Expert Recommendations for better **Management of Primary Immunodeficiency** (PID)

Recommendations of the PID Expert group chaired by Jorgo Chatzimarkakis MEP

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EUROPÄISCHES PARLAMENT

Jorgo Chatzimarkakis

MEMBER OF THE EUROPEAN PARLIAMENT

Primary Immunodeficiency (PID) consists of a group of **rare disorders, mostly genetic in nature,** that share the similarity that a part of the immune system is missing or does not function correctly. The symptoms include a **markedly increased vulnerability to serious illness and infection, organ damage and the immune system also attacking the body's own tissues and cells.**
Primary Immunodeficiency is largely treated with therapies derived from human plasma, and in the most severe forms, replacement of stem cells. The rarity of these disorders often means **that information on treatment options and access to care is not optimal.** Unnecessary healthcare and associated costs are incurred due to the use of expensive medication (e. g. antibiotics/antifungals), a higher rate of hospitalisation, increased number of missed days of school and work and increased infection.

There have been previous initiatives at EU level on the topic of Primary Immunodeficiency, for example a European Union PID Consensus Conference in Langen, Germany at the Paul-Ehrlich Institut (supported by the European Commission) in 2006 and a European Parliament lunch debate on Rare Plasma Protein Disorders that I co-hosted with my colleague Miroslav Mikolasik MEP in December 2008. These activities have proven excellent at raising awareness of PID at EU level, and now we are looking to build on these actions with a more **targeted and long-lasting initiative that can make a tangible difference to patients' lives.**

In June 2009 the European Council adopted Recommendations on Rare Diseases, incorporating a number of commitments to tackle rare conditions and improve patients' lives. The Council Recommendations, while encouraging, can of course not take into account the specialist steps needed to tackle specific conditions or disease subgroups within the broad range of Rare Diseases. That is why I decided to develop the EU Expert Group on Primary Immunodeficiency (PID) made up of expert patients' organisations, physicians, EU level policy makers, representatives from Member State regulatory bodies and other relevant stakeholders.

The aim of this Expert Group is to provide the **appropriate basis for future decision making** for this complex yet specifically defined Rare Disease area. This Recommendations Paper is an excellent start that I hope will lead to a **better management of care for PID** at EU and Member State level. This is an issue that I care about, and would be most satisfied to see progress on in the EU in the interests of the people who are suffering from it. I firmly believe that patients can benefit from actions taken at both European and Member State level, and I hope that this Expert Paper can make a positive contribution.

I will take this opportunity to give thanks for the dedication of all the Experts involved in the drafting of this Recommendations Paper. Their work together on this paper is a perfect example of how all voices can and should be heard in providing guidance for policy making. I am determined to take forward their views in the interests of patients with Primary Immunodeficiency in the European Union.

Jorgo Chatzimarkakis
Member of the European Parliament

1. WHAT IS PRIMARY IMMUNODEFICIENCY?

Primary Immunodeficiency (PID) consists of a group of genetic conditions that affect the efficient working of the body's immune system. To date there are 200-250 specific conditions identified. Primary Immunodeficiency leaves the patient vulnerable not only to dangerous infections but in certain diseases also to inflammatory and malignant diseases. **Babies born with the most severe types of PID would be expected to live a maximum of six months if left untreated or treated incorrectly.**

What are the symptoms of PID?
• Infection with uncommon agents and/or at unusual anatomical sites
• Infants have difficulty in gaining weight and height
• Unusually frequent infections of the ear, nose and throat
• Recurrent bacterial, fungal and viral infections
• Recurrent pneumonias and pulmonary complications are common
• Antibiotics not effective in tackling infections
• Recurrent abscesses of skin and other organs
• Family history of PID

Current diagnosis levels suggest that around **1 in 8-10,000 people have a genetic primary immunodeficiency** that significantly affects their health.

In a person with a working immune system, the body recognises pathogens and responds with the production of immune cells and antibodies against that organism. The pathogen can then be eliminated, and the immune system 'remembers' the threat and can respond more efficiently to the same pathogen in future, so preventing repeat infections. **People with PID are missing one or more of the vital weapons the body has against infection.** "Deficiencies in immunity can vary in severity, depending on whether one or several parts of the immune system are non-functional"[1].

