



## Alpha-1 in the European Union Expert Recommendations

Recommendations of the Alpha-1 Expert Group  
Initiated and chaired by Members of the European Parliament.







## Foreword

Alpha-1 antitrypsin deficiency (Alpha-1) is a rare genetic condition that can cause ultra-rare cases of pulmonary emphysema, chronic liver diseases or panniculitis, a serious skin condition. It is known as the “Viking disease” due to its origin in Sweden, but it affects patients all over the EU. There is currently no cure for Alpha-1, but appropriate treatment and a high standard of clinical care can save patients from having to undergo heavy medical interventions such as organ transplantation.

Patients lack information on treatment options, and their access to effective therapy is often restricted. This is often related to individual Member States pointing to a perceived lack of clinical data, which cannot be produced due to the rarity of the condition. This has created obvious health inequalities, depending on the country patients are affiliated with, on the region where they live and, in some cases, on the date when their condition was diagnosed.

The European Union (EU) has prioritised the needs of patients suffering from rare diseases or conditions for over a decade now. Since 2009, additional key policies that should have addressed the issues of patients suffering from Alpha-1 have been adopted. EU legislation was passed on organ transplantation and on improved cross-border access to treatment and care, notably for patients suffering from rare or ultra-rare conditions. Important initiatives are still being developed, such as the adoption of national plans for rare diseases, legislation on information to patients, the revision of the Clinical Trials Directive and the identification of health inequalities in Europe.

The European Union has successfully developed policies and legislation on rare diseases and orphan medicinal products. These have resulted in more favourable national policies for patients whose needs were previously neglected and have led to the development of therapies treating their diseases. This success illustrates how EU legislation can have a direct positive impact on patients’ lives, but if patients cannot eventually access therapies that have been developed for their condition, efforts at EU and national level would lose their *raison d’être*.

The lack of understanding of Alpha-1 is one of the main reasons why Alpha-1 patients’ needs are still widely ignored. This document, which has been produced with contributions from some of the most prominent experts in the field, highlights Policy Recommendations that bring pragmatic solutions to existing issues and provides policy and decision-makers with a roadmap for ensuring patients’ access to the treatments and care they need.

This report will therefore outline the following items:

- A common understanding of Alpha-1 as a rare disease
- An analysis of current Policy and Legislation with direct impact on Alpha-1
- Recommendations for concrete policy improvements addressing the needs of Alpha-1 patients.

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### I. Recommendations

1. Member States and the EU must ensure appropriate recognition of Alpha-1 as a rare condition and Alpha-1 related emphysema as a specific ultra-rare disease.
2. Member States must raise awareness of Alpha-1 in the medical community and the general public in order to ensure a timely and fast diagnosis that will increase the chances of preventing irreversible tissue damage.
3. Member States must prevent and put an end to health inequalities affecting patients suffering from Alpha-1 and other rare diseases.
4. The EU must ensure that all Member States respect the EU definition of rare diseases.
5. Future EU and national policies with a relevance to rare and ultra-rare diseases should respect the spirit and the letter of existing EU policies addressing these issues.
6. EU Member States should ensure that policies and legislation in the field of rare diseases are not jeopardised by cost containment measures. Such measures should not have a negative impact on areas where long-term investments are needed to make a difference, such as public health.
7. Each EU Member State should develop and implement ambitious national plans or strategies on rare diseases, as recommended by the Council of the European Union's recommendations on action in the field of rare diseases.
8. Member States should ensure that Alpha-1 patients can access the treatments they need, notably when implementing the Cross-Border Healthcare Directive.
9. The EU should work towards better standardisation of treatments and devices supporting breathing to ensure that patients can enjoy their freedom of circulation.
10. The EU should develop an ambitious strategy on information to patients so that all patients can make informed choices about their treatment options.
11. Member States should ensure that the optimal guidelines for the treatment of Alpha-1 are implemented in order to reduce the need for lung transplants and thereby contribute to increasing the availability of lungs for transplantation.
12. Patients should be given the possibility to decide with their physician whether and when they should undergo organ transplantation.
13. Member States, national HTA experts and policy makers must acknowledge the reality of clinical research on therapies for rare and ultra-rare conditions and accept alternative evidence validated by experts. Gold standard randomised, placebo-controlled and double-blind clinical trials with a sufficient number of patients are impossible to conduct and unethical. Physicians treating Alpha-1 patients should be asked about effectiveness when a therapy is being assessed.
14. The EU and Member States must provide support to Alpha-1 expert groups, including academic and patients' groups, in order to pool expertise and build on it.
15. The EU and Member States should support the creation and the management of Alpha-1 patient registries and seek the advice of Alpha-1 experts who are already running them.

