung diseases in Europe

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## Summary

The approach to treating a rare disease is different to that taken for more common diseases. Small patient cohorts alter clinical trial design and limit enrollment, and the picture for rare lung diseases is further complicated by the fact that most are composed of a variety of clinical phenotypes. Since the outcome measures of lung impairment have considerable test-to-test variability, potential new therapies face a substantial challenge. In this paper we will review the current sources of clinical data for rare lung diseases and the regulatory challenges encountered by their treatment, with particular reference to alpha<sub>1</sub>-antitrypsin deficiency, lymphangiomyomatosis, cystic fibrosis, and pulmonary alveolar proteinosis. Strategies will also be identified for the better utilization of available data from patients with rare lung diseases, recognizing that the development cost of new therapies and the number of patients who will ultimately use them may not be aligned. Also important is improved communication

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between patients and their organizations, basic researchers, clinicians and their registries, drug developers, regulators such as the European Medicines Agency, and national health services. At present, licensing and reimbursement requirements are not aligned, either nationally or internationally, and variations also exist in drug availability between countries because of different national licensing and reimbursement rules. The changes needed to optimize European rare lung disease therapies include a commitment to develop empowered patient communities as advocates for therapy, the development of novel trial designs with new endpoints, and for regulatory bodies to be willing to accept nontraditional models of efficacy for orphan drugs.

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## Introduction

Randomized, double-blind, placebo-controlled clinical trials are the gold standard for assessing the therapeutic effect of any drug. However, in assessing therapies for rare diseases with limited numbers of affected patients, it is often not achievable to recruit a critical sample size in order to meet this gold standard. Small patient populations and rare or variable phenotypes make it difficult to enroll sufficient patient numbers to randomized clinical trials, leading to a lack of statistical power. Therapies may fail to meet traditional measures of efficacy.

In the case of rare diseases, the patients, as well as being low in number, are often isolated and dispersed, resulting in further patient recruitment challenges. There is also insufficient clinical knowledge and poor recognition of rare conditions by the medical community that often leads to a delay in the diagnosis and identification of patients. Furthermore, there is a paucity of quality patient information and little research is carried out compared with more common diseases. Those who suffer from orphan diseases, together with their immediate families, may feel isolated and may receive inadequate attention and thus care. It is clear that an inequality of healthcare provision

exists compared with other conditions, and there is often a lack of interest from drug developers when they are faced with a lengthy time period and difficulties in obtaining sufficient clinical evidence for regulatory approval of their products. There may be an imbalance between the development costs of bringing a drug into clinical use and the expected return for the high cost of development. In fact, over 95% of rare diseases still do not have a specific treatment.<sup>1</sup>

The purpose of this article is to review and broaden the discussion on current sources of clinical data for rare lung diseases and the regulatory challenges that treatments for the disorders encounter. It is based on a roundtable meeting attended by the 8 authors in December 2010 where these issues were discussed. In the paper we will consider that the requirements for demonstrating clinical effectiveness of drugs may have to be more flexible in rare diseases compared with common conditions. We will put forward perspectives and identify strategies for the better utilization of data from patients with rare lung diseases. For example, consideration should be given to the validation of new outcome parameters for clinical trials that correlate with classically used endpoints, but are more sensitive, hence requiring a smaller sample size. Other sources of data and tools should be utilized, such as patient

registries, postmarketing surveillance studies, cohort studies, or studies with novel designs.

The article will also review the need for more aligned clinical, licensing, and reimbursement approaches to enhance the level of clinical evidence in these diseases, and will discuss how access to therapies can be improved and accelerated for patients. Drawing upon our experiences in the respiratory disorders alpha<sub>1</sub>-antitrypsin (AAT) deficiency, cystic fibrosis (CF), pulmonary alveolar proteinosis (PAP), and lymphangioleiomyomatosis (LAM), in particular, we will propose alternative approaches to improve the accessibility of therapies for patients in Europe affected by rare disorders.

