Ethical Aspects of Rare Diseases Research: Best Practices for Expert Patient Engagement

Roberta Martina Zagarella*, Elena Mancini*

Abstract: As rare diseases continue to pose challenges to patients, caregivers and researchers, they have been increasingly recognised as a public health and social issue, as well as a crucial research topic. The growing focus on the priorities and needs of the rare disease community is accompanied with growing efforts to bring the patients' voice in the multidisciplinary field of rare disease research. The paper discusses ethical aspects of rare disease research, giving special consideration to the concept of "expert patients" as real partners in research. Best practices and self-regulatory guidelines for improving patients' engagement with rare disease research are presented. On the other hand, the paper focuses also on critical aspects and ethical concerns about the institutional roles of expert patients, especially in ethics committees, highlighting the need for a critical reflection on ethical principles and values which should orient their activities.

Keywords: Patients' engagement, Rare diseases, Research ethics, Advocacy.

1. Background

Rare diseases (RDs) include a wide variety of diseases and conditions, which generally cause serious chronic complications or progressive physical degeneration, disability and premature death[1]. Although few patients are affected by any specific RD, approximately 300 million people (3.5%-5.9% of the worldwide population) live with a rare disease[2].

There is no single definition of rare disease prevalence: in the European Union, a disease is considered rare when the number of affected persons is not more than 5 per 10.000[3]; other regions use different definitions. To date, over 6000 distinct RDs have been identified, most of them with a genetic basis; on average, five new RDs are described every week in the scientific literature[4]. Most rare diseases are incurable.

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* CNR Interdepartmental Center for Research Ethics and Integrity, Rome, Italy.

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Approximately 95% of them have no approved treatment[5]; very often, no research is being conducted on them.

This paper discusses ethical aspects of general rare disease research (rather than research on a specific rare disease), particularly focusing on recent good practices concerning the involvement of "expert patients".

2. Challenges and special problems

Rare diseases pose particular challenges to the affected individuals and their families, to the clinicians who care for such patients, and to the scientific communities who study their conditions[6]. Among others, some of the most prominent problems are the following: useful, reliable and timely information may be hard to find; research activities are less common; treatments are sometimes very expensive; developing new medicines may not be economically feasible; in developing countries, the problems are compounded by other resource limitations[7]:

> The thousands of different pathologies defined as "rare" have in common specific features that enhance patient vulnerability: their low prevalence – thus the isolation and marginalisation of patients affected by them; the heterogeneity of diseases with different research needs and therapeutic responses, as well as the complexity of diseases often affecting different organs – thus requiring multidisciplinary responses; research is actually conducted only on a small number of inventoried diseases; fragmented knowledge or no knowledge at all on the pathogenesis/pathophysiological mechanisms and epidemiology of many RDs, which make diagnosis difficult to make and therapy slow to develop. Frequently incorrect diagnosis, reduced life expectancy and critical transition from paediatric to adult healthcare are additional features making RD patient especially vulnerable individuals[8].

Challenges posed to patients and their caregivers mostly concern being diagnosed, receiving optimal care, affording disease-specific treatments[9], as well as social aspects and other consequences of living with a rare disorder. A study conducted by the European Organisation for Rare Disorders (Eurordis)[10] shows that 40% of patients first received an erroneous diagnosis that may have led to inappropriate treatments or medical interventions. A quarter of patients experience long delays in diagnosis, ranging from 5 to 30 years from early symptoms to confirmatory diagnosis of their disease; people often have to travel to a different region or country to access expert care and obtain a final diagnosis[11].

Rare diseases can lead to a significant reduction in quality of life for patients and other family members. The impact of rare diseases frequently includes constraint or physical limitations, cognitive and communication disabilities, lack of autonomy, dependence on others to manage daily activities or everyday needs, emotional distress, perceptions of stigma and social exclusion; all this poses challenges for patients in their social interactions, work and education, as well as a considerable strain on families. RDs also raise psychological issues related to the lack of knowledge about the rare disorder, uncertainty about the future, insecurity associated with the evolution and

progression of the condition, loneliness, loss of confidence, guilt related to the risk of passing the condition on to children, etc.[12].

In the last two decades, the challenges and problems associated with rare diseases have been increasingly recognised not only as an important public health and social issue, thanks to the significant efforts of many stakeholders in the public and the private sectors[13], but also as crucial research topic.

3. Patient-centered approach in RDR

The main priorities of people living with rare disease have been recently summarised as follows:

- allocation of more funds to basic, translational and clinical research;
- development of disease registries and harmonization of data collection;
- setting-up of registries and biobanks-network and their coordination;
- reinforcing multidisciplinary European Networks of Reference for Rare Diseases and Centres of Expertise, national experts, diagnostic and research laboratories and patient associations;
- fostering public-private partnerships;
- establishing training on rare disease for researchers;
- exploring broad treatment strategy/protocol trials;
- developing research in social and human sciences[14].

The increasing focus on the priorities and needs of the RD community goes together with growing efforts to include the patients' perspective in the multidisciplinary field of rare disease research (RDR), from basic to translational, clinical and social sciences research.

