POSITION PAPER ON RARE DISEASES

FARMINDUSTRIA

EUROPEAN AND ITALIAN REGULATORY AND LEGISLATIVE FEATURES

Access to therapy: the importance of accessibility for rare disease patients, and pertinent legislation

A rare disease is a disease with an incidence of fewer than **5 cases per 10,000** persons.
Rare diseases number between **5,000 and 8,000** worldwide and mainly affect **children** who account **for between 50% and 75%** of all patients.
The rarity of such diseases is often a complicating factor in the research for pharmaceutical treatments.

Therefore, news of a **medicine that can finally treat a rare disease** is always greeted with **unforgettable emotion** among rare-disease patients who have had, often since birth, to coexist with the pathology.
Such treatment, by removing the suffering and limits frequently determined by rare diseases, is a first step toward a better quality of life.
And sometimes **"this" new treatment** can offer a **realistic hope** of recovery.

Studying a molecule will not itself lead to the approval of an **orphan medicinal product**. First it is necessary to **understand how the disease works** and, precisely for this reason, the **companies** in this sector are **engaged in studying and documenting** rare diseases and, consequently, also their diagnosis.

Specific therapy only exists for slightly more than 100 of these diseases.

As rare-disease patients must have immediate access to rare-disease therapies that often constitute **the only available treatment**, such access represents a **non-deferable right**.

Therefore, whatever hinders the exercise of this right adversely affects both patients and their families.

Unfortunately, access to pharmacological therapies, authorised nationally by the Italian Medicines Agency **is not equally and/or not promptly accessible** throughout the entire country. The reason is to be found in the **purely economistic calculations**, applied by regional, provincial and hospital-trust authorities, **limit** or **delay its use**, especially as regards adults afflicted by rare diseases.

Many months (**from 9 to 12**) can elapse **from diagnosis** by a reference centre **to the dispensation of a medicine**, assuming one is available. Moreover, a prescribed treatment may, in some cases, be deemed illegitimate.

This represents **a major disparity in treatment** between persons affected by the same rare disease and the same level of severity, for whom access to an approved therapy is **simply based upon the region in which they live**. In other cases, the provision of therapy encounters bureaucratic problems and may arrive too late for patients. In addition, lifesaving therapy may be suspended because a hospital lacks the necessary resources. **Such differences cause rare-disease patients to migrate** from one city to another or from one region to another in search of a therapy.

The **elimination of the regional-based access process** for orphan medicinal products and products with orphan medicine characteristics authorised by the Italian Medicines Agency prior to Regulation (EC) no. 141/2000 (commonly called "orphan-like medicines"), **could overcome these disparities**.

To surmount some regulatory-related problems it would help if the **100-day deadline** for concluding **reimbursability and price procedure** (known as the "Hundred-day procedure") introduced for orphan medicinal products and medical products of exceptional therapeutic importance **were observed**.

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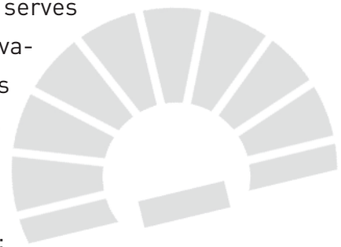
Since the last IQVIA analysis it now emerges that in Italy, between 2015 and 2018, an average of **458 days** elapsed **between European marketing authorisation and actual access to a medicine**.

Nevertheless, our country has produced some important tools (such as Parliamentary Acts nos. 648/96 and 326/03) that, in given situations, facilitate timely access to medicinal products that otherwise would not be available nationwide for the treatment of rare diseases.

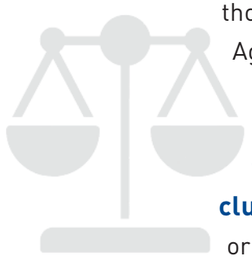
However, some of these measures were not originally intended to meet needs and problems specific to rare diseases (such as for example Act no. 648/96) and, moreover, may instead lead to longer access times.