## Orphan drug legislation

The US Rare Diseases Act of 2002 established the National Institutes of Health (NIH) Office of Rare Diseases Research.<sup>2</sup> For this purpose, a rare disease was defined as one that affects fewer than 200,000 individuals in the United States (less than 1 in approximately 1500). There are over 7000 such diseases and conditions in the United States.<sup>3</sup> The EU's definition of a rare disease is a life-threatening or chronically debilitating condition of low prevalence, affecting 5 or fewer people in every 10,000 (approximately 250,000 individuals in total).<sup>4</sup> About one half of these rare diseases affect children, and about 80% are a result of a genetic defect (others being degenerative or proliferative disorders). The total number of rare diseases is estimated to be in the order of 5000–8000 within the EU, and it is thought that 6–8% of the population will be affected by a rare disease at some stage in their life. Overall, 25 million North Americans and 30 million Europeans are estimated to be suffering from a rare disease,<sup>5</sup> and approximately 250 new conditions are identified each year.<sup>6</sup> Some diseases occur so infrequently that there may be 50 or fewer sufferers in a single country. Nevertheless, extrapolated globally, this may amount to many thousands. Examples of rare lung diseases and their prevalence are provided in Table 1.

There is a difference between the definition of a rare disease and a neglected disease. The latter, while it may be rare, may also be a common yet overlooked condition. The concept of a neglected disease is a lack of interest in the

condition rather than just its rarity. In general, new antibiotics are not being developed for some of the more common neglected diseases, tuberculosis being such a case.

An orphan drug or medicinal product is defined in the EU as being intended for the diagnosis, prevention, or treatment of a life-threatening or chronic debilitating rare or orphan disease (as described above).<sup>13</sup> Orphan drug status also applies to a medicinal product intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating condition that, without incentives, is unlikely to realize sufficient financial return to justify the investment required for its commercialization. Additionally, in order for the drug to qualify for orphan status, there should either be no authorized satisfactory method of diagnosis, prevention, or treatment of the condition in question or, if such method exists, the medicinal product should be of significant benefit to those affected by that condition (i.e., improved efficacy, safety, or ease of administration, compared with existing treatments).

The US Orphan Drug Act, which came into effect in 1983,<sup>14</sup> and which has been followed by the development and marketing of more than 350 biologic products and drugs,<sup>15</sup> paved the way for the introduction of legislation in the EU in 2000 (EU Regulation [EC] No 141/2000).<sup>13</sup> The purpose of the EU legislation, which applies to all 27 member states, was to provide incentives for the research, development, and marketing of designated orphan medicinal products. Orphan drug status granted by the European Commission gives marketing exclusivity throughout the EU for 10 years after approval, with the regulation being administered by the Committee on Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). A product originally developed and approved for another indication can gain orphan drug status for a different indication. Examples include sildenafil and iloprost, which have been granted marketing authorization for pulmonary hypertension. After 10 years of orphan drug legislation in the EU, approximately 800 products have been granted orphan status, including 47 for rare lung diseases (Table 2); EU marketing authorization has been granted for 6 of these 47 products.

The EU legislation does not overcome the barriers to the initial development of new drugs for rare diseases but it can exempt the product's sponsor from fees payable to the EMA, with small- and medium-sized enterprises being given the most incentives (Table 3). Other assistance includes the provision of scientific advice and protocol assistance to the pharmaceutical company on the manufacturing, preclinical, and clinical evaluation (including study design, sample size, establishing endpoints, and statistical analyses). This advice can be used for every aspect of the development of a drug. The onus is on the pharmaceutical company to actively seek this advice from the Scientific Advice Working Party (SAWP), asking the necessary targeted questions and proposing ways to investigate the product in order to demonstrate clinical benefit. The fact that large-scale randomized clinical trials are not feasible when evaluating treatment of rare diseases is recognized. The SAWP and, subsequently, the Committee for Medicinal Products for Human Use (CHMP) have proven willing to consider observational studies or the use of surrogate markers as an alternative to the usual regulatory requirements for the demonstration of clinical benefit.

