EDITORIAL

Clinical research in rare diseases: New challenges, opportunities and ethical issues

Investigación clínica en enfermedades raras: nuevos retos, oportunidades e implicaciones éticas

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The European Union defines a rare disease (RD) as any disease affecting fewer than 5 people in 10,000. The difficulty in the diagnosis of RDs and the absence of effective treatments make research in this field particularly urgent, but research in rare diseases poses challenges that differ from those of research in more prevalent diseases, chiefly methodological difficulties related to the reduced number of cases, their substantial heterogeneity and problems related to recruitment.

The introduction of "orphan status" designation for drugs has significantly advanced the search for therapeutic options, promoting and providing incentives for the development of treatments for RDs. Yet, despite such initiatives, the number of clinical trials sponsored by biotechnology or pharmaceutical companies is still too small, among other reasons because the low prevalence of these disease makes return of investment unlikely.

It is essential that the time frames involved in the performance of clinical trials are sped up, to this end, different clinical trial designs have been proposed as an alternative to randomised controlled and parallel group trials, such as factorial trials, adaptive trials, crossover trials and Bayesian clinical trials. In adaptive designs, the trial can be modified based on the results obtained in the intermediate analyses, increasing the efficiency of traditional clinical trials by facilitating the establishment of effective doses, reducing the number of patients exposed to ineffective or potentially toxic doses, precisely calculating the sample size and reducing both the duration and cost of the clinical development process.

The particular challenges of research in RDs, most of which have a genetic basis, involve the new "omic" technologies, access to large databases or advanced therapies, such as gene therapy. The creation of registries and biobanks as research support platforms has made available sources of reliable epidemiological data, allowing the assessment of morbidity and mortality risks and economic and social costs.

On the other hand, the availability of high-quality biological specimens allows the research of the underlying mechanisms of these diseases, developing of new diagnostic techniques and identification of potential therapeutic targets. Thus, initiatives have been launched such as RD Connect, an integrated platform that connects databases, registries, biobanks and clinical bioinformatics for RD research.

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Another relevant factor is the widespread implantation of electronic health records, which offers access to a large amount of data of each patient, along with the development of software capable of processing this massive volume of biomedical data, including genomic data. Health care big data tools and artificial intelligence allow the development of algorithms for more accurate detection, diagnosis and treatment of RDs, even in early stages of disease when there is a greater opportunity for intervention. These predictive models, set in the framework of what is known as personalized and precision medicine, must be clinically validated before being introduced in clinical practice, a setting where they will facilitate the development of telematic solutions to improve the quality of life of affected individuals and real-time support tools to assist in health care delivery. As for their application in research, the use of artificial intelligence and big data in health care will allow faster recruitment of participants and performance of studies under real-world conditions, yielding evidence on the long-term effectiveness and safety of the interventions under study.

Along with these potential advantages, big data analysis techniques may pose significant threats to privacy, so it is essential that appropriate measures are applied to control the information and adequate, transparent and safe procedures established to guarantee the highest level of confidentiality, all within a legal and ethical framework that makes ensuring data protection compatible with performance of relevant clinical research.

All research, including research in RDs, must meet a series of ethical standards: to offer social or scientific value, to be scientifically valid, to select participants fairly based on the scientific objectives of the project, to have an acceptable benefit-risk ratio, to have the project assessed independently, to allow the research subjects to freely choose to participate after being adequately informed, and lastly, to be respectful of participants and protect them. In this sense, it is essential to guarantee the privacy of participants and the confidentiality of their data, taking into account that in the case of diseases with a very low prevalence, data that have been theoretically anonymised, such as the diagnosis and the place of residence, may be enough to unequivocally identify an individual.

When it comes to informed consent, it must be ensured that it is valid in that no undue pressure has been placed on the patient and the information given to the patient is accurate, keeping patients or their proxies from having excessive expectations regarding the potential benefits of the experimental treatment without considering its potential risks, which might equal or even outweigh the potential benefits.

Approximately half of RDs have onset at birth or in early childhood, so the specific characteristics of children associated with their level of maturity and vulnerability must be taken into account. In the case of children, in addition to the informed consent of the legal guardians, the assent of the minor must also be obtained as applicable based on their ability, always respecting the will of the child.

Another challenge that has been identified is the need to guarantee the prompt and effective translation of basic research findings to clinical practice. Although there are mandatory clinical trial registries, not all results are published despite it being a legal and ethical obligation, especially in this field where patients have such high expectations. If results are not disseminated, there is a risk that similar studies could be repeated even if the previous results have not been positive potentially harming participants, slowing the process of science, wasting essential resources and diminishing the trust of society in research.

Another objective is to guarantee access to experimental treatments through models such as compassionate use. Furthermore, we ought to keep in mind that the development of drugs for treatment of certain RDs could be threatened due to lack of funding; thus, despite the efforts of patient associations to secure resources, they frequently fail to reach their desired target. This is why new initiatives have emerged in which patients themselves or their relatives fund the clinical trial in which the patient will receive the experimental treatment, frequently raising money through crowdfunding. Although these models could allow accelerating the translation of preclinical research to clinical practice, this must be done in compliance with ethical principles, especially the principle of justice according to which the selection of participants must be based on adequate eligibility criteria and not in the ability to pay.

Last of all, we ought to highlight the role of patients and patient associations in RD research. Their involvement is essential both to guide research toward their actual needs and to ensure participation. The patient-centred approach is also important for research ethics committees, which guarantee the protection of patients in biomedical research and have included representatives of patients’ interests among their members, in compliance with current regulations on the subject.

The ultimate objective of research must be to expand scientific knowledge with the purpose of offering an accurate diagnosis and appropriate therapies to patients. This requires international cooperation of research groups to expand the recruitment pool and facilitate the obtention of necessary resources. There are high expectations for emerging technologies, but their application must be accompanied by a rigorous analysis to ensure adherence to the highest ethical standards. In this regard, ethics committees can play a key role as reviewers of biomedical research and consultants for the scientific community.

**References**