PID is a treatable Rare Disease
• Patients can be treated with immunoglobulin (IG) therapies, which replace or supplement the ineffective antibodies that the patient produces
• These complex medicines are derived from donated human plasma. The therapy is either infused into the blood (intravenously) or into the layer of fat just below the skin (subcutaneously)
• PID patients are able to live a normal and productive life given the necessary amount of therapy
• Other treatments such as antivirals, antibiotics and antifungals, granulocyte colony stimulating factor can be utilised to back up the immunoglobulin replacement therapy. The imperative for a patient is that their medical support system finds the combination best for their condition.
• In the most severe cases, bone marrow or stem cell replacement may be utilised

[1] Chapel, H and Arkwright, P.D. What Are Immunodeficiencies? (2008) – Chapter in Focus on Immunodeficiencies, Eds. Valverde, J.L and Watters, D. Pharmaceuticals Policy and Law Volume 10. p. 8

Most commonly Primary Immunodeficiency means that the patient cannot produce antibodies correctly. Antibodies, also known as immunoglobulins, are made up of proteins and are produced by specialised white blood cells in response to the presence of pathogens. The antibodies produced are specific to each threat. Antibodies bind to the part of the pathogen known as the antigen, thus marking them for removal by the immune system. In some cases the antibody can even destroy the pathogen themselves. Take this weapon away from the immune system, and pathogens are free to infect and multiply in numbers, as well as there being no immune memory to prevent re-infection.

Expert Recommendations – Primary Immunodeficiency (PID)

1. Funding research into better understanding of Primary Immunodeficiency is vital in terms of both diagnosis and management of the conditions and general understanding of the immune system. This must be done at both EU and national level.
2. Patients must be provided with the therapies that they need to live a more comfortable and productive life with a near-normal life expectancy.
3. An appropriate supply of safe plasma for immunoglobulin extraction to be collected each year, from both blood donations and plasmapheresis, in order to ensure patients can receive safe and effective blood therapies that they need.
4. General Practitioners, Pulmonary Specialists, Haemotologists, Ear Nose and Throat specialists and other physicians need to be made more aware of PID through training in medical school and awareness campaigns to ensure better diagnosis of patients.

2. PRIMARY IMMUNODEFICIENCY – THE CONTEXT IN EUROPEAN UNION RARE DISEASES POLICIES

The European Union has in recent years recognised the importance of tackling Rare Diseases, and the contribution that can be made to the lives of patients.

The first step that the European Commission took in the field was the "Programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003)"[2]. This programme, adopted by the European Parliament and European Council on 29 April 1999 aimed to improve care for patients with Rare Diseases, specifically by improving knowledge and information on conditions at EU level.

More recently, DG SANCO's mission document "Together for Health"[3], launched in October 2007 further emphasised the EU's role in addressing Rare Diseases by committing to more direct action as a matter of priority. This action came in the form of a Council Recommendation on Rare Diseases, which was released in November 2008 by the Commission and adopted by EU Member States in June 2009. The Council Recommendation calls for **further pooling of expertise, resources and knowledge between Member States and the implementation of dedicated Action Plans** to tackle rare conditions. Whilst this proposal is not mandatory or legally binding, it has been adopted by the European Parliament and European Union Member States and therefore **a commitment has been made**. The potential for EU level action on Rare Diseases to be significantly strengthened over the coming years is there.

„The very rarity of low-prevalence diseases and conditions and the lack of information, research, diagnosis, treatment and expert availability may mean that the people affected do not benefit from the health resources and services they need. Rare diseases are considered to have little impact on society as a whole, as the prevalence of each disease is low. Yet they pose serious difficulties for sufferers and their families."

- European Commission, DG SANCO[2] -

EU Actions on Primary Immunodeficiency

In light of the developments detailed above, direct actions have been taken to support patients with Primary Immunodeficiency. This represents recognition by EU institutions that addressing specific conditions, in addition to general action on Rare Diseases, allows a more focused approach to the specific challenges of each disease:

- **European Awareness Day for Primary Immunodeficiency** (23 October 2002)
- **STOA Workshop on Primary Immunodeficiency** (17 March 2004) hosted in the European Parliament by Antonios Trakatellis MEP (European Parliament rapporteur on proposal for a Council Recommendation on Rare Diseases, 2009) and Giuseppe Nistico MEP.
- **EU PID Consensus Conference**[4] (19-20 June 2006), supported by the European Commission at the Paul Ehrlich Institut in Germany. A consensus document representing the views of the European Commission, physicians, patients groups and industry was adopted.
- **European Parliament lunch debate on Rare Plasma Disorders** (January 2008) hosted by Miroslav Mikolasik MEP where 9 members of the European Parliament debated policy options for tackling rare plasma disorders such as PID.
- **European Parliament debate on European Commission Rare Diseases proposals and the implications for patients with Rare Plasma Disorders** (December 2008) hosted by Jorgo Chatzimarkakis MEP and Miroslav Mikolasik MEP. The European Commission presented their proposals, which were then debated by patient groups, physicians and parliamentarians. A Call for Action document, headed by both host MEPs and developed by the stakeholders was launched.

2 http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf
3 http://ec.europa.eu/health/ph_overview/Documents/strategy_wp_en.pdf
4 http://www.eupidconference.com/Publications_Consensus.aspx

It can be seen that the importance of tackling Rare Diseases, and specifically Primary Immunodeficiency, at EU and Member State level has been recognised throughout the undertaking of these actions. However, much more needs to be done to support patients with PID.

European Co-operation on PID
• Physician co-operate both in Europe and worldwide on research into the conditions
• Over 10,000 patients are registered in the ESID (European Society of Immunodeficiencies) database which aids better understanding of PID and patients
• ESID (European Society of Immunodeficiencies) run summer schools for physicians interested in specialising in Immunodeficiencies
• FIND-ID – A physician led program aiming to increase the number of patients being effectively found and diagnosed with their condition

The field of Primary Immunodeficiency is a perfect example of co-operation between European Union Member States to tackle a problem collectively. However, this is mostly due to the private initiative of patients associations, physicians and industry. **These excellent programs must be supported by funding and logistical support where necessary.**

Expert Recommendations – European Union action
1. The European Union must continue its promising work in supporting its citizens that suffer from Rare Diseases. However, more tangible positive impacts on patients' lives must be targeted now that the groundwork has been done.
2. Excellent private initiatives are ongoing in the field of PID – they must be supported with funds from both the EU and Member States.
3. The European Union should help Member States with less money to invest in their health-care system, by sharing knowledge and expertise from Member States who are performing well in tackling Rare Diseases.
4. PID patients' associations must be consulted by the European institutions on any legislation or communications that concerns them. This is especially important as plasma derived medicines are regulated at EU level through the EU Blood Directive.

3. LIVING WITH PRIMARY IMMUNODEFICIENCY

Primary Immunodeficiency affects the patient deeply, in many areas of their life. Especially for patients who have not yet been diagnosed, and therefore cannot understand why they are ill and cannot be treated for their condition, **PID is a devastating disorder.**

Patients often report the following factors as being major concerns:

HEALTH – BEFORE DIAGNOSIS

Infections, feeling frequently unwell, concerns about long-term health, fear of dying prematurely, frequent hospitalisations, effects on mental health, unsure of future, consequences of wrong diagnosis and ineffective treatments.

HEALTH – AFTER DIAGNOSIS

Concern at finding the right treatment for them, ability to finance the necessary treatment, worry about long term damage to their body (especially if they were not quickly diagnosed), added concern with virulent infections such as swine flu, worry that treatment may not be adequately financed in future. Even with the right treatment, the patients are prone to all sorts of infections such as pneumonia, bronchitis, gastro-intestinal diseases and their life is dominated by PID.

FAMILY

Families worried about their condition, the burden of high levels of support that are needed from family members (especially before effective diagnosis and treatment), fear that children may be born with PID, difficulty in child care, ensuring that children with PID get as regular an upbringing as possible can be hard to achieve.

FINANCIAL PLANNING

PID can lead to many days off school or work which can jeopardise a career, concerns about being able to sustainably financially support their own treatment, attaining loans, mortgages and insurance can be problematic.

PLANNING FOR THE FUTURE

Period before diagnosis can feel like being “in limbo”, difficulty in planning a career and family, concerns about being able to sustainably financially support a family in the event of worsening illness, life must be planned around treatment.

EFFECTIVENESS OF TREATMENTS

Immunological therapies are relatively new and any uncertainty about the ongoing health status of patients after treatment is of great concern to patients. Registries of therapy outcomes provide such information and help to find the most effective use of treatments.