**Table 1** Examples and prevalence of rare lung diseases.

Disease	Approximate prevalence (per 10,000 population)
CF	EU: 0.737 <sup>7</sup> US: 0.797 <sup>7</sup>
AAT deficiency (PiZZ genotype)	Europe: 2–2.5 <sup>8</sup> US: 3.3 <sup>9</sup>
LAM	Worldwide: 0.01 (women) <sup>10</sup>
PAP	Worldwide: 0.037 <sup>11</sup>
Children's interstitial lung disease	UK and Ireland: 0.036 <sup>12</sup>
Idiopathic pulmonary fibrosis	Worldwide: 2 (men); 1.3 (women) <sup>11</sup>
Small-cell lung cancer	Worldwide: 0.5 <sup>11</sup>

**Table 2** Summary of orphan medical products designated by the EMEA for lung diseases (as of November 30, 2010).<sup>16</sup>

Condition/disease	Number of medical products designated as orphan
Prevention/treatment of graft rejection after lung transplant	4
Treatment of acute lung injury	7
Treatment of bacterial lung infection in CF	7
Treatment of small-cell lung cancer	4
Treatment of subtype of non-small-cell lung cancer	1
Treatment of pulmonary lung infection	1
Treatment of idiopathic pulmonary fibrosis	9
Treatment of pulmonary hypertension	14
Total	47

## Issues and challenges for rare lung diseases and their treatment

### Disease phenotypes and patient numbers

Although it is common rather than rare, the diagnosis and treatment of chronic obstructive pulmonary disease (COPD) is associated with many of the challenges that clinicians face when presented with a rare lung disease. As a result of their polygenetic origin, common lung conditions such as COPD are associated with considerable heterogeneity of clinical presentation and disease progression; variations are observed in symptoms, frequency of exacerbations, response to therapy, rate of disease progression, or premature death.<sup>18</sup> Rather than being considered a single disease, COPD should be viewed as a syndrome made up of multiple separate disorders that overlap.<sup>19</sup> The diversity of patient COPD phenotypes included in two large-scale trials, Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT)<sup>20</sup> and Toward a Revolution in COPD Health (TORCH),<sup>21</sup> likely contributed to neither of these studies achieving their primary efficacy endpoint (loss of forced expiratory volume in one second [FEV<sub>1</sub>] over time, and reduction in mortality, respectively).

**Table 3** EMA incentives for pharmaceutical companies to develop orphan drugs.<sup>17</sup>

- Scientific advice in protocol development
- Centralized market authorization
- 10-year marketing exclusivity
- Financial benefits
  - Exemption from fees for protocol assistance and follow-up
  - Exemption from fees for pre-authorization inspections
  - New application fees reduced by 50% (total exemption for small- to medium-sized enterprises)
  - Exemption from postauthorization activities (small- to medium-sized enterprises only)
  - Assistance with translation of product information documents (small- and medium-sized enterprises)

More recently, stratification of COPD patients according to disease phenotype has been used to demonstrate efficacy in relatively short-duration studies in smaller numbers of patients. The benefit of the phosphodiesterase-4 inhibitor roflumilast, for example, in reducing the occurrence of exacerbations in patients with a history of frequent COPD exacerbations was shown in two placebo-controlled studies comprising a total of 1537 patients treated for 52 weeks.<sup>22</sup> Asthma is another example of a common respiratory disease with varying severity of symptoms. Eosinophilic inflammation of the airways is associated with a risk of asthma exacerbations. A placebo-controlled study in 61 patients with asthma and airway eosinophilia found a significant reduction in the number of exacerbations over a 50-week period associated with the use of an anti-interleukin-5 monoclonal antibody.<sup>23</sup> In the light of phenotypic influence on study outcomes, these are examples of a trend in the study of different aspects of disease toward more personalized medicine, and to finding the right population that will benefit most from a particular treatment.<sup>24</sup>

