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Introducing ‘Health Vulnerability’. Towards a Human Right Claim for Innovative Orphan Drugs?

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Abstract

Although several European law instruments specifically promote the development of orphan medicines, rare disease patients still suffer from an excessive lack of access to orphan drugs. In order to base a claim for equity of access to research benefits, health vulnerability is introduced as a human-rights based public health concept. It represents a potentially valuable and powerful means in European law for rare disease patients to claim for an improved public action to develop innovative orphan drugs, including through the use of novel data-driven technologies like computer modelling and simulation as they have the potential to palliate some of the obstacles in the current development process of orphan medicines. The human-rights based approach would be all the more valuable than it would simultaneously draw attention on privacy aspects of vulnerability for orphan disease patients, especially regarding increased risks stemming from the processing of highly sensitive health data.

Keywords

health vulnerability – orphan medicines – equity of access to healthcare – computer modelling and simulation – research ethics – European law – human rights

1 Introduction

Particularly in the case of orphan diseases, and although they do sometimes overlap, health vulnerability and decisional vulnerability have to be distinguished. Only health vulnerability justifies the intervention of the European Union law in the research and development of orphan medicines as will be explained in the following.

Most of the time, the notion of vulnerability is restricted to decisional vulnerability, *i.e.* to an individual perspective of vulnerability mainly linked to autonomy or lack thereof. Hence, it is often focused on decision-making capacity, on the ability of the person to consent and make rational decisions to protect his/her interests, and thus only on the regulation of the informed consent process.¹ Patients suffering from rare diseases are not categorised as vulnerable, and rightly so considering this frequent restriction to decisional vulnerability. On the contrary, decisional vulnerability will not be the approach of this article as the aim is to introduce the concept of health vulnerability.

¹ CNCDDH, Avis sur le consentement des personnes vulnérables, *J.O.*, n°0158, 10 July 2015, Text n°126; Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Health-related Research Involving Humans, in collaboration with the World Health Organization (WHO), Geneva, 2016 (Hereafter CIOMS Guidelines), Guideline 15; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practices, E6(R1), Geneva, 1996, §1.61.

Health vulnerability is meant in a collective perspective and as a public health concept related to justice issues in health like equity of access to health care and equity of access to research benefits and innovation.² Clinical trials and health research are crucial to the development of quality medicines with increasing safety and efficacy. Yet too many people are excluded from research design and trial recruitment (e.g. children, pregnant women or frail elderly adults), in the case of orphan disease patients, because of commercial unattractiveness. This exclusion, even if sometimes well-intentioned, is harmful in the long term as it marginalises whole groups of people. Excluding them from health research excludes them from research benefits and access to health care and quality treatments.

In that perspective and when considering vulnerability in its collective dimension and public health perspective, orphan disease patients can undoubtedly be considered as vulnerable. So did the Council of the European Union characterise them as well.³ It also stated that “the principles and overarching values of universality, access to good quality care, equity and solidarity, as endorsed in the Council conclusions on common values and principles in EU health systems of 2 June 2006, are of paramount importance for patients with rare diseases”.⁴

There are many overlapping definitions of orphan and rare diseases.⁵ We will choose to use the definition given in European Union law⁶ which consists in three elements: 1) there has to be no satisfactory method of diagnosis, prevention or treatment of the condition; 2) it has to be a life-threatening, chronically or seriously debilitating condition and; 3) it has to concern less than 5 cases in 10 000. The number of cases can be higher than 5 in 10 000 when it is demonstrated that the market is unlikely to ever be attractive enough to generate sufficient return on investment.