Targeted measures are required. The Social Affairs Committee of the Chamber of Deputies has recently **begun scrutinising the consolidated text** of a **bill** designed to **sustain research** and **production for orphan medicinal products** as well as healthcare for rare diseases (TU C. 164 and abb.).
This is **an important indication of a renewed interest in rare diseases** while the bill itself contains relevant provisions to facilitate patients' access to medicines. Above all, it includes a provision (Article 5, subsection 3) stipulating that the orphan medicines included within a schedule of the existing Parliamentary Act no. 648/96 should be immediately available, whether or not included in local authorities' hospital formularies. Moreover, the proposal to accelerate the availability of medicines for rare diseases would guarantee the right to health protection, as enshrined in Article 32 of our Constitution, for those patients for whom treatment with other therapies is inappropriate.

However, the bill before Parliament requires some clarification. As also pointed out by the Italian Medicines Agency, the current wording of the measure lends itself to misunderstanding as concerns the part specifying that the orphan medicines benefitting from this clause, are to be inserted in a special section of the list referred to in the foregoing Parliamentary Act no. 648/96. However, this list serves other purposes (innovative medicinal products whose marketing is authorised in other Member States but not on a national scale; medicinal products not yet authorised but subjected to clinical trials; medicinal products to be used for an indication different from that authorised) that have nothing to do with rapid access to regularly registered therapies.



Therefore, it is essential that **the proposed provision** be **completely reformulated** to eliminate all references to Parliamentary Act no. 648/96, thereby **ensuring** that all medicinal products authorised by the Italian Medicines Agency for the treatment of rare diseases can be **made available** by the regions **regardless of whether or not they are included in hospital formularies** or similar lists.



Proposed actions

- Making the Italian Medicines Agency aware of the importance of **complying with the 100-day deadline** for concluding the reimbursability and pricing process as laid down for orphan medicinal products and medical products of exceptional therapeutic importance.

- Raising the awareness of both the Parliament and the Health Ministry about the need to amend existing legislation so as to **eliminate regional-based arrangements for accessing orphan medicinal products** and medicines with the characteristics of orphan medicinal products that completed their reimbursability and pricing process before Regulation (EC) No. 141/2000 (commonly called orphan-like medicines) came into force.

- Heightening the awareness of the Social Affairs Committee of the Chamber of Deputies on the need to redraft article 5, subsection 3, of the bill designed to sustain research and production for orphan medicinal products as well as care for rare diseases by eliminating all references to law no. 648/96 and thus ensuring that all **medicinal products authorised** by AIFA for the treatment of rare diseases can be **made available** by the regions **regardless of whether or not they are included in hospital formularies** or similar lists.

National Rare Diseases Plan: an integrated strategy for rare diseases

The **approval of the new National Rare Diseases Plan** and the provision of **sufficient funding** is another very important question. It is hoped that the new National Plan will be approved by the Health Ministry as soon as possible and drafted

after **constructive dialogue with all the parties** concerned.

The main objective of the plan should be to develop a medium-term, integrated and wide-ranging strategy for rare diseases, centred on the needs of the person and his/her family and defined with the involvement of all stakeholders. The plan should not only take account of the experience acquired but also be anchored within the framework of European recommendations.

Proposed action

Heightening the Health Ministry's awareness of the need to **approve the new Rare-Diseases National Plan**, in concert with the Conference State-Region, by providing **adequate funding** and **initiating constructive dialogue with all stakeholders**.

The rare-diseases assistance network: in Italy and Europe

Ministerial Decree of 18 May 2001, no. 279, set out the general framework of the **national rare diseases assistance network** and introduced **safeguards for persons affected by a rare disease** into our health system that cover:

- assistance and referral;
- welfare and healthcare;
- selecting specific national and local diagnostic and monitoring capabilities in the health centres of regional health networks.

The **National Rare Diseases Network** (RNMR) - an integral part of the NHS - comprises **all the facilities and services of the regional health systems** that, depending on their specific capacities and functions, work together to implement prevention and monitoring, improve diagnosis and treatment and promote information and training.