## II. What is Alpha-1?

### 1. A treatable rare condition

Alpha-1 antitrypsin deficiency (Alpha-1) is a potentially life-threatening rare genetic condition and, however treatable, affects approximately 4 in 10,000 people in the EU<sup>1</sup>. It can cause diseases that can be considered as “ultra-rare” in the sense that it is estimated that they affect less than 1 in 50,000 persons across the EU. Alpha-1 is caused by the lack of a protective protein produced naturally by the human body. It can cause severe debilitating diseases such as chronic liver disease but, most notably, pulmonary emphysema. This is a life-threatening disease, irreversibly destroying the tissues supporting the function of the lungs and therefore causing severe shortness of breath, which usually prevents patients from working or taking part in simple physical activities.

Alpha-1 related emphysema cannot be cured yet but its progression can be slowed down considerably. If the condition is diagnosed at an early stage and is appropriately managed, patients have the possibility to lead a normal and productive life. If not, patients will have a poor quality of life, some may need to undergo lung transplantation and have the risk of an early death. Emphysema when not related to Alpha-1 usually affects heavy smokers. Cancer prevention has been a priority for the EU for several years and efforts are being made to ensure that all lung cancer patients can access the highest standards of treatment. Unfortunately, patients are denied Alpha-1 antitrypsin augmentation therapy in most Member States, even though the disease that affected patients develop are of genetic origin. Due to the little attention that patients with rare inherited conditions receive, a correct diagnosis is often only made after a long delay and patients receive insufficient treatment. Early screening measures would enable a reduction in the progression of Alpha-1 related diseases by adopting appropriate therapies.

International expert treatment guidelines indicate that optimal management of Alpha-1 should include strict lifestyle standards, including smoking cessation, exercise, diet and symptomatic treatment. In some ultra-rare cases, patients whose lungs deteriorate particularly rapidly (known as “fast decliners”) in spite of strict lifestyle standards and symptomatic treatment should receive Alpha-1 augmentation therapy. Neonatal screening allows early diagnosis of patients which means that these measures can be taken promptly and as such can be cost effective in terms of prevention of eventual healthcare costs. This therapy increases the concentration of the deficient protective protein in the blood and lungs to prevent rapid lung deterioration. Patients generally receive symptomatic treatments only. These temporarily alleviate the symptoms but are not sufficient to halt emphysema progression. Two main issues stand in the way of improving this situation:

- Patients are not given the possibility to take preventive measures due to the lack of policy initiatives making an early diagnosis possible. Such initiatives should typically include programmes to raise awareness of Alpha-1 in the medical community and the general public, and appropriate recognition of Alpha-1 as a rare genetic condition that can lead to ultra-rare diseases.
- In the EU, “fast decliners” requiring augmentation therapy often struggle to receive it when they need it, although it is the only therapy available for their specific condition. This is surprising since estimates suggest that augmentation therapy reduces mortality by about a third<sup>2</sup>, and studies indicate that it reduces the loss of lung tissue by 33-50 percent<sup>3</sup>. Augmentation therapy is available and has been used in the United States and Canada since 1988. By 2011, three products were approved by the FDA, the United States’ agency regulating medicinal products. Augmentation therapy is authorised in the EU but it is only readily available in a few Member States such as Germany (since 1989), Austria, France, Italy, Spain and Portugal.