The concept of a respiratory disease as a syndrome (with a specific set of symptoms), and a phenotyping strategy for investigating treatments, is also relevant to rare conditions. In individuals with severe AAT deficiency, the development and manifestations of COPD are highly variable. Among patients with the same genotype, some have reduced lung function and some have normal function, certain patients are fast decliners, and there are individuals who have bronchiectasis while others may be colonized with specific airway microflora.<sup>25</sup> Correspondingly, in LAM, there are stable patients and others who decline quickly. In women with LAM, only about 40% develop renal angio-myolipomas.<sup>26</sup> In the case of PAP, there is a wide range of symptoms and varying pathophysiologies.<sup>27</sup> In CF, some patients display the classical manifestations of the disease from infancy and have a relatively poor prognosis, while others have much milder or even atypical disease manifestations and a marked variation in the organs involved.<sup>28,29</sup> Clinical observation shows that siblings with CF can manifest different phenotypes (both in terms of disease severity and degree of different organ involvement), despite being affected by the same gene mutations, presumably due to the presence of gene polymorphisms.

In a number of rare diseases, the clinical phenotype is more clearly defined than in common diseases, which could confer an advantage on the study of these conditions. This

means less confounding factors such as the inclusion of subjects with different phenotypes. Subtypes of rare diseases can be investigated to find meaningful outcomes when applying a therapeutic strategy, and by dissecting the phenotypes it may be possible to demonstrate specific improvements. For example, molecular phenotyping in PAP can be carried out to study a particular subtype of the disease, and, in lung cancer, specific epidermal growth-factor receptor mutations have been targeted for treatment. In the case of CF, genotype-specific trials of therapies for different types of CF transmembrane-conductance regulator mutations are being carried out.<sup>30,31</sup>

In the Multicenter International Lymphangioliomyomatosis Efficacy and Safety of Sirolimus (MILES) trial, patients with moderate lung impairment were predefined and enrolled into the trial; those with normal lung function, where a signal would not be expected in rate of decline in FEV<sub>1</sub>, were not selected.<sup>32</sup> In AAT deficiency, augmentation therapy has been shown to slow the decline in FEV<sub>1</sub>, an effect that was most markedly observed in a small subgroup of rapid decliners.<sup>33–35</sup> Therefore, in rare diseases, the study population needs to be well characterized (i.e., phenotyped and selected carefully) in order to be able to show a treatment effect, and it is not necessarily the case that studies with large patient numbers have to be conducted. However, once the biologic effect is proven in a subgroup of individuals with a specific biomarker that is sensitive to change, expansion of the therapy to larger cohorts within the rare disease is sometimes plausible.

### Clinical trial design – appropriate outcomes

The issues associated with conducting clinical trials when only a limited number of patients are available have been addressed in guidelines published by the EMA.<sup>36</sup> These guidelines conclude that “the need for statistical efficiency should be weighed against the need for clinically relevant/interpretable results; the latter being the most important” and stress that the regulatory assessment may accept different approaches if they ensure that the patients’ interests are protected. Emphasis is placed on the importance of the sponsor obtaining scientific advice/protocol assistance for the acceptability of the planned approaches. This may include a discussion on alternative clinical outcome parameters.

There has been considerable recent research into the development of biomarkers that could replace the classic lung function parameters. The ECLIPSE study is a non-interventional, observational, multicenter, 3-year study. In addition to the characterization of susceptibility to exacerbations,<sup>37</sup> the cohort from this study has been used to evaluate new biomarkers (serum Clara cell secretory protein-16, serum surfactant protein-D, sputum neutrophils, and computed tomography).<sup>38–40</sup> In the MILES trial in LAM, serum levels of vascular endothelial growth factor D (VEGF-D) were used as a biomarker and a reduction in these levels was a secondary endpoint.<sup>32</sup> Further study is required to establish that VEGF-D is a biomarker of treatment response, but such biomarkers, if validated, may be equally appropriate for other rare lung diseases.