The State-Region Agreement of 10 May 2007 envisaged - regional organization permitting - **the introduction of Regional or Interregional Coordination Centres** operating as the network's backbone. Over time ever-larger interregional areas were set up, characterised and accompanied by a higher level of standardisation of healthcare proposals.

The **network's nodes**, instead, are constituted by **accredited centres** - chosen by the regions on the basis of documented experience in the treatment of one or more rare diseases - and they must also comply with EU requirements if they are to fulfil their role as expert centres and participate in the European Reference Networks (ERN).

These **centres** are **interconnected with hospitals and peripheral healthcare services** close to the homes of rare-disease patients so that they, as expert centres (operating as functional units, and comprising one or more organizational/operational sections), can ensure the **correct referral and overall supervision of patients**.

However, **many differences** still exist in the operational relations between the centres and the peripheral/local healtcare services that, together with other deficiencies in many parts of the national territory, prevent rare-disease patients from enjoying equal access to the medicines available. It is hoped that the Regional and/or Interregional Coordination Centres will be able to perform a more rigorous monitoring action and where necessary assist these centres and their allied local healthcare services pursuant to the guidelines laid down by a joint committee instituted at the secretariat of the Conference State-Regions as well as by the permanent Expert Committee set up by the Health Committee of the Regions.

A **National Rare Diseases Register** (RNMR) was **established at the Superior Health Institute** in 2001 (in execution of Article 3 of Ministerial Decree no. 279/2001) and implemented following the State-Region Agreements of 2002 and 2007, with **data** culled from the regional or interregional registers. However, these registers differ one from another as regards the type and organizational form of the data collected and how individual regional administrations make use of them. Some are mainly used for epidemiological and planning purposes, while others are structured to perform support and assistance to coordinate referrals of rare -disease patients.

The RNMR, which is kept at the National Centre for Rare Diseases, was set up at the Superior Health Institute in 2008 for the purpose of prevention, treatment and surveillance. Instead, the **National Rare Diseases Centre** (CNMR) was given the **mission of research, consultancy and documentation** on rare diseases and orphan medicinal products and **cooperates** with national and international **institutions** and **patient associations**.

However, the **National Rare Diseases Register** exhibits **important shortcomings**, especially in terms of the completeness and updating of the data to be transmitted to it, the National Register, and the methodology used to process them.
In this field, **data must be uniform and complete** because they must be shared with European bodies. The CNMR would, therefore, be advised to arrange training sessions at the register's offices.

In view of the small number of patients and the limited experience available, the European Commission deemed that it was essential to set up a **European rare diseases Reference Network** to guarantee the diagnosis and treatment of these pathologies. At present **24 European reference networks** are operational, with which **Italy participates in 23**.

The EC considers it essential to share various instruments, among which registers and databases, guidelines, images transmitted online and training activities.

The reference documents used to set up networks and select participatory facilities are outlined in two recommendations[1], which were subsequently incorporated into the European Commission's Decisions 2014/286/EC and 2014/287/EU of 10 March 2014 in the field of European reference networks.

Proposed actions

1. Emphasizing the importance of adopting more effective monitoring by **Regional and/or Interregional Coordination Centres** and, where necessary, providing support to healthcare centres and territorial facilities.
2. Raising the awareness of the National Rare Diseases Centre on the **importance** of providing **training** to ensure standardisation and completeness in data collection for the National Register and subsequent transmission to European bodies.

Measures promoting rare-disease R&D: European legislation

The EU has also taken practical steps in **recognizing the special nature of rare-disease R&D** with the issue of Regulation (EC no. 141/2000), whereby, under article 8, **regulatory benefits** are granted to companies engaged in the research and development of orphan medicines so that greater healthcare provision can be offered to rare-disease patients. Such benefits include the introduction of a ten-year marketing exclusivity after the issue of marketing authorisation, which, however, may be lowered to six years if at the end of the fifth year, requirements for designating the medicine as an orphan medicinal product drug cease to apply.
Given this exclusivity clause, the European Commission cannot therefore grant additional marketing authorisations or accept other applications for the extension of existing marketing authorisations for similar medicines with the same therapeutic indications.