Primary Immunodeficiency patient organisations – essential support for PID patients
• The International Patient Association for Primary Immunodeficiencies (IPOPI) (www.ipopi.org) supports patients with information and advice on their condition
• IPOPI is represented locally in several European countries
• IPOPI has joined forces with patient organisations supporting people with rare plasma disorders that face similar challenges through PLUS (Plasma Users Group).
• PLUS advocates for patients with rare plasma disorders at European level, and holds regular consultations with Members of the European Parliament and high level European Commission figures
• The Jeffrey Modell Foundation (www.info4pi.org), which operates worldwide to support better diagnosis and treatment provides invaluable support for patients in Europe to receive better care for their condition. There are JMF centres in several EU Member States.
• These organisations support patients and also contribute to better public awareness - the more the Public understands PID and the life of a PID patient, the less the nature of plasma derived medicines will be misunderstood!

Expert Recommendations – Supporting Primary Immunodeficiency patients
1. Early diagnosis of PID should be a policy priority for Member States
2. Treatment with immunoglobulin and other therapies should be available to all patients that need it.
3. The European Union must support its Member States in better diagnosing and treating patients, through financial means and by encouraging sharing of knowledge and best practice.
4. Patient associations and patient registries should be recognised and financially supported both locally and at EU level, for the value they can add to patients' lives.
5. Patients should be consulted through relevant patient associations, such as PLUS and IPOPI, whenever policies are introduced or reviewed that may affect their lives.

4. RAISING DIAGNOSIS LEVELS – GOOD PRACTICE AND CONCRETE STEPS FOR FINDING THE PATIENT

The most significant challenge that patients with a Rare Disease such as a PID will face is being diagnosed correctly and in timely fashion. Effective treatment, which exists for PID and can help patients live a full and productive life, obviously cannot begin until the condition has been correctly identified.

Diagnosing Rare Diseases is difficult for GPs because they usually do not have direct experience with seeing the condition (it is estimated only 1 in 3 will ever see a PID patient), and they will not have learned about them specifically during their training.

The main presentable symptoms of PID are regular infections and illnesses such as ear, chest and gut infections. These infections are regularly misdiagnosed, or not considered a serious enough problem by the GP to undergo more rigorous screening. Consequently, thousands of people with PID are being treated for the infections they receive rather than the underlying immune deficiency[5]. A cheap and simple blood test can detect the majority of Primary Immunodeficiencies. The more specific condition that the patient has can then be determined by specialists using genetic diagnostic tests.

The European Society for Immunological Diseases (ESID) co-ordinates a registry of Primary Immunodeficiency patients. This registry enables many insights into the care that people are receiving[5]. Patient registries such as ESID allow an overview of conditions and their nature also, and represent a vital tool in the fight against Rare Diseases. The registry shows significant disparities in levels of diagnostics available between different Member States of the EU. Late diagnosis or mis-diagnosis makes patients' lives more difficult and increases the risk of premature death. It also results in costs to society, both direct and indirect.

Early diagnosis of PID:

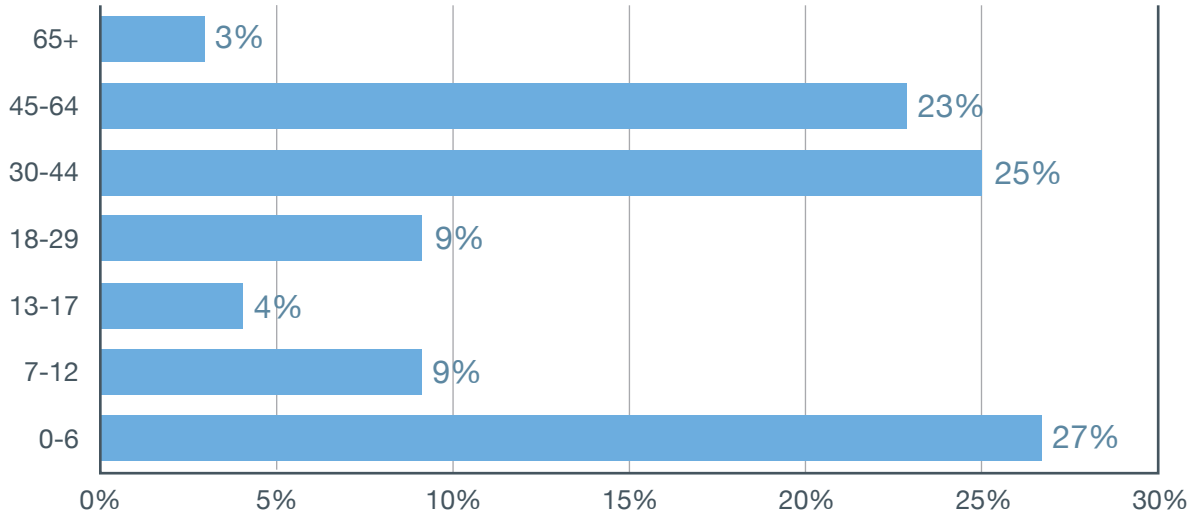
- Saves lives
- Improves health, quality of life and lifespan in identified patients through effective treatment
- Allows patients to receive effective treatment that enables them to live a productive life; working and contributing to society
- Allows cost effective treatment