It has been progressively acknowledged that RD research on treatments should be developed following a patient-centered approach aimed to improve patient outcomes, minimize side-effects, and enable patients to receive personalised treatment:

> RDs are at the forefront in personalised medicine, which applies genetic information about each patient to tailor treatments medical care to individual needs. Today, certain drugs are increasingly being targeted specifically to the best responder patient subgroups, to improve patient outcomes, minimise side-effects and reduce costs. Indeed, some diseases are so rare that their proper diagnosis and ground-breaking treatment has to be personalised, e.g. for extremely rare tumours[15].

Taking into consideration the patient's perspective about medical treatments is necessary in order to understand what could be done to improve care protocols and services, as well as to enhance the quality of the doctor-patient communication and, in general, to be concerned about the meaningfulness of the information provided for the patient's comprehension and decision-making[16].

Equally important for a patient-centered approach in this specific research area is to integrate epidemiological studies on the diseases' natural history with quality

of life studies on effective strategies to cope with a rare disease, and social science research on the communicative dimension, the cultural aspects and the socio-economic implications of living with a rare disease[17]. A vision of a *radical interdisciplinarity* – which integrates aspects of biological, psychological, social and humanities approaches in the concepts and methods of the health sciences and public health in order to promote sustainable interventions capable of engaging with the complexity of health, disease and sickness[18] – allows for the daily lives of individual patients and groups of patients to be embedded in the design of rare disease research.

Interestingly, "supporting the development of more research projects centred on patient quality of life and on a patient-centered approach, including how patients manage and cope with RDs" is included among the higher priorities for rare disease research identified by Eurordis[19]. The shift toward patient-centered care implies that patients acquire an increasing relevance and play a prominent role in RDR[20]: they "often become 'experts' of their own disease by capturing substantial information during their long odyssey through healthcare systems"[21].

4. The roles of expert patients

Patients can be considered health 'experts' on their own diseases[22]; in the same way, family members are seen as 'lay experts'. The particular roles of 'expert patients' and 'lay experts' in the rare disease area primarily regard the doctor-patient information exchange and decision-making processes[23]. Actually, "expert patients have the unique opportunity to clarify patient values and priorities, which in turn may better inform clinical decision-making"[24] as well as to identify "some needs that are not considered or are only poorly considered by doctors and other healthcare professionals"[25].

A recent qualitative study on the potential of patient perspectives in medical decision-making reports an interesting anchor example of physicians' reactions toward information exchanges with expert patients about rare diseases:

> That he comes to me, and then somehow has enormous expectations and wants to tell me how it needs to be done [or not done], that's difficult for me; but he can be right. Thus, I mean, who is the specialist for these diseases? Actually it's the person afflicted. 'Well, he's got the symptoms, he knows how it was diagnosed, and he also knows what works for him.' The real specialist on the disease is in general the sick person. When it comes to common diseases, we are also experts, because we experience them so often. When it comes to rare diseases—well, I think if the physicians were honest, they are sometimes just helpless, because, they just do not have it that often (Physician, female, 42 years, KA07)[26].

As this interview underlines, while information about common diseases has long been acquired, knowledge of rare diseases is limited. Patients with rare conditions acquire both unique experience and precious knowledge – difficult to find elsewhere – of their individual condition, in addition to self-management skills, and they are essential for fostering knowledge sharing.

In recent years, the general concept of 'expert patient' has been widely analysed, criticized and has evolved: "these patients are now considered, not only to be more efficient in the management of their own condition and communicating effectively with health professionals, but to also act as educators for other patients and as resources for the last, provide feedback on care delivery, and be involved in the production and implementation of practice guidelines, as well as in the development and conduct of research initiatives"[27]. The possible expert patients' roles are discussed by Boulet[28], who identifies four domains of expertise: clinical, educational, research, other (e.g. lobby health care authorities, represent patients in various committees, participate in activities of patients' associations, and contribute to the development of support groups).

The importance of academic involvement and research engagement for the current definition of an expert patient is stressed by many studies. In the research domain, expert patients may, for example, set the research agenda, incorporate the patient perspective into study design and participate in discussions about the results; provide input regarding the choice of research questions and define patient-relevant outcomes; identify strategies for increasing enrolment in trials; contribute to the evaluation of new treatments and advice on side-effects management; help to design and implement end-of-study knowledge translation plans; disseminate findings[29].

As mentioned above, the role of expert patients is particularly crucial in the rare diseases field, which is why one of the guiding principles for conducting rare disease research at the national and EU level identified by Eurordis is to empower patients in research[30]:

> Empowering patients in research means recognising that patients are full and equal partners, developers, funders of research in RD. In practice this should translate into fostering:
> - participation of patient groups to EC-funded research projects via simplified procedures;
> - capacity-building of patient organisations via training of their representatives;
> - inclusion of patients in research infrastructures and increased patient-driven governance;
> - patient involvement in each step of clinical trial development, e.g. in evaluation and ethic committees[31].

This Eurordis position paper, which presents an overall strategy based on what are the RDR's priorities and how to achieve them, highlights the need for patients and patient groups to be partners in research not only as participants or as study subjects, but as "real" partners with a complementary knowhow[32]. However, while it is progressively accepted that "empowerment of expert patients as true partners in clinical studies and therapeutic trials has become an ethical necessity"[33], barriers to the development of expert patients has been recognised (primarily related to the requirements to become and remain an expert patient)[34], as well as concerns about the process of research engagement (related to time, resources, logistical issues, possible biases or conflicts of interests, ethical concerns about patient rights, lack of training, absence of policies)[35].