#### Strict lifestyle standards

- Smoking cessation
- Diet
- Physical exercise

#### Symptomatic treatment

- With regular review

#### Augmentation therapy

- For patients with a rapidly declining lung function
- Young patients have a higher chance of benefitting from therapy

### 2. A condition neglected in several Member States

Alpha-1 patients struggle seven years on average before receiving an accurate diagnosis<sup>4</sup>, as Alpha-1 is often misdiagnosed as “regular” smoking-induced chronic obstructive pulmonary disease (COPD) or asthma. In addition, several Member States do not recognise the specificity of Alpha-1 and bundle it together with regular COPD, without recognising its specificities, genetic origin and the fact that it is caused by the lack of a natural protective protein as is also the case in other rare diseases, such as Fabry’s disease.

A case in point is the United Kingdom, where the disease is not widely recognised as a rare disease even though the country is home to the biggest physician-led patients’ registry in Europe. NICE, the National Institute for Health and Clinical Excellence, does not differentiate between Alpha-1 and smoking-induced COPD or asthma. As a result, patients are not granted access to optimum treatment and often receive minimal information about their condition and how to prevent its life-threatening consequences. Poor awareness results in late diagnosis or no diagnosis at all, which far too often leads to irreversible, serious lung damage.

The treatment provided to Alpha-1 patients also varies from one country to another<sup>5</sup> and regional differences in access to augmentation therapy heavily discriminate against patients who are “fast decliners”:

- Access to treatment was not de facto made possible in Sweden and Denmark despite the fact that therapies had received a marketing authorisation. After denying patients optimal treatment for years, Sweden recently changed its relevant guidelines which now recommend augmentation therapy for fast declining patients<sup>6</sup>. Denmark, on the other hand, has still not changed its position even though several experts and Members of the Parliament (Folketinget) have been raising the issue with the Government for years.
- Augmentation therapy was available and almost completely reimbursed in Belgium until mid-2010. 26 patients received it then, and some were treated with product imported from Germany. In 2010, the National Institute for Disease and Invalidity Insurance (INAMI/RIZIV) recommended continuing to reimburse augmentation therapy only for those patients who were already receiving it, but not for any additional patients who are in need of this treatment, thus barring them from accessing the same level of care and creating a clear case of inequality between citizens within an EU Member State. Patients who were not consulted and Alpha-1 medical experts who were heard but whose opinion was not taken into account prior to this decision still struggle to understand such a recommendation and the ministerial decision to implement it.
- Member States and the EU must ensure appropriate recognition of Alpha-1 as a rare condition and Alpha-1 related emphysema as a specific ultra-rare disease.
- Member States must raise awareness of Alpha-1 in the medical community and the general public in order to ensure a timely diagnosis that will increase the chances of preventing irreversible tissue damage.
- Member States must prevent and put an end to health inequalities affecting patients suffering from Alpha-1 and other rare diseases.