The study of biomarkers is especially relevant when planning smaller studies in rare diseases. Unfortunately, the

requirement for a biomarker to be correlated to mortality may be too high a hurdle for rare diseases. Therefore, new biomarkers could be borrowed from similar but more common lung diseases. For instance, new quality-of-life questionnaires in general COPD could be applied to AAT deficiency.

Another important step forward is the use of computed tomography (CT) to determine emphysema progression. CT measurements of lung density are now accepted by the Food and Drug Agency (FDA) as a primary outcome parameter for clinical trials in patients with COPD due to AAT deficiency.<sup>41</sup> Lung density directly measures the emphysema caused by AAT deficiency, so it may have advantages as an outcome measure. The optimum use of CT densitometry data for the assessment of augmentation therapy on the progression of emphysema in AAT deficiency has been extensively examined in the EXAcacerbations and CT scan as Lung Endpoints (EXACTLE) trial.<sup>33,42</sup> CT was found to be more sensitive than lung function parameters when measuring the progression of emphysema in patients with AAT deficiency,<sup>33</sup> and also in patients with COPD caused by smoking.<sup>43</sup>

The COPD Foundation (a US patient organization) brought together scientific leadership and the FDA to establish the COPD Biomarkers Qualification Consortium to validate outcome measures in COPD. The 5 outcome measures that seem to have sufficient validity for COPD research trials include FEV<sub>1</sub>, CT lung density, inspiratory capacity, the St George’s Respiratory Questionnaire, and serum fibrinogen. The measures had to meet criteria for robustness across studies and correlate with mortality. This approach could transform COPD trials in the United States, and implies that the same could be done in Europe, where a nonregulatory authority would advise on clinical trial endpoints in order to identify potential outcome measures. The challenge for rare diseases would be to perform the numbers of studies required to validate such endpoints. The CF Gene Therapy Consortium in the United Kingdom, in common with the CF Foundation in the United States, has research already in progress to investigate outcome measures and biomarkers.

Draft EMA guidance on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with COPD is recommending that efficacy should be demonstrated in two coprimary endpoints, lung function assessment combined with symptomatic-based parameters.<sup>44</sup> CT densitometry is proposed as a secondary endpoint. For rare lung diseases, another potential endpoint not currently under consideration could be treatment failure, with the need to switch to alternative therapy.

All endpoints have underlying technical issues with quality consistency so the need for standardization of endpoints across different centers is important. However, with better characterization of the patient populations, use can be made of new outcome measures and studies can be powered according to these endpoints. Patients could be included in future clinical trials, therefore, who are not selected solely on the basis of impaired lung function and genotype.

### Alternatives to randomized clinical trials

Whereas the strongest evidence to demonstrate efficacy of a therapy is gained during placebo-controlled

randomized clinical trials (RCTs), it may not always be feasible to obtain these data to evaluate drugs to treat rare diseases. For example, the size of the patient sample in AAT deficiency required for such randomized studies using the traditional physiological measure of FEV<sub>1</sub> as the primary endpoint<sup>45</sup> is considered to be impractical, and due to the relative rarity of AAT deficiency being diagnosed, sufficient numbers of patients were not easily recruited at the time of early studies. A placebo-controlled crossover trial in LAM was estimated to require approximately 80 patients to have 90% power to detect a 50 ml difference in change in FEV<sub>1</sub> over 1 year.<sup>46</sup> Furthermore, there are ethical issues in conducting placebo-controlled clinical trials in countries where there is already access to treatment.

