Clinical Trials and Europe's Responsibility to Humanity

Margrete AUKEN

MEP, Group of the Greens / European Free Alliance, European Parliament

For drugs tested in the EU there are ethical concerns to be dealt with and we have the legal framework in place to do so. For drugs tested outside the EU, often in developing countries, the ethical concerns are even more numerous and the legal framework often weak or nonexistent. The questions that must be answered are difficult; how do you ensure informed consent if the trial subjects are illiterate and uneducated? How do you guarantee that the treatment for side effects is sufficient in countries without universal healthcare?

Clinical trials are a necessary evil. Drugs need to be tested on humans in a controlled environment before they can be deemed safe for the population at large. However, the pharmaceutical companies increasingly follow the profit margin to test drugs in poorer countries where the cost is lower, the participants more willing and the regulation less stringent.

The large majority of people in developing countries must be considered more vulnerable both economically and socially, and vulnerable people should not be allowed to participate in clinical trials. Many of the horror stories that have come to light revolve around desperate people, so poor that they have no other choice than to participate in drug trials that might harm or even kill them. They are often uneducated and unable to make an informed decision about the trials they participate in, even if poverty had not left this as their only remaining option of survival. They are not informed about the dangers of participating in more than one trial at a time and it is almost certain that they will not receive follow-up treatment or compensation if something goes wrong.

And even more unfortunate, most of the drugs tested on poor people in developing countries will never benefit the people of those countries. There is far too little money to develop new medicine for the most common diseases in the world: Malaria, cholera, rotavirus etc. The large majority of people who suffer from them are poor. Most research is therefore meant for the European and American markets where there is money to be made. And yet the trials are only moved to Europe or America when many of the kinks have been worked out. We essentially use the poor people in Asia and Africa as modern day food tasters.

Over the last 10 years, we have seen many clinical trials move to countries like India or Uganda. Most of these are so-called phase 1 clinical trials which involve a group of people who are not necessarily suffering from the ailment that the drug will treat. After a phase 1 and maybe phase 2 clinical trials have been done in a developing country, phase 3 and 4 will then often be moved to a European country, which is where the drug will mostly be sold after it is authorized.

The main aspect that we as European legislators must consider is how we ensure that the well-being of our citizens is not based on the ill-treatment or even death of someone without a voice in Europe? Part of the answer must be to help the national authorities in the developing countries create a legal framework to protect their citizens where it does not exist and improved it where it does.

The Commission proposal moves in the right direction on this issue, but I believe that we must go even further. In the future, in order for phase 2, 3 and 4 clinical trials to be authorized in the EU, the previous phases must take place in a country with the same or an equivalent system as the one in place in Europe. It will be up to the Commission, together with the European Medicines Agency, to approve other countries' legal frameworks to ensure that they live up to this standard.

This carrot and stick approach is a step in the right direction but I fear that it is not enough. We must ensure that the ethical considerations done prior to authorization of a clinical trial in Europe, include the practice and location of precious clinical trials. This involves total transparency into where and how clinical trials are conducted even abroad as well as a focus on the ethical aspects of clinical trials in the authorization process in general.

The results of clinical trials on humans belong to humanity at large, whether positive or negative, leading to publication or not. In the European Parliament, we are working on complete transparency when it comes to both results and patient data from trials in Europe so that independent researchers can check the findings and the pharmaceutical companies can benefit from each other's knowledge. This is a small step towards what is really needed: complete global transparency on clinical trials. That will be a valid way to make sure that no poor person is harmed or exposed to drugs in vain due to pharmaceutical companies' search for profit.