### III. Alpha-1 and European Union policies for rare diseases: missed opportunities?

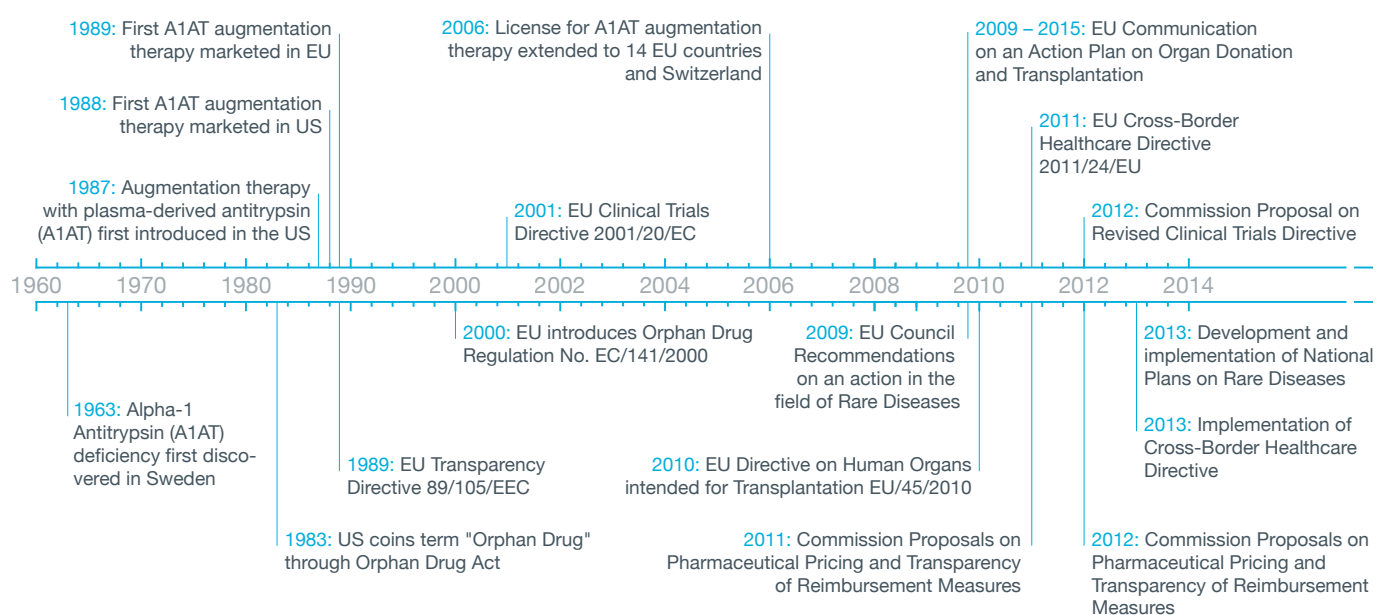
#### 1. The unexpected negative consequences of the OMP regulation on Alpha-1

The European Union has successfully developed policies and legislation on rare diseases and orphan medicinal products since the European Regulation EC/141/2000 on Orphan Medicinal Products (OMP)<sup>7</sup> was adopted which introduced the definition of rare diseases. These policy initiatives have resulted in more favourable national policies for patients whose needs were previously neglected due to the low prevalence of their condition. This success illustrates how EU legislation can have a direct positive impact on patients' lives.

However, this has not yet fully benefited the Alpha-1 community. Therapies which were developed prior to the OMP Regulation could not get an official OMP designation, even though they were treating rare diseases or conditions. Between 1996 and 1999, the European Medicines Agency (EMA) provided support for eight centrally authorised medicinal products which were indicated for patients with rare diseases but were authorised prior to the OMP Regulation<sup>8</sup>. In order to support these "already existing orphan-therapies", the EMA created an ad-hoc designation ("Orphan-like products") and granted fee exemptions to marketing authorisation holders<sup>9</sup>. These products were approved by the EMA<sup>10</sup> through the centralised procedure. Such measures could be explained by the Agency's desire to respect the spirit of the upcoming Regulation 141/2000, which was not retroactive and did not foresee any "Orphan-like designation". This ad-hoc designation helped some therapies in receiving appropriate recognition and support as their specificities were acknowledged.

Alpha-1 augmentation therapy was not granted such support because it had been introduced into the market more than 10 years prior to the Regulation, and additional financial support from the EMA was not sought. Later, this contributed to a misunderstanding of Alpha-1. Some decision makers questioned the rarity of the disease and stopped granting appropriate attention to existing treatment options. They argued that the lack of an official OMP designation necessarily meant that Alpha-1 augmentation therapy should be treated in the same way as therapies for more "common" diseases, and hence an unrealistic level of clinical evidence demonstrating the benefits of this therapy is expected.