In this context, the implementation of best practices and guidelines to bring the patients' voice to the rare disease research community is essential to fill these gaps. In the next two paragraphs (§§ 5-6), we will introduce recent self-regulatory activities for improving patients' involvement in RDR; in the last paragraph (§ 7), we will discuss some ethical challenges and ongoing issues.

5. The IRDiRC Policies and Guidelines

The International Rare Diseases Research Consortium (IRDiRC), launched in 2011, brings together relevant international stakeholders (governmental and non-profit funding bodies, patient organizations, policy makers, companies, and scientific researchers) with the aim of promoting the advancement of rare diseases research and in order to foster research collaboration worldwide[36]. As a first step towards improving coordination of global research efforts, in April 2013 (updated in May 2020) the IRDiRC Consortium Assembly developed and adopted a set of policies and guidelines, to be incorporated in members' funding calls and in research conduct. These guidelines place emphasis on collaboration in RDR, on the involvement of patients and their representatives in all relevant aspects of research, as well as on the sharing of data and resources. The starting point of the process was the need for better integration of RDR:

> There is an urgent need for better integration of rare disease research, in particular with a view to sharing approaches, resources and data that will enhance the development of better diagnoses and therapies, and not reinvent the wheel. This integration mandates a cultural change while respecting data protection and ethical approvals, and the direct involvement of all relevant stakeholders (scientists, doctors, patients, industry, and regulators) to collectively focus on the key outcome which is improved health, through better diagnoses and therapies, for people living with rare diseases worldwide[37].

The IRDiRC document defines (both in the 2013 and in the 2020 versions) a *consortium policy* as "a principle which consortium members agree to follow", whereas *consortium guidelines* are "recommendations made by IRDiRC scientific committees/ working groups that offer advice as to "best practices" at a given time"[38]. Both policies and guidelines are likely to be reviewed periodically. Among the policy and guidelines for researchers involved in IRDiRC-associated projects, a specific section is dedicated to the "Participation by patients and their representatives in research":

> *Policies*:
> RD research should involve patients and/or their representatives in all relevant aspects of the research.
> *Guidelines*:
> The impact of research on people living with a RD should be a key consideration for each project. Best ethical practices for ensuring the interest of the individuals living with RD should be applied.

> Patients and/or their representatives should be involved in the governance of RD registries and biobanks.
> Patients and/or their representatives should be involved in defining the objectives, the design, the outreach, and the analysis of clinical research and natural history studies.
> Research projects should appropriately acknowledge the contribution of patients and their representatives[39].

The evolution in the Consortium's vision, goals and governance, e.g. the IRDiRC Vision and Goals for 2017-2027 document, confirms what was originally established in 2013:

- Patient engagement in research and clinical networks should continue to be facilitated[40];
- Placing patients at the center of clinical research, drug development, and evaluation is increasingly recognized as paramount to fully understanding a disease and to identifying meaningful end points. Their knowledge, contribution, empowerment, and participation are crucial to increasing the efficiency of such efforts[41].

The new goals that IRDiRC members have committed to accomplishing by 2027 "can only be achieved with fundamental changes in the conduct and sharing of science, and application of that science as rapidly as possible to advance the care of rare disease patients (…), with continued commitment to scientific excellence, rapid and ubiquitous sharing of approaches and data and resources, and continued monitoring of progress and constant re-evaluation of direction based on new data"[42]. In this context, the patients' involvement in health policy planning and in task forces/expert panels for setting guidelines – which has been crucial in the past years – may contribute to the achievement of the new goals[43]: to reach diagnosis within one year, to develop 1,000 new therapies and to create methods for assessing the impact of diagnoses and therapies on patients' well-being.

As a specific best practice related to the patients' engagement, IRDiRC included patients in the committees and task forces formed to promote policy changes since 2013[44]:

> Representatives from patient organizations are participants in IRDiRC Committees and Task Forces in order to ensure patients' views are taken into consideration during strategic planning and on all activities, carried out in line with the agreed principles described in the IRDiRC Policies and Guidelines. Patient organizations that are also funders of research reinforce the implementation of these principles through their funding programmes, external representatives are systematically invited to provide their input on various aspects including recommendations to improve rare disease research policies and practices, and a newly formed Patient Advocates Constituent Committee will identify further common barriers to be addressed through collaborative actions that apply the IRDiRC Policies and Guidelines[45].

This organizational structure contributed in strengthening trust relationships between patients and the scientific community, improving the quality of research collaboration and promoting transparency and accountability in the RDR domain. Particularly interesting in our view is the Patient-Centered Outcome Measures Task

Force, established in 2015 following the recommendations issued by the Therapies Scientific Committee of IRDiRC:

- Encouraging, supporting and establishing early and continuous dialogue on clinical development strategy and wide evidence generation (e.g. natural history, registry, clinical trial design, clinical endpoints, surrogate endpoints, patient relevant outcomes, regulatory strategy, medical practice, public health strategy) with all relevant stakeholders such as patients' representatives, medical experts, researchers, scientific societies, regulators, health technology assessors, payers and sponsors when appropriate. This could be done through dedicated workshops, safe harbors where knowledge could be shared in a non-competitive manner.
- Encouraging, supporting and developing patient focused/relevant outcomes (e.g. exploring the use of appropriate surrogate endpoints). This is an essential step to gather more successful outcomes at the time of benefit-risk assessment[46].