Even though access to orphan drugs falls within national competencies regarding public health policies, several reasons are justifying the intervention of EU law to complement national legislations. Even if orphan diseases are rare by definition, there is an estimated number of 36 million patients in Europe because there are between 6000 and 8000 different orphan diseases.⁷ Isolated research teams or even national health and research policies cannot cope with the fact that patients are scattered throughout Europe, and so are knowledge and expertise on each orphan disease. As a consequence, there is a significant lack of research on orphan medicines,⁸ and there is poor access to health care for orphan disease patients because of the frequent delays and errors of diagnosis and treatment. Besides the consequent need to rationalise scientific efforts and resources, there is also a clear need for financial rationalisation.⁹ The research and development of orphan medicines is extremely expensive whereas the actual marketing is very uncertain and when an orphan drug is put on the market, the return on investment is very low.

² É. Gennet, *Personnes vulnérables et essais cliniques. Réflexions en droit européen* (LEH Editions, Coll. Thèses, 2020) in press.

³ Council recommendation of 8 June 2009 on an action in the field of rare diseases 2009/C 151/02, Recital 5.

⁴ *Ibid.*, Recital 2.

⁵ T. Richter *et al.*, ‘Rare disease terminology and definitions – a systematic global review: report of the ISPOR rare disease special interest group’, *Value in Health* (13) (2015) 906-914.

⁶ Regulation (EC) N° 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, Article 3.1.

⁷ Council recommendation of 8 June 2009, Recital 5.

⁸ European Commission, Rare Diseases: Europe's challenges, Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, COM(2008) 679 final, Brussels, 11 November 2008; EURORDIS, EURORDIS' position on rare disease research, 2012 ; Regulation 141/2000, Recital 1.

⁹ Regulation (EC) N° 141/2000, Recital 3.

Consequently, it is clear that rare disease patients are in a situation of “health vulnerability”. Whatever the reasons for this are, the underrepresentation of their needs and interests in the research and development processes of (orphan) medicines has the damageable consequence to marginalise them from health research benefits and innovation because of a lack of innovative orphan drugs. This marginalisation constitutes a rationale for international collaboration and rationalisation in order to optimise resources and expertise, notably at the European level.

Has this “health vulnerability” or marginalisation from research benefits triggered an intervention in European law aiming at improving research and development of innovative orphan drugs? What are the main means of action in European law used to improve the availability of orphan drugs, how efficient are they and how could their use be improved?

The analysis of this question will be conducted by the identification of relevant actions by European institutions, be it from the Council of Europe or the European Union. Hence, the study will include European law in a broad sense: binding and non-binding legal instruments, official reports, opinions, statements and guidelines, and even programs or any activities in the field. The results of this analysis show that the means of actions in European law are mainly restricted to the law of the European Union, notably its framework on the internal market or on its framework on research and innovation. Thus we will present the EU framework on clinical trials for the marketing of orphan medicinal products (2) and the EU framework on innovative data-driven technologies for the development of new orphan medicines (3). Introducing a human rights-based approach to the proposed concept of health vulnerability, it will then be argued for more equity in the availability and access to quality treatments for orphan disease patients. Although human rights are not (yet) being used for this specific purpose, it is suggested here that they could potentially constitute a valuable and powerful means of action in European law for rare disease patients to claim for an improved public action to develop innovative orphan drugs (4).

2 The EU Framework on Clinical Trials for the Marketing of Orphan Medicinal Products

The European Union legal framework on clinical trials is described in Directive 2001/20/EC,¹⁰ which is soon to be replaced by Regulation 536/2014,¹¹ entered into force in 2016 but still not applicable. Interestingly, even before putting the framework into place, the European legislator had already elaborated a legal framework specifically meant to improve the development of orphan medicines (2.1). However, not even after a decade of implementation, the latter already shows serious limits in increasing availability to orphan medicines to patients (2.2).

2.1 The EU Framework Promoting Research and Development of Orphan Medicines

The legislator of the European Union elaborated Regulation (EC) 141/2000 implementing incentives and providing for funding to promote research and development. Article 4 created an expert committee, the Committee for Orphan Medicinal Products (COMP) within the

¹⁰ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

¹¹ Regulation (EU) n° 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

European Medicines Agency in order to evaluate the orphan medicine designation and to produce scientific expertise.