As a consequence, patients in Europe still struggle to get appropriate recognition of their condition and their specific needs. This leads to inequalities in healthcare, which clearly breach the spirit and the letter of the rare disease policies initiated by the EU. CVZ, the Dutch Health Care Insurance Board, still refuses to consider Alpha-1 augmentation therapy products as medicinal products treating a rare disease, a decision that predates the spirit of Regulation 141/2000. While the tasks of CVZ include providing advice and implementing the Dutch statutory health insurance, based on financial, societal and care related considerations, the needs of Dutch Alpha-1 patients are ignored.



## 2. The fragmented implementation of the EU definition on rare diseases

The definition of rare diseases has been introduced de facto in the Regulation 141/2000<sup>11</sup> and affirmed in the Directive on Cross-Border Healthcare<sup>12</sup>. The European Union (EU) considers diseases to be rare when they affect no more than 5 per 10,000 persons in the EU.

Any definition based on prevalence necessarily has limitations but this one has been fit for purpose considering the greater attention that is now granted to rare diseases and most Orphan Medicinal Products (OMP). The European Commission is aware of this and is constantly aiming to improve its approach and communication with regards to rare diseases. Europe's challenges<sup>13</sup> called for a refined definition on rare diseases.

The Council Recommendations of 2009<sup>14</sup> that followed the Commission Communication requested a more coherent and coordinated approach to rare diseases through the development and implementation of National Plans on rare diseases by 2013. These should pave the way for ambitious rare diseases policies, starting with an appropriate common definition and recognition of rare diseases in order to ensure the appropriate circulation of information, the exchange of best practice and optimal management of rare diseases.

Nonetheless, some Member States are still reluctant to apply the main EU definition of rare diseases that was first introduced in 2000. In several countries, the fact that Alpha-1 is not recognised as a rare condition that can potentially lead to ultra-rare diseases often serves as an excuse for cost containment measures, barring patients' access to the therapies and targeted care they need.

There is no common EU definition which has been implemented in all EU Member States. Sweden considers diseases to be rare in the country if they affect no more than 1 per 10,000 people<sup>15</sup>; Denmark considers diseases to be rare in the country if they affect no more than 2 per 10,000 persons<sup>16</sup>. In addition, Alpha-1 is sometimes not recognised as a rare condition because Member States categorise it as smoking-induced COPD<sup>17</sup>. Alternatively, there is an erroneous perception of its prevalence across Member States. Some decision makers with little experience of Alpha-1 actually confuse the prevalence of the genetic predisposition for Alpha-1 with the actual manifestations of the diseases it can cause, which are even rarer. Within the pool of patients with the genetic condition Alpha-1, the group of patients whose lungs deteriorate the fastest and who need augmentation therapy represents a very small and defined sub-group (the "fast decliners", see above). For this reason, Alpha-1 related emphysema is to be considered ultra-rare. This situation can only be addressed if Member States appreciate that the rarity of Alpha-1 makes it hard to understand and study the disease.

- The EU must ensure that all Member States respect the EU definition of rare diseases.
- Future EU and national policies with a relevance to rare and ultra-rare diseases should respect the spirit and the letter of existing EU policies addressing these issues.
- EU Member States should ensure that policies and legislation in the field of rare diseases are not jeopardised by cost containment measures. Such measures should not have a negative impact on areas where long-term investments are needed to make a difference, such as public health.
- Each EU Member State should develop and implement ambitious national plans or strategies on rare diseases, as recommended by the Council of the European Union's recommendations on action in the field of rare diseases.

### 3. Patients are denied freedom of circulation and free choice of treatment

The EU Cross-Border Healthcare Directive<sup>18</sup> initially intended to regulate access to healthcare by European patients beyond the borders of their Member State of affiliation. This Directive at last introduced and developed a number of broader concepts and policies that were not mentioned in legislative texts or policy initiatives before. While the European Union is still developing its legislation on information to patients, this Directive already enhances patients' rights to make informed choices and lays the ground for better access to early diagnosis and optimum treatment and care.