In order to further promote the **health protection** of **persons affected by a rare disease**, subsection 3 of Article 8 envisages **three exceptions to the foregoing rule**: the first two refer to circumstances attributable to the holder of the orphan medicine authorization (whereby marketing authorisation is given to another similar medicinal product, whenever the holder of the exclusivity is unable to provide sufficient volumes of the medicine), while the third is premised on the existence of medicinal product that appears safer, more effective or otherwise clinically superior with respect to a similar but authorized product.

This is **important measure** operates separately from patent coverage. It is part of a framework of regulatory and procedural measures rather than that of intellectual property rights and has the indirect objective of **protecting investments carried out in scientific research**.

LESSONS LEARNED IN THE CURRENT PHASE AND POST COVID-19 PROPOSALS

1. Access to care programmes

Wherever possible and applicable, **pharmaceutical companies** have for years been implementing **patient support programmes and home therapy**, whose numerous advantages for rare disease patients and their families, include:

- facilitating therapeutic compliance and access to medicines;
- improving the clinical monitoring of the pathology;
- minimizing possible risks for fragile patients (for example, when visiting hospitals or hospital pharmacies);
- simplifying caregivers' day-to-day work by providing practical support.

During the Covid-19 health emergency, pharmaceutical companies have **redoubled their efforts** in this field specifically in order **to manage the special fragility** of persons suffering from rare diseases.

At the same time, **the Italian Medicines Agency** has **extended the validity of its therapeutic plans** for medicinal products subject to monitoring, where the clinical conditions of the patient/pathology make this possible, in order to reduce the risk of infection from Sars-CoV-2 in elderly patients and/or with chronic diseases, and therefore also rare-disease patients, and in so doing has reduced the number of visits to specialised surgeries.

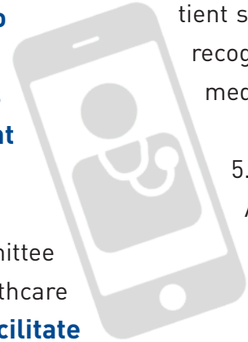
The **therapeutic plans and the Registers of the Italian Medicines Agency** are instruments to **monitor and control the use of orphan medicinal products** reimbursed by the NHS.
They ensure that such medicines are used **appropriately** and administered only to patients who may benefit from them, and at the same time guarantee the **garnering of field data on safety and efficacy**.

Proposed actions

1. Reminding the Health Ministry of the need to **create** and **standardize therapeutic diagnostic assistance procedures** by laying down appropriate general guidelines, to be adapted and supplemented according to pathology, through the adoption of national regulations.

2. Reminding the Italian Medicines Agency of the importance of arrangements **to extend the duration of therapeutic plans and monitoring registers and simplify their management procedures**.

3. Urging the Ministry of Health's Committee responsible for updating basic healthcare standards (LEAs) to take steps to **facilitate a procedure for including rare diseases within these LEAs** (for example, by laying down immediate and certain deadlines for including a rare disease in the LEA list), and to do so by amending national rules.



This procedure should be subsequently implemented by the regions thereby allowing persons suffering from rare diseases to **benefit from freely available healthcare and pharmacological services**, which at this time of profound economic crisis is an even more critical benefit.

4. Making the Regions address the need to **enhance the use of tools such as remote visits and telemedicine**, by putting standardised platforms in place (for hospitals, outpatient surgeries, etc.) at the regional level and recognising the validity of the use of remote medical services on such platforms.

5. Cooperating with the Italian Medicines Agency to **encourage dialogue** - through ad hoc administrative measures – by using **"smart" technology** (such as video conferencing, teleconferencing, etc.), in order to accelerate the adoption of new orphan medicinal products as fast as possible.