This Task Force made suggestions for developing outcome measures with rare disease patients in mind, so as to improve the quality of future trials and provide the patient community with information that was relevant to them[47]. Patient-Relevant Outcomes, or Patient-Centered Outcomes, are used to measure patients' perception about their health status and quality of life, facilitating communication, understanding and treatment of their conditions[48].

6. The Eurordis Community Advisory Board (CABs) Programme

In the same vein, in 2018, the European Organisation for Rare Disorders (Eurordis) started a patient-engagement programme to support patient organisations in creating a CAB for a specific disease and in establishing patient-oriented collaborations with companies and research sponsors[49]. CABs are groups created and led by the patients to practice community engagement in health research. They were of great importance in the 1990s for HIV/AIDS product development[50] and are now mostly used in haematology, cancers and rare diseases. Inspired by these experiences, where patients with the same disease join together, meet with relevant developers and discuss all aspects of the research[51], the Eurordis CABs are groups of about 7-20 volunteer patients (and/or close family members or carers, and/or members of patient organisations) who offer their expertise to public and private sponsors of clinical research in the same disease area. CABs "are involved in scientific as well as policy-related issues (i.e., access). They provide expert advices to all stakeholders involved in the research, development and service provision of medical treatments"[52]. Members are not selected nor invited by the sponsors. The structure of the CABs is developed by patients. Also, the agenda of the meetings and the secretariat is driven by patients, who are considered 'patient investigators' or, in fact, 'expert patients'[53].

As already stressed, patients can provide an added value in setting research priorities, in discussing research design and planning (e.g. inclusion/exclusion criteria, Patient Reported Outcomes, drop-out risks, etc.), in influencing research conduct,

in the evaluation and dissemination processes, in the post-approval phase and in pharmacovigilance. People from a CAB can also join trial steering committees, be involved in data safety monitoring boards, give advice on informed consent, provide valuable insights on access and other policy-related issues, and provide input on a wide variety of topics that are meaningful to patients:

> Topics discussed cover the target population, the study feasibility, the endpoints including patient reported outcomes, the comparator choice and/or the acceptance of a placebo controlled trial, the quality of life, the practical aspects of the trials, and the identification of previously unknown or unmet patient needs/preferences.
> This represents a well-structured programme for the engagement of patients, where collective thinking and exchange between different patients ensure high quality dialogue with developers and can inform HTA[54] also[55].

A central part of the programme consists in mentoring and training initiatives with the purpose of turning patients into expert patients, who will be able to advise researchers and help clinical trials become more patient-friendly and patient-relevant. Training activities are especially addressed to those who are less experienced with the development and evaluation of health technologies.

Another important aspect is that the programme is part of a broad process of definition of a common framework for collaboration between patient organisations and companies or academic sponsors of clinical studies in the field of rare diseases. The 2019 "EURORDIS Charter for Collaboration in Clinical Research in Rare Diseases"[56] recognises that, as patients increasingly develop expertise in their disease and organisations foster exchanges of individual experiences, patient associations are clearly the legitimate partners of clinical studies' sponsors. The Charter underlines the importance of the function of CABs and patient organisations' expertise in facilitating every stage of the trial, from design to dissemination of data and follow-up, including ethical evaluations: "when CABs have been involved in the design of the protocol, ethics committees can rely on them to know that the study is as patient-centric and patient-friendly as possible. In fact, while not the same patients, patients are encouraged to be on ethics committees. This collaboration is time-saving and contributes to the elaboration of a patient-oriented project, taking into account the possible individual and collective risks and benefits"[57].

Regarding the nature of the collaboration between CABs and sponsors for a given trial, the Charter states that it is oriented towards reaching and maintaining high quality standards in research:

> For a given trial, the CAB and the sponsor establish a collaboration in which the CAB brings its expertise on a rare disease to accelerate the production of quality data of scientific relevance and to optimise the use of time and means for the development of safe and effective treatments. This collaboration is based on total transparency on the part of both the sponsor and the CAB, and does not call into question their respective legal responsibilities[58].

Particularly, collaboration would optimise the choice of parameters such as: the main objective of the trial, in order to adequately evaluate the potential therapeutic

benefits for the patients and meet their expectations; the number of participants, considering the limited population of rare disease patients, the choice of adequate trial designs and any ability to involve patients; the acceptable constraints for participants (expectation of some therapeutic benefits vs. acceptability of the constraints for the population of patients); the rules for terminating individual participation (safety of participants vs. protection of the trial); the planning of possible interim analyses and their consequences, and the organisation of the independent monitoring committee (where patient representatives can also be involved).

In order to respect principles and criteria of collaboration, a Charter Agreement is established for each study by EURORDIS-Rare Diseases Europe and the sponsor, and a specific Memorandum of Understanding is signed between the CAB and the company. Time will be needed to evaluate the results of these strategies of collaboration.