Among other measures, the establishment of European Rare Diseases Networks is encouraged in order to ensure that expertise reaches the patient. Indeed, Member States are required to request scientific advice if they do not have the expertise needed to assess an individual case for treatment, or when such assessment is inconclusive. Furthermore, patients suffering from a rare disease should have the possibility to seek treatment and care abroad, when a specific treatment is not available in their Member State of affiliation, which is their so-called 'home Member State' where they are resident, but is available in another. However, patients will not be able to automatically do so under the EU Cross-Border Healthcare Directive once it is fully implemented by all EU Member States in October 2013. They would need 'prior authorisation' first, which is authorisation from their country of residence. However, with 'prior authorisation' it would be possible for a patient using new 'rights' under the EU Cross-Border Healthcare to receive any medicinal product authorised for marketing in the Member State of treatment<sup>19</sup>, which is the country the patient would go to in order to receive such healthcare. The patient has this right, even if the medicinal product that he or she seeks is not authorised for marketing in their Member State of affiliation. It should be made clear that the Directive recognises that nothing should oblige the Member State of affiliation to reimburse a patient's treatment costs if the patient would not be entitled to the medicinal product in their Member State of affiliation. The Directive further recognises the principle of an EU patients' right to be treated abroad in order to have access to different methods of treatment than the ones provided in their Member State of affiliation<sup>20</sup>, allowing for patients to receive all relevant information in order to make an informed choice concerning their treatment options<sup>21</sup>.

As has already been outlined, this ground-breaking legislation will be implemented by October 2013 by each EU Member State. Alpha-1 patients hope that this will contribute to securing better access to the therapies and care they need, when and where they need them. Nonetheless, this new legislation may shift the problem as Member States keep the right to limit access to reimbursement on several grounds, including the desire to control costs<sup>22</sup>. While this legislation will make access to Alpha-1 augmentation treatment virtually possible for those patients gaining prior authorisation from their Member State of affiliation, patients coming from Member States not widely recognising Alpha-1 as a rare disease may not be reimbursed the costs for the supplementary oxygen and augmentation therapy affected patients need. This would highlight the fact that some Alpha-1 patients will de facto be denied access to the treatment they need. This illustrates how much of an impact national policy makers' decisions can have on the lives of Alpha-1 patients.

The legal embodiment of patients' rights reflected in this Directive represents an important step ahead, especially with regards to diagnosis and treatment. However, Member States need to address the issues faced by patients so that they can lead a life as normal as possible. Many patients do not know about their treatment options because information is scarce and not always provided. Others cannot enjoy the simple freedom of circulation within the EU, one of the main rights introduced by the EU Cross-Border Healthcare Directive. The cheap and seemingly simple refilling of the oxygen tank that many patients need becomes a dreadfully complicated operation due to the lack of standardised connectors and the non-recognition of prescriptions issued abroad. Patients have therefore very limited autonomy and must choose their 'destination of travel' according to their possibility to access treatment, which may even differ across the city they live in.

- Member States should ensure that Alpha-1 patients can access the treatments they need, notably when implementing the Cross-Border Healthcare Directive.
- The EU should work towards better standardisation of treatments and devices supporting breathing to ensure that patients can enjoy their freedom of circulation.
- The EU should develop an ambitious strategy on information to patients so that all patients can make informed choices about their treatment options.

#### 4. The cost of not complying with the EU Strategy on Organs for Transplantation

Patients with Alpha-1 who do not receive optimal treatment and care have a higher likelihood of requiring lung transplantation. In Sweden, 19% of lung transplantations are performed in Alpha-1 patients<sup>23</sup>. Transplantations are highly invasive, complicated operations that bear significant risks, including organ rejection as the EU Directive on organs for human transplant<sup>24</sup> re-emphasised. In addition to the risk of rejecting a transplanted organ, the transmission of blood-borne viruses cannot be excluded.