More importantly, there are three main incentives in the regulation. First, article 8 gives 10 years of commercial exclusivity which is meant to compensate the costs of research and development of an orphan medicine. Second, article 7 provides for a centralised authorisation procedure for orphan medicines, which at the time did not exist yet. Most of all, this article foresees fees waivers to the European Medicines Agency.¹² Third, article 6 tasks the European Medicines Agency with offering free scientific advice, which later demonstrated to be a determining factor for obtaining marketing authorisation.¹³

Other incentives, as foreseen in article 9, consist in providing for research funding through framework programs. In fact, the European Commission tripled the amount of funding for rare diseases research between the 6th (2002-2007) and the 7th framework program (2008-2013) which provided for 620 million Euros,¹⁴ There has been an ongoing project of a European register for rare diseases in order to coordinate the 62 already existing ones in Europe.¹⁵ The 8th framework program Horizon 2020 is supporting research on rare diseases, notably through the funding of the E-RARE project aiming to coordinate activities between research centres in Europe,¹⁶ or through the funding of the European Joint Programme on Rare Diseases (EJP RD), focusing on communication, funding of research, sharing of data and resources, capacity building and translational research in the field of rare diseases.¹⁷

Finally, the European Commission also brought up expert groups on rare diseases, successively the Rare Diseases Task Force in 2004, which was replaced by the EU Committee of Experts on Rare Diseases (EUCERD) in 2010, itself replaced by the EC Expert Group on Rare Diseases since 2014. The Commission also gives financial support to the International Rare Diseases Research Consortium (IRDiRC) that recently published the “Orphan Drug Development Guidebook” for both academic and industrial researchers describing available tools and best practices.¹⁸

Despite these incentives and efforts at the European level, the initial success of Regulation 141/2000 has nonetheless fallen short on the longer term.

2.2 Mitigated results: a persistent lack of access to orphan medicines

After a few years of implementation, applications for orphan medicines had significantly increased and some new treatments were developed.¹⁹ However, these positive results were not sufficient to have a noticeable impact on the general quality of health protection for orphan diseases.²⁰ To date, 167 marketing authorisations have been granted for orphan medicines.

¹² European Commission, Inventory of Union and Member State incentives to support research into, and the development and availability of orphan medicinal products, 2015, SWD(2015) 13 final, State of play, p. 4.

¹³ European Commission, Commission staff working document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained, SEC(2006) 832, Brussels, 20 June 2006, p. 8.

¹⁴ European Commission, Inventory of Union and Member State incentives (...), *supra* note 12, p. 6.

¹⁵ European Commission, Implementation report on the Communication from the European Commission, Rare Diseases: Europe's challenges and Council Recommendation of 8 June 2009 on and action in the field of rare diseases, COM(2014) 548 final, Brussels, 5 September 2014, p. 9.

¹⁶ E-Rare Project Website, , <http://www.erare.eu/>, accessed 15 September 2019.

¹⁷ EJP RD Website, , <https://www.ejprarediseases.org>, accessed 27 January 2020.

¹⁸ IRDiRC Website, <http://www.irdirc.org/activities/task-forces/orphan-drug-development-guidebook-task-force/>, accessed 3 February 2020,

¹⁹ European Commission, Inventory of Union and Member State incentives (...), *supra* note 12, p. 13.

²⁰ European Commission, Rare Diseases: Europe's challenges, *supra* note 8, p. 3; Directorate General for Research, Ethics, research and globalisation. Europe and its partners building capacity in research ethics, Conference proceedings, Brussels, 14-15 May 2007, Publications Office, 2007, p. 34.