7. Expert patients and advocates' roles and commitments

The collaboration between the delegates of patients' associations and the institutions and organisations involved in the development, testing and marketing authorisation of drugs for rare diseases has therefore become increasingly intense and coordinated over the years. At present, we are witnessing a transformation in *advocacy* action, which has led to the recognition of the para-institutional role of patients' associations, i.e. the recognition of the legal legitimacy of the requests proposed in the production of standards and application tools. An increased political power has been recognized by the regulatory agencies, and a specific agreement between the EMA (European Medicines Agency) and the FDA (US Food and Drug Administration) has recently been signed, with the aim to "share best practices on involving patients along the medicine's regulatory lifecycle within the respective agency's to support each's aim to further improve and extend its current actives in this area"[59].

Representatives of the Eurordis federation have attended prominent EMA technical committees, such as the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO), the Committee for Advanced Therapies (CAT), the Patients' and Consumers' Working Party (PCWP); committees that have played an important role in the production of legal instruments of extreme importance, such as the EU Regulation on Orphan Medicinal Products (Regulation 141/2000), the EU Regulation on Medicinal Products for Paediatric Use (Regulation 1901/2006), the EU Regulation on Advanced Therapy Medicinal Products (Regulation 1394/2007)[60].

These results are of great importance, clearly affecting not only the associations of rare disease patients, but in their case contrasting the marginalization experienced routinely and thus assuming a remarkable significance. As noted by Eurordis' top management in commenting on the results achieved by the federation in its first 20 years of activity, mere participation in institutional bodies has progressively given rise to an ever-increasing impact in decision-making processes[61]. Equally significant was the impact of patient association representatives in other venues. The ePAGs, the European advocacy groups operating within the European Reference Network

for Rare Diseases (ERNs), which was established as a result of a project promoted by Eurordis, played a key role through their participation in the technical committees, a role which led to an improvement in the management of ERNs themselves:

> In 2016 EURORDIS, in collaboration with the European rare disease community, established 24 European Patient Advocacy Groups (ePAGs) as forums to optimise the involvement of patient representatives of the rare disease community in the 24 ERNs. Each ePAG corresponds to the scope of one of the 24 ERNs, aligning patient organisations and clinicians, experts and researchers working on the same rare or complex disease or highly specialised intervention. Today there are over 300 ePAG patient advocates participating in the different groups. The ePAG advocates have been involved in the development of ERNs' applications and are currently members of the ERNs Boards, Steering Committees and task forces[62].

The current objective of Eurordis is the inclusion of representatives of rare patients from different member states in the European Parliament, selected from the network of national advocates, who have functions and delegations comparable to those of elected parliamentary members (European Network of Parliamentary Advocates for Rare Diseases). This power of political action naturally implies greater responsibility, of which the associations themselves are aware. The definition of the role of *advocate*, as well as the training of semi-professional figures such as the "expert patient", soon became priority objectives in the planning of the activities of the associations, also in order to make their action more effective[63]. In addition to training entrusted to the organisational capacity of the associations themselves, structured courses have been proposed by the federations, the contents of which have been the subject of greater selection and planning, with a clear thematic focus on the process of legislative elaboration, on the roles and functions of the bodies and institutions of reference, on the ability to network and activate collaborations with research institutions and groups[64]. For example, a Eurordis training initiative was aimed at enhancing the technical knowledge and skills of patient delegates in ePAGs groups: the training focused on topics such as healthcare programs and clinical guidelines, Clinical Patient Management System (CPMS), political influence capacity and ERN (European Reference Network). EURORDIS also developed a leadership training school for ePAGs, launched in 2019 as part of the EURORDIS Open Academy[65].

8. An ethical analysis

In addition to the objective of developing a 'technical' preparation aimed at making advocacy more effective, it has to be stressed that there is an increasing need to highlight the possible ethical challenges related to this activity and to identify ethical principles and rules of conduct. The various codes and guidelines for lobbyists, drawn up by associations in different sectors, are clear examples of this. The *International Code of Ethics for Professional Lobbyistics* identifies ethical principles more directly related to professional ethics, such as integrity, intellectual honesty, duty of continuous

training and respect for confidentiality and the application of protection measures in the processing of data and information. The federations of patients' associations, which differ from lobbies for the voluntary nature of their work and for the intrinsic moral value of the interests they protect, have rather identified transparency, capacity for representation, and continuous training as the essential elements of the "professional" quality of the expert patient.

Remaining adherent to our field of interest, which is the ethics of research, below we examine the aspects that most directly affect the action taken by expert patients. In this context, it seems appropriate to distinguish between the role of *advocates* and the role of *expert patients*. What characterizes the activity of advocacy is the aim to achieve institutional, scientific and cultural recognition of the interests, preferences and experiences of patients affected by rare diseases. The main contribution of expert patients should instead be that of representing these interests in more limited contexts, such as the organization of clinical trials.

The participation in an ethics committee for clinical trials is one of the contexts in which the contribution of expert patients can be of great relevance and impact, especially for the development of orphan drugs. As already mentioned, the knowledge of the disease by expert patients often represents, for rare diseases, the main basis of information about its outbreak, natural history, evolution of symptoms, possible epigenetic factors, familiarity and, in some cases, the estimation of the possible spread in the population. This information basis is, as evident, of crucial importance in the definition of the design of clinical trials and in the identification of primary and secondary endpoints. As is well known, primary endpoints consist mainly of healing, medium or long-term survival, remission, or symptoms control. These endpoints are defined in the experimental design based on knowledge of the disease and research that led to the development of the new molecule used in the trial, or – as is often the case for rare diseases – the study of off-label use of existing drugs.