Primary Immunodeficiency represents a challenge to healthcare systems because of the range of conditions (estimated between 200 and 250) and the challenges that they pose for effective treatment. There is a severe lack of expert physicians in the field of immunology, even in financially well of countries. This is a vital problem to be addressed if care is to be improved for patients.

[5] European Primary Immunodeficiencies Consensus Conference, Consensus Report and Recommendations, June 2006, page 12
Quote by Professor Reinhold Schmidt, Director of Clinical Immunology, Hannover Medical School, Germany

[6] European Society for Immunological Diseases
http://www.esid.org/esid_registry.php

Patient Age at PID Diagnosis[7]



FIND ID is a German physician driven network initiative to facilitate early identification of patients with PID and referral of patients to treatment centres for appropriate diagnosis and treatment. Its aim is to create a win/win situation for specialists and GPs in diagnosis of PID. It was instigated by a JMF (Jeffrey Modell Foundation) & PPTA (Plasma Protein Therapeutic Association) – meeting at ESID (European Society for Immunodeficiencies) in Den Bosch – Oct 2008. Founders are Prof. T Niehues (Krefeld) and Prof. V Wahn (Berlin) FIND ID is set up as a national program with an independent coordinator, including regular contact with the producers of plasma derived medicines and the German PID patient group (DSAI) monitored by a steering group of experts. It aims for development of tactical proposals in tackling Primary Immunodeficiency. The project is formally supported by several scientific Immunology and Paediatrics Societies.

Another type of project is the **French National Reference Center of Primary Immunodeficiencies** (CEREDIH) which was established in 2005 and now constitutes a nationwide network of pediatric and adult medicine departments in university medical centers. The registry comprises a total of 3,083 patients (mainly children), with an overall prevalence of 4.4 cases per 100,000 inhabitants. CEREDIH provides a basis for both further studies and activities aimed at raising the physicians‘ awareness of PIDs (notably in adults).

The **Jeffrey Modell Foundation European Reference Paper on PID**: Driving Diagnosis for Optimal Care in Europe which provides practical advice, tools and templates for PID awareness and advocacy initiatives in Europe will soon be available, which will further contribute to better diagnosis.

[7] Immune Deficiency Foundation Survey (2007) Primary Immunodeficiency Diseases In America: The Third National Survey of Patients

Education and awareness about a Rare Disease cannot start early enough. A new parent (even with no PID history) should be made aware of the possibility of such a disorder and can therefore contribute immensely to early diagnosis. Support for patients and their families can be aided by provision of services such as:

- Financial support for and implementation of newborn screening
- Pamphlets, flyers and posters with the warning signs at doctor's rooms
- Information and workshops at Nursery Schools for teachers, parents and children. Age-appropriated material i.e. painting books, easily understandable patient's stories
- Workshops for teachers and students at school. There is a stigma attached to immunodeficiency due to lack of understanding. Better knowledge of the immune system would help integration among their peers of PID patients in schools.
- Workshops for GPs and Nursing Staff
- Specialised training for medical students
- Support for GPs and Paediatricians who would be interested to specialize

It is clear that diagnosing PID patients is in the best interest of patients, for healthcare systems and society as a whole.