2. Distributing medicinal products

The measures implemented by some regions to facilitate access to treatment with Hospital-Territory Formulary medicinal products during the Covid-19 emergency (such as those adopted for example in Tuscany or Campania) provide food for thought.

Some medicinal products could be easily removed from the PHT (Hospital-Territory) formulary and assigned to the medicines ordinary distribution circuit used by the large-scale supply networks of local pharmacies.

In full Covid-19 emergency, **moving A-PHT medicines from direct distribution to pharmacy-mediated distribution** (DPC) was intended to reduce the risk of contagion for the most fragile patients, i.e. the elderly or debilitated, in hospital structures. However, when the emergency is over this **change in distribution could become a permanent fixture throughout the entire country in order to remodulate healthcare assistance**, especially as regards widely used medicinal products, with public structures left only to distribute those medicines for which special conditions apply.

In this regard, the regions' use of **e-prescriptions** should be **increased** in order to facilitate the dispensation of medicinal products to patients.

The direct delivery of **"special medicines"** on the part of **public structures** should, however, be maintained should there arise a need for **periodic inspection** at the structure, or a therapeutic criticality or a differential diagnostic requirement, but without creating inconvenience to patients as they must still attend such structures for periodic monitoring.

Similarly, it might also be feasible to **transfer** the administration of **certain medicinal products**, where possible and any in case **under the strict indications of a specialist**, to **local facilities** separate from hospitals, thereby ensuring **therapeutic continuity** and helping rare disease patients and their families.

On the basis of the experience of the Region of Tuscany which provided indications for the management of rare disease patients during the Sars-CoV-2 epidemic certain **therapies can be identified** that could **be transferred to the PHT direct distribution formulary**.

Proposed action

- Making the regions duly aware of the advantages of **automatically inserting A-PHT medicinal products** for rare diseases in the list of **medicines for pharmacy-facilitated distribution** in order to redistribute healthcare assistance cross the territory and ensure the widespread distribution of these medicines in all regions.

3. Home therapy

Effective **home care** has **numerous advantages** for the patient as it combines clinical care with health and welfare services. This need is acutely felt by rare disease patients.

Home therapy, which must always be **evaluated and agreed upon by the physician** of the reference centre has several benefits:

- it ensures **therapeutic compliance and correct treatment**;
- it engenders **psychological improvement** in patients which helps them cope with their disease better;
- it enables a **therapy to be administered in a family environment**, guaranteeing the patient's right to privacy in respect of his/her pathology;
- it allows patients to **choose a day** for treatment;
- it means not having to lose a day at work or in school.

In recognition of the fact that at this time of health emergency the fragility of rare disease patients is a critical issue, the **Italian Medicines Agency** passed a resolution on 30 March 2020 embodying recommendations for the home administration of medicines for enzyme replacement therapy, which represents a **widening of access to home therapy**.
This measure **minimizes potential risks deriving from treatment discontinuities** occasioned

by the fear of contracting contagion in hospital environments.

For years patient associations have been requesting more widespread use of **home therapy**, but its authorisation **varies** from **one region to another**.

The **European Parliament** has been debating this issue for some time, and different parliamentary groups have submitted **various proposals** that go in the direction of **providing assistance and care at home** for rare disease patients. However, to date there has been no meeting of minds and none of these proposals have been accepted.

The **regions** have adopted **different approaches**: some allow rare disease patients to take advantage of home therapy. Others, despite being unable to assist patients with comprehensive home-care assistance (ADI), are still unwilling to agree to alternative forms of private home care, although it could improve the patients' quality of life and reduce NHS spending.

Based on the positive experience obtained during the health emergency, it would be **important** to return first to a document of 2012 addressing the administration of high-cost medicinal products to rare disease patients at home and approved by the Conference State-Regions as it contains a series of indications for carrying out home therapy, and second to **define an organizational model to ensure patient safety** that would also embrace regional health systems.