A Pan-European Perspective on the Challenges of Patient Recruitment for Clinical Trials in Rare Diseases

Dr. Alexander NATZ

Secretary General European Confederation of Pharmaceuticals Entrepreneurs (EUCOPE)

Rare diseases have been identified as a priority area for Community action within the framework for action in the field of public health[1]. On December 16th 1999, the EU adopted Regulation (EC) 141/2000 aiming at providing incentives for the research, development and placing on the market of designated orphan medicinal products[2]. This Regulation has proven to be an effective tool to foster research and development of orphan medicinal products and develop new therapies for patients with high unmet medical needs. However, conducting clinical trials remains an essential but difficult step in the development of these new medicines, as unique challenges exist when it comes to recruiting patients with rare diseases, challenges which are amplified for very rare diseases – or ultra-rare diseases[3], due to their extremely low prevalence. Indeed, these rare diseases sometimes affect only a handful of patients per country, yet multiple clinical trial sites are still often required.

As a result, patient recruitment can be a significant challenge for research in this area, due not only to the very low number of patients but also because patients are located disparately across European Member States. Manufacturers must conduct clinical trials for these diseases across a wide geographical scope to ensure a sufficient level of participation by patients. Given so few patients with rare and ultra-rare diseases are even eligible for treatment in a clinical trial, multiple trial sites must be opened to accommodate patients wherever they are identified, thus compounding the cost as well as the administrative and regulatory complexity involved in initiating sites and conducting clinical trials. Yet despite the very small patient numbers, the impact of these rare and ultra-rare diseases on patients, their families, and even on society can be profound as many are severe, chronic and progressive, and are often marked by pain, disability, systemic damage, and high mortality rates. As such, a clinical trial is sometimes the only possibility for rare disease patients to access treatment, particularly where, the patient requires urgent care and where no therapeutic alternatives are available.

There are many reasons which explain higher administrative burden and lengthy processes to enrol patients with rare diseases in clinical sites:

- Identifying the sufficient number of patients scattered throughout the European Union while the awareness of the disease and its diagnostic tools are very limited;

- Opening multiple clinical trials sites in various Member States so as to enrol the required number of patients ensuring sufficient and robust results;

- Preparing and submitting the clinical trial application for each hospital site in various Member States;

- Responding to Member States diverging national transposition measures.

All these challenges account for delaying the launch of a clinical trial goes frequently beyond the average of 152 days[4]. Delays in launching the trials may have fatal consequences, at its worst endangering the patient's life, for some patients affected by debilitating and life-threatening rare and ultra-rare diseases with no alternative treatment options. Clinical trials should therefore be authorized in a fast manner to avoid delaying their initiation. Especially in the area of rare diseases, multinational clinical trial decisions need to be fast and efficient, incorporating science and ethics, in order to fulfill the expectations of these patients.

The review of the European legislation on Clinical Trials provides an important opportunity to ensure the legal framework regulating clinical trials takes into consideration the specifics of rare diseases and diseases with unmet medical needs, enabling research to be carried in all fields. For instance, clinical trials in these diseases could be judged for statistical relevance with methodology that takes appropriate account of the patient population, the severity of the disease and the therapy alternatives existing. In addition, the new legislation could take into account the urgency of the situation of rare and ultra-rare disease patients, when affected by very severe conditions and a lack of treatment options. In these cases, the initiation of clinical trials and the enrolment of these patients could be accelerated if not prioritized. These specificities and suggestions could be reflected in the upcoming revision of the Clinical Trials Directive 2001/20/EC in which an appropriate regulatory framework should adapt timelines and requirements for the approval of clinical trials as to factor in the life-saving potential of the therapy being investigated.

1. Regulation (EC) n° 141/2000 of the European Parliament and of Council of 16 December 1999 on Orphan Medicinal Products, recital 11, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2000R0141:20090807:EN:PDF.

2. Regulation (EC) n° 141/2000, article 1.

3. See European Commission Proposal for a "Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC", COM(2012) 369 final, page 3: "Moreover, other causes (such as salary costs and the need to conduct multinational studies to reach recruitment targets) have been aggravated through regulatory requirements and consequential costs of the Directive 2001/20/EC." where the Commission is recognizing the need for companies to reach recruitment targets as one problem of the existing legislation.

4. See European Commission Proposal for a "Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC", COM(2012) 369 final, page 3.