Beatrice Lorenzin
Minister for Health
Via Lungotevere Ripa, 1
00153 ROMA

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Open Letter to the Italian Minister for Health Beatrice Lorenzin on the need for an informed public debate on stem cell therapies and the correct, safe and ethical implementation of effective medical treatments

The current situation

Today, between 6000 to 8000 rare diseases affect an estimated 2.5 million people in Italy. The majority have no cure. For most people living with rare disease and their families, everyday life is a fight. The perspective of appropriate care and therapy is what they dream of and strive for. For the perspective of a cure, patients families and their organisations interact and work actively to be "subjects of research", not only through their direct and informed involvement in clinical trials, data collection and recovery of biological samples, but also by helping to direct, evaluate, monitor research through a constant dialogue with all actors, participating in regulatory and ethical committees, raising funds and providing their skills, knowledge, experience and energy wherever they may be needed.

Italian citizens have been questioning themselves when faced with the promises offered by the Stamina method. Specifically, Italian patients and families affected by those rare diseases for which the Stamina Foundation seemed to offer hope. However patients and citizens were not provided with the tools to make an informed choice.

Not only was information on the Stamina method not disclosed, but also uncertainty still reigns on the conclusions of the Scientific Committee called to evaluate that method. Additional confusion was generated following the TAR Lazio ruling no. 08730/2013 REG.RIC. that put into question the legitimacy of the Scientific Committee. Finally, the public debate was dominated by "attention-grabbing" media statements, which resulted in a chaotic situation. As patient representatives we look with dismay at these outcomes. A great opportunity for provision of information and communication has been missed and a great gap between citizens and institutions was created. Patients and families, who are often alone in their daily fight against the disease and in absolute need for care, found themselves even more isolated facing a crucial choice for themselves or their loved ones. This situation must be redressed and must not be repeated.

What we request

The current situation is clearly harmful to the patients, to medical research and to the general public, **therefore we urge the Italian Minister of Health to redress the widespread confusion generated and to bring order to this chaotic situation by:**

1) disclosing relevant information not accessible to the public;

2) exposing crucial concepts essential to providing accurate information on the context of the Stamina case.

1) We call on the Minister for Health to disclose essential information and notably to make the results of the work of the 2nd Stamina Scientific Committee public; in addition, as a consequence, to disclose the protocol submitted to this Committee and to appraise whether the 3rd Scientific Committee is going to evaluate the same method. This will avoid the circulation of unsubstantiated statements for or against the Stamina method through the media and make the information available for anybody to judge for themselves based on objective data.

When it comes to experimentation on stem cells, the scientific landscape is evolving extremely rapidly, the scientific questions are complex and the social impact is tremendous: patients must have access to all relevant information before embarking on medical trials or experiments. This is even more important when we talk about advanced therapies. Transparent communication and comprehensive information would support an informed public debate, which is essential. The Oviedo Convention, to which Italy is a signatory, states that "the fundamental questions raised by the developments of biology and medicine are the subject of appropriate public discussion in light of, in particular, relevant medical, social, economic, ethical and legal implications, and…their possible application is made the subject of appropriate consultation".

It is essential therefore that the Italian government fulfills its institutional mission and, in pursuit of public interest, contributes to implement processes of transparent communication. Hence, all data and documents on which the Scientific Committee has based its opinion and the deliberations of this Committee should be made accessible to the public in order to enable patients to make their decisions on an informed basis. The new Committee should also operate under no restriction of non-disclosure agreements and - conversely – to make all available data, minutes and the final decisions available for the evaluation and understanding of the public and interested patients and families.

2) Moreover, we call on the Italian government to take action consistent with its institutional responsibility and redress the current situation that is in conflict with Italy's legal commitments under European legislation. In particular, we request that the Italian government:

a) **Justifies that the methods of scientific validation provide the best existing protection for patients**

The current procedure of scientific validation of medical products that applies in Europe and in the USA is the best safeguard for the patients who are the ultimate beneficiary of those products. The procedure that product developers have to undergo has been designed to ensure that the products are safe and efficacious; the numerous requirements that developers need to comply with at different phases of a clinical trial ensure that the products that make it to the market deliver results and do not in principle pose unacceptable risks to patients' health.