Under such circumstances, observational data from patient registries have been used to obtain information on the efficacy and safety of drugs in rare diseases. The numbers of patients included are usually greater than those enrolled in RCTs and patients are not excluded on the basis of comorbidities or concomitant medications. Furthermore the long-term longitudinal data collected in observational studies is more likely to provide information on adverse reactions and drug interactions.<sup>47</sup>

In the E.U., conditional marketing authorization may be granted for treatments for rare diseases, based on the opinion of the CHMP; the treatments are conditionally approved and further confirmatory studies are agreed upon to establish clinical benefit.<sup>1</sup> In such cases where regulatory authorities acknowledge that the acquisition of full data from a RCT is not feasible, pharmaceutical companies may be required to collect long-term data in a drug registry as part of their authorization, and these regulatory databases will be managed by the company.<sup>48</sup> Acceptance of this approach by the regulatory authorities is dependent upon these registries being well maintained. This is not always the case because of the lack of standardization and completeness of the information entered by different centers and poor quality control of the data. The quality and comprehensiveness of data submissions into such a registry are dependent on the physicians, and they should be properly supported in this task.<sup>48,49</sup>

In the E.U., marketing approval has been granted for orphan drugs, often under exceptional circumstances, other than on the basis of the findings of classic RCTs. Examples from an analysis of all European orphan medicinal product designations from 2000 to 2004 include an uncontrolled phase II trial, exclusively retrospective data, and submission of a literature analysis only.<sup>50</sup> Furthermore, a number of trials consisted of 50 or fewer patients. These examples demonstrate that the EMA can be very flexible regarding trials in rare diseases. On the other hand, however, the reason why relatively few designated orphan drugs had gained marketing authorization over the period of the analysis was considered to be due to the poor quality of the dossiers submitted; these included such issues as the use of nonvalidated surrogate markers and trial duration being too short in relation to the natural history of the disease.<sup>50</sup> This emphasizes the importance of proactivity from the sponsors and then seeking scientific advice from the EMA at an early stage of protocol development.

## Registries

Patient registries are central to clinical research in rare diseases and to improving our understanding of these conditions. They are also essential to assess the feasibility of clinical trials and to facilitate their planning. Established at a national and especially an international level, registries can greatly assist in the identification of suitable patients to support enrollment and to ensure that clinical trials are adequately powered.<sup>51–55</sup> Contact registries inform patients and their families of clinical research studies.

In the United States, the Rare Lung Disease Consortium (RLDC) is a network of cooperating clinical and research centers and patient-support organizations that are working with the NIH in order to accelerate clinical research and improve the delivery of medical care to individuals affected by rare lung diseases. Toward this aim, the RLDC serves as a database for research information on a variety of rare lung diseases, as well as being a contact registry. This contact registry, which was set up as a result of patient pressure and reflects their eagerness to participate in clinical trials, has proven successful in identifying patients eligible for different trials evaluating the treatment of AAT deficiency. This approach has allowed the limited number of patients available to be allocated to different studies.

The Alpha One International Registry (AIR) captures information on individuals with AAT deficiency from 4 continents and 21 countries (15 of which are in Europe).<sup>56</sup> The Alpha-1 Foundation Research Registry is available to assist clinical trial enrollment in North America.<sup>57</sup> Registries for CF and PAP are organized on a national level, and, in addition, the European Cystic Fibrosis Society Patient Registry holds data on more than 20,000 CF patients from 16 countries.<sup>58</sup> A patient/clinician LAM registry has been recently established in the United States.<sup>59</sup>

Registries not only help researchers identify and recruit patients who are eligible for participation in future research into rare diseases, but are also a source of longitudinal data.<sup>60,61</sup> Although establishing a registry is relatively simple and inexpensive, the cost of maintaining it can be prohibitive, especially as funding is often limited. Registries should not just be a list of patients, but be as comprehensive a source of information as possible. The linking of registries with tissue banks to assist with the investigation of rare diseases should also be considered.