Expert Recommendations – Diagnosis
1. Specialised training for medical students in Clinical Immunology is practised only in a few member states. Medical Students who want to specialise in Primary Immunodeficiency, and other Rare Diseases, should be supported.
2. Knowledge about Primary Immunodeficiency should be improved through targeted information campaigns to GPs. Initiatives aiming to tackle this, such as the FIND-ID project in Germany should be recognised for their value and supported by national healthcare systems.
3. The creation and support of patient registries that can provide invaluable support for patients and also scientific insights into the make-up of PID.
4. Provision of basic blood tests for PID, and the option for GPs to refer patients for genetic tests for more specific diagnosis should be a priority.
5. Reference centres for PID should be encouraged as a means of tackling under diagnosis, and improving knowledge among the medical community about the condition.
6. Neo natal screening would improve diagnosis and hence treatment of PID.

5. THE VALUE OF IMPROVING TREATMENT FOR PATIENTS WITH TREATABLE RARE DISEASES

In the last ten years, policy makers and healthcare providers have been increasing their focus on preventing illnesses as a cost effective way of tackling public health. The European Commission Health unit DG SANCO sums up this approach as 'Health is Wealth'.

"Health is important for the wellbeing of individuals and society, but a healthy population is also a prerequisite for economic productivity and prosperity. In 2005, Healthy Life Years (HLY) was included as a Lisbon Structural Indicator, to underline that the population's life expectancy in good health – not just length of life – was a key factor for economic growth"[8].

This focus by the European Commission applies to diagnosis of PID because of the contribution to society that can be made by patients who are correctly diagnosed and can undergo treatment to help them live healthy lives. With correct diagnosis and treatment, people with PID can become net contributors rather than net receivers in a society and this is exactly what patients would like to do. This point was emphasised by members of the European Parliament (MEPs) during Parliament lunch debates on rare plasma disorders in January and December 2008. A study by the Jeffrey Modell Foundation in the United States found the following enlightening figures:

- Each undiagnosed person with an underlying Primary Immunodeficiency costs the healthcare system an average of $102,736 annually
- Each diagnosed person with an underlying Primary Immunodeficiency costs the healthcare system an average of $22,696
- The economic impact of undiagnosed Primary Immunodeficiency patients to the healthcare system in the US is therefore $80,040[9]

The viewing of healthcare budgets narrowly, i.e. treatment as just a healthcare cost rather than a social investment, avoids seeing the overall benefits to the budget and society as a whole.

It is worth emphasising that the figures are so clearly in favour of diagnosing and treating people suffering from PID because the treatments available are capable of supporting patients in living a healthy and productive life. **Primary Immunodeficiencies are in this respect very different to many other Rare Diseases in that effective treatment is already widely available, and patients can have a normal work and family life;** it is possible to be a net contributor to society with PID. This is what patients want, and we should support them to do this.

Expert Recommendations – The value of improving treatment for PID patients

1. Treatment with immunoglobulin should be available to all patients that need it. Physicians should not be restricted in prescribing immunoglobulins as and when they consider it an efficacious treatment.
2. Health systems should consider the effiency of treatment for PID, i.e. the potential for patients to contribute to society by working and paying taxes, when considering the value of Immunoglobulin treatments.
3. To ensure that PID patients can be correctly treated, EU regulation should emphasise the difference between blood and plasma. Currently there is a risk of treatment supply to patients being jeopardised by misunderstandings on the unique nature of plasma derived medicines.
4. The lack of clinical immunologists is a major hurdle to good treatment of patients with PID and other conditions related to the immune system. Medical students should therefore be encouraged and incentivised to enter this field.
5. Research into stem cell and gene therapy treatment should be supported because of the high potential for future treatment benefits.

[8] European Commission White Paper: Together for Health - A Strategic Approach for the eu 2008-2013: http://ec.europa.eu/health/ph_overview/Documents/strategy_wp_en.pdf

[9] Figures from Jeffrey Modell Foundation Quality of Life survey

6. EXECUTIVE SUMMARY OF RECOMMENDATIONS

Expert Recommendations – Primary Immunodeficiency (PID)

1. Funding research into better understanding of Primary Immunodeficiency is vital in terms of both diagnosis and management of the conditions and general understanding of the immune system. This must be done at both EU and national level.
2. Patients must be provided with the therapies that they need to live a more comfortable and productive life with a near-normal life expectancy.
3. An appropriate supply of safe plasma for immunoglobulin extraction to be collected each year, from both blood donations and plasmapheresis, in order to ensure patients can receive safe and effective blood therapies that they need.
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