However, this represents only about 2% of the necessary medical treatments to the existing 8000 orphan diseases as many of them target the same disease.²¹

The contrasting results in terms of actual access to orphan medicines have been highlighted as, depending on countries,²² some medicines were commercialised a few weeks after the obtention of the marketing authorisations whereas in other countries it could take months, years if the drug was even being commercialised at all.²³ When the drug is commercialised, it has also been demonstrated that the health technology assessment and national decision related to reimbursement can also take a long time²⁴ and harm the efficient access to orphan drugs.²⁵ Besides, the Directorate-General for research and innovation also emphasised the problem of the cost of orphan medicines, market incentives also having the negative effect of allowing the increase of drug prices.²⁶ High prices may decrease the level of reimbursement because of the lack of cost-effectiveness.²⁷ Moreover, as the European Parliament highlighted in its 2017 Resolution, Regulation 141/2000 is sometimes misused by sponsors who manage to develop an orphan medicine and benefit from the financial and marketing incentives, but already knowing that once on the market the medication will actually be used off-label for another (non-orphan) disease.²⁸ Patent protection has also demonstrated to block or considerably delay generic market access of orphan medicine²⁹. The European Commission is thus actively assessing several aspects of the orphan and paediatric regulations regarding the efficacy on actual access to medicines, for instance, the actual impact and suitability of current market incentives. The final report on the “Evaluation of the legislation on medicines for children and rare diseases (medicines for special populations)” was planned for the third quarter of 2019 but is not available yet.³⁰

In 2017, the European Commission published a report entitled “Rare diseases. A major unmet medical need”, confirming that the current incentives are not enough to compensate for the difficulties and costs related to the development of orphan medicines. Five recommendations are formulated in this report, including one that is promoting collection, exchange and reuse of health and genetic data for research.³¹ This growing aspect of research and development, for orphan diseases but for health research in general as well, gives a glimpse into the promising opportunities offered by new technologies.

²¹ European Commission Website, http://ec.europa.eu/health/human-use/orphan-medicines_en, accessed 29 May 2018; EURORDIS, EURORDIS’ position on rare disease research, 2012, p. 27.

²² T. Gammie, C.Y. Lu and Z.U.D. Babar, ‘Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries’, *PLoS ONE* 10(10) (2015) e0140002.

²³ European Commission, Commission staff working document (...), *supra* note 13, p. 9; European Commission, Rare Diseases: Europe's challenges, *supra* note 8, p. 3.

²⁴ M. Bourdoncle, B. Juillard-Condât and F. Taboulet, ‘Patient access to orphan drugs in France’, *Orphanet Journal of Rare Diseases* 14 (2019) 47.

²⁵ G. Iskov G. and R. Stefanov, ‘Post-marketing access to orphan drugs: a critical analysis of health technology assessment and reimbursement decision-making considerations’, *Orphan Drugs. Research and reviews* 4 (2014) 1-9.

²⁶ Directorate General for Research, Ethics, research and globalisation, *supra* note 20, p. 34.

²⁷ E.H. Davies, E. Fulton, D. Brook and D.A. Hughes, ‘Affordable orphan drugs: a role for not-for-profit organizations’, *British Journal of Clinical Pharmacology* 83 (2017) 1595-1601.

²⁸ European Parliament Resolution of 2 March 2017, Recital 50.

²⁹ M. Minn, ‘Development of Orphan Drugs under European Regulatory Incentives and Patent Protection’, *European Journal of Health Law* 24(3) (2017) 239-263.

³⁰ European Commission Website, https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807_en, accessed 17 March 2020.

³¹ European Commission, Rare Diseases: Europe's challenges, *supra* note 8, p. 28.

3 The EU Framework on Data-driven Technologies for the Development of Orphan Medicines

As science is making health research and medicine development evolve and progress towards more efficiency notably thanks to data-driven technologies, opportunities are emerging for innovative ways to develop orphan medicines (3.1) and they are all the more so than they are promoted by the European Union (3.2).