Proposed action

- Heightening the Health Ministry's and Parliament's awareness of the importance of a **clear regulatory framework** to allow recourse to **home therapy** throughout the entire national territory, and a framework, moreover, that the regions would have to adopt so as to guarantee equality in the treatment of rare-disease patients while also offering the possibility of **public-private partnerships**.

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4. Training caregivers

The **caregiver** plays a **fundamental** role as regards **caring** for rare-disease patient and the figure is of great social and economic value for the country. And although caregivers are often persons who are themselves elderly there is no shortage of suitable young people for this role.

Given their key role, **training** caregivers is increasingly **important** to improve skills and knowledge with regard to the pathology, patient rights and the health and welfare networks in whose framework they operate. Moreover, it is necessary that a training scheme should pursue the objective of developing a **greater awareness** of this figure's **social value** in terms of benefits for the public and improving operational and relational skills.

Patient associations long active in this field have been providing training programmes and practical help on various issues through either face-to-face or remote meetings.

The Covid-19 emergency has given **training** a **further boost** not only by expanding educational programmes but also by further developing the use of remote communication technologies.

It is, therefore, deemed essential to continue to promote **training**, especially in **cooperation with doctors and nurses**, via **online platforms** that are best suited for family assistance while ensuring flexibility in their implementation and guaranteeing possibility of access to the programmes available.

Proposed action

- Raising the awareness of the Ministries of Health and Labour and Social Policy of the need to **earmark part of the resources** of the **fund** set up under Parliamentary Act no. 205/2017 to **structured training programmes for caregivers** by issuing an executive decree to reapportion these resources.

NEONATAL SCREENING AND EARLY DIAGNOSIS

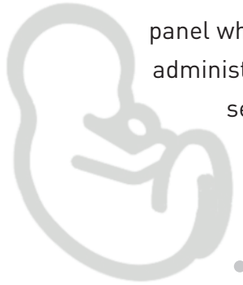
As we are dealing with complex and strongly debilitating pathologies, **early diagnosis** is **extremely important** in helping to reduce the symptoms and complications associated with the natural progression of the disease and/or patients' death.
The **diagnosis** of many rare diseases **often** requires an **extended period of time**, sometimes extending over **several years**.

Many of these diseases are genetic in origin and their **diagnosis can** often only be confirmed **by specific DNA examinations**.
Neonatal screening is therefore fundamental for **the timely treatment** of patients suffering from diseases for which research has found therapies that are effective in preventing degeneration and it should, as such, be considered an **indispensable investment for promoting public health**.

In the field of neonatal screening Italy has emerged as a **European leade**r. The current system of extended neonatal screening comprises a **panel of over 40 rare, invalidating or lethal metabolic diseases**, and is based upon a network of regional cooperation under the direction of the Superior Health Institute.

Furthermore, as a result of the many pilot projects carried out in different regions, Italy has decided to **further enhance early diagnosis**, by giving the Ministry of Health powers to **update**, by 30 June 2020, the **panel of pathologies** subject to neonatal screening, in order to take account of the **evolution** over time of **scientific evidence** in the diagnostic-therapeutic field, commencing from genetically originated **neuromuscular diseases, severe congenital immunodeficiencies** and **lysosomal storage diseases**. Moreover, provision has been made for an **accumulative financial allocation** to enable the regions to deliver these services.

It would, therefore, be desirable, in the light of available therapies, to **fully implement regulations** on the **updating** of the **neonatal screening** panel whose efficacy is linked to prompt administration and systems for specific, sensitive and sustainable tests.



Proposed action

- Making the Health Ministry aware of the importance of fully implementing law no. 167/2006, by convening, **at the earliest possible date**, a **working table** tasked to review the panel of **pathologies subject to neonatal screening** (genetic neuromuscular diseases, severe congenital immunodeficiencies and lysosomal storage diseases) and put arrangements in place for the panel's **annual update**.