Regarding the definition of endpoints in clinical trials, there is a wide-ranging debate about the possible role of expert patients in their identification, especially with regard to primary endpoints. On the one hand, there is an increasing recognition of the contribution of patients in the identification of secondary endpoints, which concern aspects more directly related to quality of life and symptom control. On the other hand, the identification of primary endpoints appears to be of clear clinical pertinence, as they refer to the biological mechanisms that allow for disease control. An intervention by the expert patients may be mainly affected by elements of interest to patients, such as the modalities and timing of drug administration or the duration of treatment, with a clear bias in the evaluation of the endpoints' relevance.

Moreover, it must be stressed that the control of symptoms, the reduction of disability, and in general a better management of the disease, are aims of such importance as to justify the organization of a clinical trial for many rare diseases. For example, the classification of the severity of side effects of an experimental drug requires, in addition to the use of objective and validated clinical parameters, the collection of participant reports, as the subjective tolerance of such effects is an essential element in the estimation of treatment outcomes. From this point of

view, too, the action of patient associations has often been decisive in leading to the recognition of the importance of listening to patients and in translating patient reports into clinically appreciable indicators.

In any case, the contribution of expert patients in defining the design of clinical trials (as well as in their evaluation) is legitimated by the delegation received from patient associations, whose mandate is the representation of patients. In Italy, for example, patient associations themselves felt the need to have a policy document. This document would offer a framework of ethical and deontological rules to inspire the work of the representatives of patients and that of the patients themselves as experts in clinical trials; at the same time, it could be a reference document for the clinical investigators themselves. In collaboration with the "Persone non solo pazienti" initiative, which brings together sixteen patient associations, the CNR Interdepartmental Center for Research Ethics and Integrity has drawn up the *Charter of Principles and Values. Ethical Toolkit for the Participation of Patient Associations in Clinical Trials*[66]. With regard to the role of expert patients in the definition of clinical trials, the Charter states that, as delegates of patient associations, they can contribute to "drawing up a list of secondary endpoints of the clinical trial, providing useful information on the types of side effects – often hardly noticeable to investigators – on which it is important and of priority to focus during the current trial, in order to promote the well-being of patients and improve the feasibility of the study"[67].

It is worth noting that, while expert patients as delegates of associations can help draw up a list of endpoints, the significant difference between the action of patient associations and the role of expert patients has to be highlighted. The action taken by patient associations is more eminently political than the action of expert patients, which should be primarily carried out on an ethical level, with an elective position within ethical committees for clinical trials. Nonetheless, the long and careful training, the important and demanding task carried out, the explicit and implicit delegations needed, the privileged – if not exclusive – interaction with sponsors and institutional stakeholders, lead us to the *professionalization* of the expert patient role. This professionalization of the expert patient risks producing an excess of power, control and monopolisation of contacts and of the process of building shared rules, crystallized in bureaucratic procedures. This is a risk often highlighted by patient associations themselves, and can be somewhat mitigated through a clearer definition of delegation and, above all, of the scope of action which, as we said, should be limited – in our opinion – to the ethical evaluation of clinical trials.

This task certainly requires cross-cutting skills and technical knowledge, but also the ability to comprehend the specific health conditions of a particular group of patients and to interpret their needs, preferences and values. It is therefore not a "political" commitment, but a purely ethical one, focusing on issues closely related to clinical trials and the very role of the ethicist.

A distinction between the roles and competencies of patient advocates, patient organisation representatives, and expert patients, has been proposed by Eurordis. While patient advocates have a competence, largely due to the experience of their disease and the medical knowledge they have acquired, that enables them to act effectively on their

own pathology, patient organisation representatives have the function of conveying the needs, preferences and opinions of a wider community of patients. A more specific role in the ethical committees is attributed by EUPATI (European Patients' Academy) to expert patients:

> *Patient experts* (…) have a comprehensive understanding of all aspects of the medicines development process, and can actively participate in all aspects of the ethical debate on the same level as the other ethics committee members. They are not joining the ethics committee in a representative role but have much exposure to other cases due to their activities in their patient organization. Their contribution to ethical review of trials for other diseases could also be valuable because of their knowledge of R&D (research and development)[68].

The role of an ethics committee member requires, evidently, a clear identification of the ethical principles and values that should guide its action in the process of an ethics review of research protocols, summarised as follows by EUPATI (European Patients' Academy)[69].

> *Relevance*: Patients have knowledge, perspectives and experiences that are unique and contribute to ethical deliberations.
> *Fairness*: Patients have the same rights to contribute to the ethical review of clinical trials as other stakeholders and have access to knowledge and experiences that enable effective engagement.
> *Equity*: Patient involvement in the ethical review process contributes to equity by seeking to understand the diverse needs of patients with particular health issues, balanced against the requirements of the industry.
> *Legitimacy*: Patient involvement facilitates those affected by regulatory decisions to participate in regulatory activities; contributing to the transparency, accountability and credibility of the decision-making process.
> *Capacity building*: Patient involvement processes address barriers to involving patients in ethical reviews and build capacity for patients and ethics committees to work together[70].