3.1 Innovative Technological Opportunities for Orphan Medicines

Clinical trials and pharmacovigilance data collection and reuse in orphan diseases represent crucial opportunities to develop new treatments. As has been done in the past, it can be used for drug repurposing in rare diseases.³² It consists of finding a new indication for an already existing drug, but with different dosages and ways of administration.³³ However, emerging technologies allow, thanks to the gathered data, to develop (orphan) medicines thanks to computer simulation and modelling. Computational drug repurposing is being used in order to develop new treatments in general but especially in rare diseases.³⁴

Computer modelling can also be even more ambitious when it aims at simulating clinical trials: *in silico* trials. Using machine learning techniques, it is possible to create virtual subjects and stratify the different responses to a drug, depending on many variables that would be almost impossible to represent with orphan disease patients because of the lack of participants.

Modelling and simulation methodology is based on the concept of data collection (*in vivo*, literature, preclinical, clinical), assumption testing (attempt to elucidate the data on the basis of mathematical/statistical models), learning (retaining assumptions that are informative of the test system), prediction (simulating outcomes on the underlying assumptions that can be used to predict and optimise future experimental outcome) and confirmation of model assumptions (when compared with external data).³⁵

In silico trials are already being used in difficult cases where there are not enough participants to conduct a trial, and particularly in the case of orphan paediatric diseases.³⁶ Data-driven technologies have very interesting potential for the development of orphan drugs in several ways. First, if they were to partly replace clinical trials once their reliability is proven, *in silico* trials and computational drug repurposing would significantly reduce the time needed for developing an orphan drug. Quicker development leads to quicker marketing and commercialisation, and faster access for patients. Second, computer simulation reduces the need for human participants, thus palliating one of the biggest problems for orphan drugs. *In silico* trials would thus lead to a lower number of risky trials and improved reliability of trial

³² E.A. Moreira de Oliveira and K.L. Lang, 'Drug repositioning: concept, classification, methodology, and importance in rare/orphan and neglected diseases', *Journal of Applied Pharmaceutical Science* 8(8) (2018) 157-165; P. Minghetti *et al.*, 'From off-label to repurposed drug in non-oncological rare diseases: definition and state of the art in selected EU countries', *Med Access @ Point Care* 1(1) (2017) e87-e97.

³³ T.T. Ashburn and K.B. Thor, 'Drug repositioning : identifying and developing new uses for existing drugs', *Nature Reviews Drug Discovery* 3 (2004) 673-683.

³⁴ B. Delavan *et al.*, 'Computational drug repositioning for rare diseases in the era of precision medicine', *Drug Discovery Today* 23(2) (2018) 382-394.

³⁵ E. Manolis *et al.*, 'Role of modelling and simulation in paediatric investigation plans', *Pediatric Anesthesia* 21 (2011) 214-221.

³⁶ A. Carlier, A. Vasilevich, M. Marechal, J. de Boer and L. Geris, '*In silico* clinical trials for paediatric orphan diseases', *Scientific reports* 8 (2018) 2465-2473; Nony P. *et al.*, 'A methodological framework for drug development in rare diseases', *Orphanet Journal of Rare Diseases* 9 (2014) 164.

results. Finally, computer simulation would significantly reduce the costs of the research by reducing the need for expensive and uncertain trials. Reducing the costs of research would leave the remaining resources for more fundamental and clinical research. It could lead to a rationalisation of financial resources for the development of orphan drugs, and all the more so as reduced costs would also mean an increased economical attractiveness for private companies because of a more likely return on investment. Ultimately, reduced costs for the pharmaceutical industry would also have a positive play in the health technology assessment as it would reduce orphan drug prices, leading to a better reimbursement thereof and thus improved access for patients.