Alpha-1 patients also have to cope with the uncertainty of whether they will receive a life-saving organ on time. Organs for transplantation are very scarce. In its Communication on an Action Plan on Organ Donation and Transplantation (2009-2015), the European Commission noted that “the demand for organs exceeds the number of available organs in all Member States” and that this demand is increasing faster than organ donation rates<sup>25</sup>. As a result, in 2007 there were more than 56,000 patients waiting for a suitable donor organ within the European Union<sup>26</sup>.

Patients therefore end up on waiting lists before they can hope to receive a suitable organ. It can be months or years during which they live with an extremely poor quality of life as they cannot breathe normally. The EU developed legislation and policies on organs for transplantation in order to increase their safety and their availability. Member States, who started exchanging best practices in this regard, should therefore ensure that optimal treatment guidelines are respected as this would contribute to decreasing the demand for organs for transplantation. It would also protect patients from the risks related to transplantation and save some Alpha-1 patients from a highly invasive, traumatic and dangerous surgical procedure.

- Member States should ensure that the optimal guidelines for the treatment of Alpha-1 are implemented in order to reduce the need for lung transplants and thereby contribute to increasing the availability of lungs for transplantation.
- Patients should be given the possibility to decide with their physician, whether and when they can undergo organ transplantation.

## 5. The neglected clinical evidence and expertise

The Clinical Trials Directive was approved shortly after the first EU policy initiatives on rare diseases, and it did not foresee the specific challenges posed in this field. The Directive's framework is not adapted to diseases with low or ultra-low prevalence, such as Alpha-1 related emphysema. Due to their lack of expertise in Alpha-1, several Member States do not accept the available evidence supporting the efficacy and the use of Alpha-1 augmentation therapy. These Member States de facto ask for clinical data that cannot be produced due to the low prevalence of Alpha-1 related emphysema. This leads some Member States to argue that there is no effective treatment, ignoring the needs of patients suffering from this condition.

Alpha-1 experts are the first to acknowledge that no conclusive placebo-controlled trial has been performed to date to confirm the therapeutic benefits in augmentation therapy according with the same statistical significance required for more common diseases, which is what some Member States are calling for. However, there is wealth of data from observational studies and patient registries available, which could be further developed and should be accepted as sufficient proof of evidence. The definitive "gold-standard" clinical trial that some Member States request simply can not be performed. Depending on the primary outcome parameter, such a trial would require up to 500 patients<sup>27</sup>, with each patient receiving a weekly infusion for three years. The combination of issues posed by the need to recruit a high number of patients in such a rare disease, the need to ensure full compliance with a complex treatment regimen and a long study duration makes such a trial technically impossible. The pressure such a trial would put on patients requested to travel to the research facilities every week is huge. In addition, the weekly intravenous administration of a placebo in patients needing the active treatment would be unethical, especially if one considers that patients in several countries such as the United States, France, Germany, Italy or Spain have been receiving augmentation therapy for up to 21 years.

Augmentation therapy has one of the strongest evidence bases in the field of rare diseases when taking into account all available data from observational studies in existing registries<sup>28, 29, 30</sup> concordant results from clinical trials<sup>31, 32</sup>, and combined analyses of available studies<sup>33</sup>, and the fact that this treatment has been used safely for more than two decades. Based on the available data and expert opinions<sup>34</sup>, recommendations for the use of augmentation therapy have been issued by various national and international professional bodies, such as the European Respiratory Society and the American Thoracic Society<sup>35</sup>.

Since Alpha-1 related emphysema is a rare disease, expertise is scarce and only a small number of highly specialised physicians understand its complexity<sup>36</sup>. The interpretation of the clinical data therefore requires the involvement of these experts as they have the necessary expertise to judge the clinical data and therapeutic value of various treatment options. Only experts with sufficient experience have the ability to evaluate and interpret the clinical features of a rare disease and can determine the clinical relevance and therapeutic value of a particular treatment in balance with other therapeutic options and existing needs in daily clinical practice<sup>37</sup>.