In conclusion, we would like to briefly reflect on what seem to be the strictly ethical principles: relevance and fairness. *Relevance*, here referring to the valorisation of the perspectives and experiences of the patients, recalls the ethical criterion according to which deliberation requires the identification and analysis of "morally relevant facts". In this perspective, the personal experiences mentioned in the guidelines are to be included among individual interests or preferences. On the contrary, the "factual" elements, which can be more easily described in objective terms, and which nevertheless have moral weight, are the health conditions and the expected risks and benefits of the clinical trial. This is, as is well known, a difficult and never definitive balancing act, in which the independent willingness of the recruiting subjects to participate is the decisive factor. In this respect, it is perhaps worth mentioning how individual autonomy is a central aspect of the assessment of the "best subjective interest". Autonomy, expressed in clinical trials through informed consent, is in fact understood not only as the ability to act on the basis of one's own preferences, but more

deeply to recognize the values on which one's identity as a moral agent is based, and the ideals that are an integral part of personal identity. Violating personal autonomy, therefore, is to inflict profound damage to human dignity. Not recognizing in the other person the crucial value that self-respect as a free agent has for the constitution of one's personal identity, is consequently not a simple harm, but an injury to dignity and a subversion of the assumptions of moral life. The risk that is inevitably involved in participation in a clinical trial can only be "compensated" if conditions exist that exclude any form of instrumentalization of the other person and that practice real respect for his or her will and values.

The principle of *equity* also deserves further analysis – for its axiological value. Equity, here defined in the double sense of correctness and equity proper. While correctness entails deontological duties towards colleagues and associates and their families, equity requires the duty of fair treatment and impartial consideration of all interests involved. In the case of a clinical trial, fair consideration of all interests must certainly give priority to the interests of the clinical trial participants, as responsibility toward them is direct and unavoidable. However, the virtual audience of patients for whom the drug is intended once it is placed on the market, cannot be overlooked in any way. This means, for example, that the comparison of the estimated cost of two experimental drugs is a particularly important factor in the evaluation of a clinical trial, especially in the case of rare diseases.

The cost, which may constitute an incentive for pharmaceutical companies to produce drugs for a limited number of users, is, on the other hand, an element which may seriously limit its inclusion among the drugs for which reimbursement by the national health system is provided. The introduction of drugs, devices and rehabilitative treatments within the essential levels of healthcare is, as is well known, one of the most important and challenging objectives of the advocacy action by patient association representatives. The choice of a protocol referring to a less expensive drug with a comparable level of efficacy and safety, compared to a clinical protocol referring to a more expensive drug, therefore becomes a duty of equity in order to allow as many patients as possible to benefit from the treatment, a duty which in the case of rare diseases is of the utmost importance, given the shortage and cost of available drugs.

A final extension of equity relates to the fair consideration of the interests of all rare disease patients, in the specificity of the needs and care requirements posed by the different pathologies. Here, an ethical conflict emerges, represented metaphorically by the dialectic between the "participant's perspective", which in this case leads to privileging, in advocacy action, the interests of the specific patient group sponsored, and the "spectator's perspective", which observes impartially the conditions of the different patient groups without belonging to any of them. This latest perspective should be the indispensable perspective for an ethics committee. The "archangel's point of view", as Richard Mervyn Hare would say, requires an impartial assessment of morally relevant facts. These are no longer constituted, as in the advocacy activities, by the interests of a group of people who share the same pathology, but in a more general sense by the interests of all the rare disease patients, as a community whose morally significant differences are constituted solely by the seriousness of the various

pathologies. This task requires both ethical analysis abilities and political competence: this will be the main challenge for the delegates of the Eurordis federation in the European Parliament.

Notes

[1] Benjamin et al., 2017.

[2] Nguengang Wakap et al., 2020; http://www.orphadata.org/cgi-bin/epidemio.html; https://www.eurordis.org/about-rare-diseases.

[3] European Parliament and Council of the European Union. Regulation (EC) N1141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products 2000 (Smith, 2015).

[4] Benjamin et al., 2017.

[5] Slade et al., 2018.

[6] Stoller, 2018.

[7] Forman et al., 2012.

[8] Eurordis, "Position Paper: Patients' Priorities and Needs for RD Research 2014-2020", October 2011; https://www.eurordis.org/content/position-papers-0.

[9] Stoller, 2018.

[10] Eurordis is an alliance of patients' association, founded in 1997, dedicated to improving the quality of life of people living with rare disease through advocacy, support for research and medicine development, facilitating networking amongst patient groups, raising public awareness, and many other actions designed to reduce the impact of rare diseases on the lives of patients and family; https://www.eurordis.org/what-we-do.

[11] Eurordis, "Survey of the delay in diagnosis for 8 rare diseases in Europe ('Eurordiscare 2')", 2007; https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf.

[12] Slade et al., 2018; von der Lippe et al., 2017; Schieppati et al., 2008; Forman et al., 2012.

[13] Cf. https://www.eurordis.org/what-we-do; Schieppati et al., 2008.

[14] Nourrissier, Ensini, Marvis in Wehling et al., 2015.

[15] Eurordis, "Position paper: WHY Research on Rare Diseases", October 2010; http://download2.eurordis.org/documents/pdf/why_rare_disease_research.pdf. See also Palau, 2012; Schee genannt Halfmann et al., 2017.