Any gene or cell therapy developed anywhere in a EU Member States must be evaluated by the European Medicine Agency (EMA) relevant committees and then approved by the European

Commission for marketing authorisation. So **any experimental therapeutic research, even with the best intentions that does not comply with the expected good practices and level of evidence as required by EMA and the European Commission (regulation (EC) No 726/2004), is not only a loss of time, money, human resources, opportunities for patients, but also could be considered as unethical.**

The Committee for Advanced Therapies at the EMA issued a statement[1] already four years ago, warning that the use of stem-cell medicinal products outside controlled conditions may result not only in little or no benefit to patients, but could also be detrimental. This is because, outside these conditions, checks on the quality of these products may not have been carried out, and their safety and efficacy may not be properly assessed.

Surely, over time scientific validation processes may evolve to keep pace with the rapid scientific development and thus, for example, specific validation processes may be designed for stem cell therapies. However, at present, the approved scientific validation for medicines, and for advanced therapies in particular, with its robust precautionary approach, provides for the best existing safeguard for the patients. It is imperative that citizens and patients feel that the respect of the process of scientific validation does not hinder their 'right to the cure', but protects their best interest to have a therapy that is as targeted and safe as possible. 'Right to the cure' does not mean 'right to any cure'.

b) **Rectifies the misconception on "compassionate use" rules, which cannot be invoked for the Stamina method**

Compassionate-use programmes enable a doctor to obtain treatment for a given patient while the medicine is still under development and undergoing a scientific validation procedure. As the Stamina method has never undergone a clinical trial, "compassionate use" rules are not applicable. In other words, the Stamina method cannot be lawfully used, even as a simple palliative treatment.

There is wide and deep misconception regarding the so-called "compassionate use". According to the EU and Italian legislations[2], the concerned medical product must be the subject of an application for marketing authorisation or undergoing clinical trial. The latter means that the product, although not authorised for marketing, is going through phase III trials or (in exceptional cases) has at least final, positive results from phase II studies or. This means the product is reasonably (even if not finally) proved to be safe and effective. As said, none of this applies to the Stamina method.

In conclusion

We trust that clarifying these important concepts will greatly contribute to the regular scientific information that citizens and patients need, especially with regard to the scenario of great hope that cellular/gene therapies represent.

[1] 16 April 2010, EMA/763463/2009 Public statement "Concern over unregulated medicinal products containing stem cells" http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/04/WC500089472.pdf

[2] EC Regulation No 726/2004, CHMP Guidelines EMEA/27170/2006, Italian MoH DM 5/8/2001

Italian health authorities have a unique responsibility to oversee that invitations to be included in what may appear to be a clinical trial, or is referred to as a therapy, are in line with legal procedures and requirements that provide transparency and protection to patients.

This course of action will be broadly beneficial to the debate not only in Italy but in Europe and potentially worldwide. The issue currently at stake in Italy goes beyond national borders. The use of stem cells and the correct, safe and ethical implementation of effective medical treatments, from scientific speculation to the delivery to the market of the final medicinal product, following the best possible procedures, is a challenge that Italian institutions should not face alone. They implement and defend procedures that have been adopted at European level. They should be supported by their European counterparts in facing this global challenge and in taking actions to empower patients and citizens to take part in an informed public debate on the potential of stem cell therapies and their wide societal implications.

Ultimately, public debate supported by transparent, quality information is critical to support the individual choice of each patient and family in a complex environment, where choices are not univocal. This will help those patients and families overcome their cultural and psychological isolation and will broadly contribute to building up a true scientific citizenship.

Yours sincerely,

Terkel Andersen
President
EURORDIS

Renza Barbon Galluppi
President
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