## Reimbursement

At present, there is a lack of alignment between licensing and reimbursement processes from an early stage of drug development. To address this, a closer relationship is needed between clinicians, drug developers, regulators, and payers, be it insurance companies or national health-care systems. The 2000 EU legislation concerning orphan medicinal products stated that "patients suffering from rare conditions are entitled to the same quality of treatment as other patients,"<sup>13</sup> and this is reflected in the centralization of marketing authorization in all 27 EU member states. This equal entitlement, however, does not apply to the pricing and reimbursement of orphan medical

products between the different Member States.<sup>62</sup> Negotiation of pricing and reimbursement policies are delegated to individual countries. There may also be differences at a regional level, and individual hospitals may have varying opinions on how to distribute their financial resources and how much of their total budget they are prepared to devote to the provision of orphan medicinal products. Such treatments are often considered to be disproportionately expensive. These differences are difficult to justify on medical grounds. An increased speed of approval for orphan drugs (for example, involving surrogate endpoints and shorter clinical trials) could lower their cost.

## Perspectives

Taking into consideration the issues discussed in this paper we offer the following perspectives.

### Communication

Greater collaboration and communication at all levels is crucial to ensure the increased availability of orphan medicinal products for a wider range of rare diseases. A step forward is the development of a unified orphan drug designation application form for both the FDA and EMA.<sup>63</sup> Consistency in the definition of validated study endpoints and approval of surrogate markers needs to be achieved through discussion with the regulatory authorities. Pharmaceutical companies, clinicians, regulators, payers, and patients should be involved in the regulatory process on a continuous basis and in the subsequent rulings on pricing and reimbursement.

### Patient organizations

Patient advocacy developed in the United States in the 1970s and became a driving force in the introduction of the US Orphan Drug Act. These groups have evolved and, being politically active and well-informed, subsequently formed collaborative partnerships with researchers studying rare diseases, government officials responsible for medical research, and the FDA. Patient advocacy is less well developed in Europe and patient communities are less empowered. Some European patient advocacy groups are, however, very successful with fundraising; they are now becoming proactively involved in research and fund research programs.

In CF, the role of patient organizations in Europe is relatively well advanced and there is good collaboration between patients, investigators, and drug developers. The CF Trust in the United Kingdom is a powerful voice, and following a campaign by the Trust, newborn screening was implemented throughout the United Kingdom in 2007. The rarer the disease, the less the power, but the stronger groups could lead the way forward. Childhood interstitial lung disease is an example where transatlantic cooperation could benefit from the experience of patients in the United States. In PAP, leaders in each country have been brought together, resources pooled, and a global registry can now be created. Through the Rare Lung Disease Consortium, two new patient foundations have been started. Patient

pressure to speed up the progression of drugs has been seen, for example, in the area of HIV therapy. This example of patient influence could be leveraged in the case of rare lung diseases. Patients with LAM came together to raise funding for the MILES trial, and demonstrated their willingness to be enrolled into the study.<sup>64</sup>

One of the mandates of EURORDIS, a nongovernmental, patient-driven alliance of patient organizations representing more than 461 rare disease patient organizations in over 45 countries in Europe, is to encourage the emerging networks to become well-structured, disease-specific federations at a pan-European level with a program called Rare!Together.<sup>65</sup> The aim is that newly formed patient organizations will receive advice from a mentor with extensive experience in setting up and running patient organizations. Two patient groups – congenital heart disease and hereditary spastic paraplegia – have been selected to start the program.<sup>66</sup> EURORDIS, however, does not provide funding, so there is still the issue of fundraising. The more active patient advocacy groups are addressing such issues as local access to treatment (the postal code lottery)<sup>67</sup>; other groups may also adopt this approach and lobby for better access to drugs.

### Workshops

European patient groups could take as an example the US Alpha-1 Foundation. Since its inception, the Foundation has fostered collaborations with investigators throughout the United States and Europe, working closely with the NIH and the FDA. Among its activities are NIH-funded twice-yearly workshops, set up to consider specific topics, such as the identification of biomarkers. Another example is the American Thoracic Society (ATS) Public Advisory Roundtable. During the annual International Conferences of the ATS, patients can recount their experiences at this forum. There is the potential for similar activities in Europe under the auspices of a European organization; for example, funding for workshops could be sought from the European Research Council, and a European Respiratory Society-sponsored workshop organized that includes patient advocacy groups. Such initiatives could help to set up a coalition of respiratory disease leaders from the patient community.