[16] Benjamin et al., 2017.

[17] Eurordis, "Position paper: Patients' Priorities and Needs for RD Research 2014-2020", October 2011.

[18] Clarke et al., 2019.

[19] Eurordis, "Position paper: Patients' Priorities and Needs for RD Research 2014-2020", October 2011.

[20] Babac et al., 2019.

[21] Babac et al., 2019.

[22] "The term 'expert patient' first appeared in a report presented to the UK Parliament in 1999 as a 'healthy citizen' initiative to help deal with chronic illness" (Cordier, 2014). Cf. Department of Health, *Saving lives: our healthier nation*, London, The Stationery Office, 1999. Other terms used are "autonomous", "resourceful", "involved" (Shaw & Baker, 2004).

[23] Babac et al., 2019; von der Lippe et al., 2017.

[24] Cordier, 2014.

[25] Cordier, 2014.
[26] Babac et al., 2019, Table 3.
[27] Boulet, 2016.
[28] Boulet, 2016, Table 1.
[29] Forsythe et al., 2014; Cordier, 2014; Boulet, 2016.
[30] Eurordis, "Position paper: Patients' Priorities and Needs for RD Research 2014-2020", October 2011, p. 17.
[31] Eurordis, "Position paper: Patients' Priorities and Needs for RD Research 2014-2020", October 2011, p. 17.
[32] See also Mavris & Le Cam, 2012.
[33] Cordier, 2014.
[34] Boulet, 2016; Shaw & Baker, 2004.
[35] Forsythe et al., 2014.
[36] https://irdirc.org/about-us/.
[37] Lochmüller et al., 2017.
[38] https://www.irdirc.org/wp-content/uploads/2017/10/IRDiRC_policies_24MayApr2013.pdf.
[39] https://irdirc.org/wp-content/uploads/2020/05/IRDiRC-Policies-and-Guidelines-May-2020.pdf; (first version of the document at: https://www.irdirc.org/wp-content/uploads/2017/10/IRDiRC_policies_24MayApr2013.pdf).
[40] Goal 1; Austin et al., 2018, p. 23.
[41] Goal 2; Austin et al., 2018, p. 24.
[42] Austin et al., 2018. See also Dawkins et al., 2018.
[43] See also Cordier, 2014.
[44] Dawkins et al., 2018.
[45] Lochmüller et al., 2017.
[46] https://www.irdirc.org/wp-content/uploads/2017/12/PCOM_Post-Workshop_Report_Final.pdf.
[47] Dawkins et al., 2018. See also: https://www.irdirc.org/wp-content/uploads/2017/12/PCOM_Post-Workshop_Report_Final.pdf.
[48] Mancini & Zagarella, 2018.
[49] https://www.eurordis.org/content/eurordis-community-advisory-board-cab-programme; https://www.eurordis.org/news/rare-disease-patient-advocates-sponsors-come-together-co-produce-clinical-research.
[50] Camp & Houyez, 2019.
[51] Houyez & Camp, 2019.
[52] https://www.eurordis.org/content/eurordis-community-advisory-board-cab-programme.
[53] https://www.youtube.com/watch?v=0P1HB-54Gt8.
[54] Health Technology Assessment.
[55] Houyez & Camp, 2019.
[56] https://www.eurordis.org/content/eurordis-charter-clinical-trials-rare-diseases; http://download2.eurordis.org.s3.amazonaws.com/clinical_trials/Charter_FINAL.pdf.
[57] http://download2.eurordis.org.s3.amazonaws.com/clinical_trials/Charter_FINAL.pdf.
[58] http://download2.eurordis.org.s3.amazonaws.com/clinical_trials/Charter_FINAL.pdf.
[59] European Medicines Agency, Food and Drug Administration, 2016.
[60] https://oncologypro.esmo.org/content/download/124831/2364922/version/1/file/RCE-Advocates-The-Power-of-Rare-Disease-Patient-Advocacy-WEINMAN.pdf, p. 34.
[61] https://www.eurordis.org/news/2017-looking-forward-eurordis-celebrates-20-years.
[62] http://www.rd-action.eu/wp-content/uploads/2018/09/Final-Overview-Report-State-of-the-Art-2018-version.pdf, p. 53.

[63] https://www.eurordis.org/it/news/2018-un-anno-di-empowerment-dei-pazienti; https://www.eurordis.org/news/2018-year-patient-empowerment.

[64] http://www.uniamo.org/wp-content/uploads/2018/07/Rapporto-MonitoRare_27_07_2018.pdf, p. 24.

[65] http://www.uniamo.org/wp-content/uploads/2018/07/Rapporto-MonitoRare_27_07_2018.pdf.

[66] *Carta dei principi e dei valori. Ethical Toolkit per la partecipazione delle associazioni dei pazienti ai trial clinici*, A. Grignolio Corsini, E. Mancini, C. Caporale, Consiglio Nazionale delle Ricerche, Interdepartmental Center for Research Ethics and Integrity; http://www.personenonsolopazienti.it/il-progetto/la-carta/.

[67] Ivi, p. 7. English translation by the authors.

[68] Klingmann et al., 2018; p. 8.

[69] Klingmann et al., 2018; p. 3.

[70] Klingmann et al., 2018, p. 3.

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