CLINICAL STUDIES

Research on **rare diseases** is a **specialised research area** within the **pharmaceutical industry**, and one characterized by the following aspects, each of which requiring the attention and cooperative arrangements among the subjects involved:

1. the **numbers of people affected** by each rare pathology are **small and distributed** over the entire country. In addition, the **epidemiological data available** are **limited** and the current use and dissemination of existing registers of pathology is suboptimal;

2. not all rare diseases are included in a thorough manner and **diagnosis is not always early and accurate**;

3. **there are too few specialised centres** and **clinical experts**. This can entail **logistical difficulties** for participants and an insufficient awareness of rare disease outside of such centres. Furthermore, in the long term, major problems may arise in terms of the **generational turnover among clinicians**;

4. on account of the distinctive features of these pathologies it is necessary to (a) **apply research methodologies** that increase **the efficiency** of study designs and the analysis of the data,

(b) reach a consensus on clinically significant endpoints, (c) **mitigate recruitment difficulties** and **minimise patient drop-out rates** during studies determined by logistical factors.

These **peculiarities** entail recruitment difficulties in studies and therefore **longer times in producing results** to help identify useful therapeutic alternatives. In order to **facilitate the identification** of **potential participants** it would be desirable:

- **to publicize** the fact that **clinical studies** in a given pathology are taking place through a proactive **cooperation with patient associations**;
- to facilitate or draw attention to the **compilation of national registers**;
- to promote **neonatal screening**, whenever useful;
- to facilitate the performance of **epidemiological or natural history studies**.

As regards the third point we could promote new and additional **awareness campaigns** aimed at the **medical class** as a whole to upgrade training initiatives in this field. Instead, as regards clinical research, **the creation of networks of experimental centres could be simplified**, in order to facilitate the identification of potential participants, on the basis of a ***hub & spoke***[2] or decentralized study model.

Furthermore, in order to take action on the fourth point, a **dialogue with regulatory authorities, scientific societies and companies** could help identify **clinically significant endpoints**, in the hope that Patient Reported Outcomes could also be validated as endpoints as well as an **ever-greater involvement of expert patients in the design of trials** and the preparation of study documents.

At a more functional level, some of the measures implemented during the Covid-19 pandemic emergency could be confirmed, albeit with whatever adaptations deemed necessary, in order to maintain **a continuous and constant relationship with the Italian Medicines Agency**, with which the information on **corporate pipelines** can be shared, and to which must be delegated the task of obtaining international validation (EMA) on the reliability of data obtained through procedures and arrangements hitherto not considered.

The following are examples of a few suggestions on measures that could be taken:

- allowing **participants in studies** to make use of **home therapy**;
- making more widespread use of innovation and IT in the form of **telemedicine, digital technology, wearable devices**, and ePRO apps;
- permitting **recourse** to **specialized services for participants** so as to reduce the **travelling, and board and lodging costs for transfers** to specialised centres but which families with rare disease patients, especially young patients or with a caregiver in attendance, may not be able to afford.

Dialogue and **open cooperation between the various subjects** involved in the macro-process of clinical research - regulatory authorities and the institutions, patient associations, scientific companies, pharmaceutical researchers and companies - are fundamental if the **main challenges** posed by rare diseases in the management of clinical studies are to be **successfully tackled**, and not just during the Covid-19 emergency, and if **more innovative approaches** that could redesign future clinical research **are to be identified**.

Proposed action

- Publicising the fact that the **pharmaceutical companies are willing** to continue their **full collaboration** with the **regulatory authorities and institutions, patient associations, scientific companies and researchers** in order to address the main challenges posed by clinical trials for rare diseases in the best way possible and introduce more innovative approaches.

Note

1 Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States of 24 October 2011; Recommendations on Rare Diseases European Reference Networks (RD ERN) of 31 January 2013.

2 This is an organizational model that starts from the assumption that certain conditions and complex diseases require specialized skills that cannot be comprehensively guaranteed or widespread throughout the territory. It is characterized by concentrating the more complex cases in a limited number of centres of excellence (hubs) and peripheral centres (spokes), to which persons whose condition exceeds a certain threshold of complexity are sent.

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