The EMA organized a workshop on the development of therapy for Duchenne muscular dystrophy, and the requirements of regulatory agencies were addressed at this meeting. The possibility of holding a workshop on specific aspects of a rare lung disease could be explored with the EMA. The EMA has recently created a respiratory disease drafting group whose tasks include the drafting of guidelines and providing support for scientific advice.

### EU Task Force

Finally, a major goal would be the formation of an EU Task Force, composed of physicians and respiratory experts from various countries, as well as officers of the EMA, to consider the treatment of rare lung diseases. This task force would be a permanent group meeting on a regular basis and would ultimately lead to the publication of a consensus document.

Our perspectives are summarized in [Table 4](#).

**Table 4** Perspectives to improve the access to therapies for rare lung diseases in Europe.

- Greater collaboration and communication at all levels, including all stakeholders (patient groups, physicians, drug developers, regulators, payers)
- Integration across countries and continents
- New clinical trial protocols can be developed and agreement reached on appropriate outcome measures
- Better organization of patients in Europe to improve patient empowerment and raise more interest in rare lung diseases
- Raise European funding to support initiatives, such as regular workshops
- ERS-sponsored course/workshop dedicated to rare lung diseases that includes patient advocacy groups
- Use the limited number of patients wisely; learn from the model of the Rare Lung Diseases Consortium in the United States
- Set up an expert group of respiratory physicians within the EMA
- Create and strengthen European task forces on rare diseases aimed at writing consensus documents

## Conclusions

Orphan drug legislation encourages research into rare lung conditions; however, there are many challenges in Europe for the development of new treatments for these diseases. The United States led the way in the introduction of such legislation and provided the impetus for European Orphan Medicine Products Regulation. Further lessons can be learned from the United States in raising awareness and improving the evaluation of therapies for rare lung diseases. Patients with rare diseases deserve the same level of evidence as those with common diseases whenever this is possible. However, this level of expectation should not preclude the approval of drugs likely to be of benefit but where the criteria required for common conditions cannot be met. It is important, therefore, to achieve the right balance and ensure that should an effective or potentially effective therapy become available, its development is progressed and patient access to this treatment is not delayed.

There should be increased communication with the EMA involving clinicians, researchers, and drug developers, and full use must be made of the scientific advice available. If pharmaceutical companies interact with the EMA early on in the development of their products then the prospects of a positive outcome improve. Better clinical trial protocols can be developed and agreement reached on appropriate outcome measures. Insufficient financial support is a major hurdle, both at a national and pan-European governmental level. There is a clear need for more research grants and the provision of funds for maintenance of registries, as well as tax exemptions for the research and development of new orphan medicinal products. Many processes are also hampered by limited communication between all interested parties; patients, researchers, clinicians, developers of drugs, and payers need to interact more, not just at

a national or even European level. An alignment of requirements for the licensing and reimbursement of drugs would also be a huge step forward.

Patients interested in participating in clinical research can be located through registry initiatives and then through clinical networks and alliances. Patients are a valuable resource but are not solely the participants in clinical trials and the individuals who consult physicians. They have the potential to exert considerable pressure on researchers, the regulatory authorities, and governments to increase attention to rare lung diseases and stimulate the greater availability of therapies to provide them with a better quality of life.

## Conflicts of interest

Maurizio Luisetti has received speaker fees from GSK, Kedrion, Nycomed, and Merck, Sharp & Dohme, consulting fees from Boehringer Ingelheim, GSK, and Nycomed, and grant support from Talecris.

Ian Balfour-Lynn has no conflict of interest to declare.

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