Several countries, such as the United Kingdom and Belgium, have physician-led registries, but national decision makers do not seem to fully realise their value. Registries can help to understand the disease and allow a better assessment of therapeutic approaches.

- Member States, national HTA experts and policy makers must acknowledge the reality of clinical research on therapies for rare and ultra-rare conditions and accept alternative evidence validated by experts. Gold standard randomised, placebo-controlled and double-blind clinical trials with a sufficient number of patients are impossible to conduct and unethical. Physicians treating Alpha-1 patients should be asked by decision makers about effectiveness when a therapy is being assessed.
- The EU and Member States must provide support to Alpha-1 expert groups, including academic and patient groups, in order to pool expertise and build on it.
- The EU and Member States should support the creation and management of Alpha-1 patient registries and seek the advice of Alpha-1 experts who are already running them.

## IV. Who should get tested for Alpha-1?

Genetic testing is recommended or should be discussed in specific cases only. Early detection allows the identification of the few patients who need augmentation therapy treatment in a timely fashion, hence reducing costs and optimising health outcome. Genetic testing is recommended for:

- Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators. Genetic testing should be discussed and could reasonably be accepted or declined in populations where the prevalence of AAT (Alpha-1 antitrypsin) deficiency is known to be much lower than the general North American and Northern European prevalence for diagnostic testing.
- Individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly.
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (e.g., cigarette smoking, occupational exposure)
- Adults with necrotizing panniculitis.
- Siblings of an individual with AAT deficiency.

Genetic testing should be discussed and could reasonably be accepted or declined for:

- Adults with bronchiectasis without evident etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with C-ANCA-positive (anti-proteinase 3-positive) vasculitis
- Individuals with a family history of COPD or liver disease not known to be attributed to AAT deficiency
- Distant relatives of an individual who is homozygous for AAT deficiency
- Offspring or parents of an individual with homozygous AAT deficiency
- Siblings, offspring, parents, or distant relatives of an individual who is heterozygous for AAT deficiency
- Individuals at high risk of having AAT deficiency-related diseases
- Individuals who are not at risk themselves of having AAT deficiency but who are partners of individuals who are homozygous or heterozygous for AAT deficiency

Population screening may apply in countries satisfying three conditions:

1. the prevalence of AAT deficiency is high (about 1/1500 or more)
2. smoking is prevalent and
3. adequate counselling services are available.

*American Thoracic Society / European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency. American Journal of Respiratory and Critical Care Medicine. 2003;168:818-900.*

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- <sup>5</sup> Expert Institute for Clinical Relevance (EICR). Impartial expert report on the Treatment approach of Alpha1- Antitrypsin Deficiency (Alpha-1) [Expert Report AATD, dd. 31-01-2011].
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- <sup>7</sup> European Parliament and Council Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products [OJ L 18, 22.1.2000, pp.1-5]
- <sup>8</sup> European Medicines Agency. Status report on the implementation of the European Parliament legislation on Orphan Medicinal Products. 30 March, 2011 [EMA 7381/01].
- <sup>9</sup> €1,000,000 in fee exemptions were granted between 1996 and 2000. An additional €480,000 in fee exemptions (annual fees and variations fees) was expected in 2001.
- <sup>10</sup> Central authorisation procedure through the Committee for Medicinal Products for Human Use (CHMP), as the Committee for Orphan Medicinal Products (COMP) did not yet exist at that time.
- <sup>11</sup> European Parliament and Council Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products [OJ L 18, 22.1.2000, pp.1-5].
- <sup>12</sup> Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare [OJ L 88, 4.4.2011, pp. 45-65].
- <sup>13</sup> Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenge. 11 November 2008 [COM(2008) 679 final].
- <sup>14</sup> Council recommendation of 8 June 2009 on an action in the field of rare diseases [OJ 2009/C 151/02].
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- <sup>17</sup> Please refer to Chapter II
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