3.2 European Promotion of Data-driven Technologies for Orphan Medicines

The European Union is increasingly promoting the development and use of data-driven technologies and data-sharing in general. In fact, one key policy objective of scientific research is the concept of open access scientific data.³⁷ As the European Parliament's Science and Technology Options Assessment (STOA) notes:

From one perspective it can be argued that there is an ethical and scientific imperative to share biomedical data for research purposes. From a scientific perspective, this can reduce considerable costs of conducting repeated clinical trials, whilst the ethical imperative pertains to the fact that the majority of research subjects face harm and inconvenience without compensation.³⁸

The Commission has repeatedly funded different initiatives aiming at sharing available data through transnational patient registries. In 2014 there existed 588 different rare diseases registries at the national, regional, European or global level, alternatively run by public institutions, private industries or patient associations, but their lack of interoperability was “severely jeopardising the registries’ potential”.³⁹ Thus in 2017 already, the European Commission was announcing the project of building a European Platform on rare disease registration,⁴⁰ which was finally launched in February 2019. This platform is meant to “make registries’ data searchable at EU level” and to “standardise data collection and data exchange” in order to “improve knowledge, diagnosis and treatment of rare diseases”.⁴¹

The European Commission also funded, through the seventh framework program for research and technological development the Avicenna action.⁴² The latter included 525 experts from 35 countries and lead to the elaboration of a research and technological development roadmap explaining how *in silico* trials are already used and what they could be used for in the future. Other projects related to computer simulation and modelling have been funded that were specific to rare diseases. For instance, the European Commission supported the CRESim project (Child-Rare-Euro-Simulation project) that was aiming to develop “a web-based platform to perform *in silico* experiments to assess different designs for drug evaluation in children with rare diseases”.⁴³

³⁷ European Parliament Research Service, STOA, How the General Data Protection Regulation changes the rules for scientific research, July 2019, p. 2.

³⁸ *Ibid.*, p. 16.

³⁹ European Commission, Implementation report, *supra* note 15, §4.a.

⁴⁰ *Ibid.*, p. 10.

⁴¹ EC Website, <https://eu-rd-platform.jrc.ec.europa.eu/aim-of-the-platform>, accessed 23 October 2019.

⁴² Avicenna Consortium, *In silico* clinical trials: how computer simulation will transform the biomedical industry, 2016.

⁴³ IRDiRC, Small population clinical trials task force workshop report and recommendations, July 2016, p. 35.

The activities of the European Medicines Agency regarding *in silico* trials take place in the area of paediatric medicines. This specific field of research could, however, be very beneficial to orphan diseases as 70% of rare diseases start in childhood.⁴⁴ The Agency has created in 2013, within the Paediatric Committee (PDCO), a Modelling and Simulation Working Group.⁴⁵ The role of this group is to develop the expertise to assess modelling and simulation in marketing-authorisation applications, to promote such use by the industry in areas where it can be particularly useful like first-in-human trials, paediatric investigation plans, extrapolation in elderly populations or rare diseases, to provide scientific advice to applicants and increase awareness and excellence in that field in European national authorities.⁴⁶ The European Medicines Agency is expecting modelling and simulation to be extended in the future as scientific evidence of its reliability and predictive performance will increase.⁴⁷

Data-driven technologies have the potential to palliate some of the obstacles to the development of orphan medicines and thus to contribute to the protection of health vulnerability. Still, in order for this protection to be more systematic, it is interesting to base the protection of health vulnerability in human rights. The latter would indeed permit to reaffirm the need for better equity of access to health care, while still taking into account the new human rights risks accompanying data driven technologies.

4 Vulnerability as a claim for innovative orphan medicines

More than only a descriptive notion, vulnerability becomes a very interesting concept when considered in its normative perspective in ethics and law (4.1). The concept of health vulnerability would have even more impact when associated to a human rights approach, especially considering the developments of the case-law of the European Court of Human Rights in the fields of health and vulnerability, which could help to support a claim to a reliable and equitable knowledge production system in the research and development of medicines (4.2). This claim would be all the more legitimate that it would be made easier and stimulated by the growing importance of the use, for the development of medicine and in particular of orphan medicines, of data-driven technologies.

4.1 Health Vulnerability as a Normative Concept in Public Health and Research Ethics

Despite all the different interpretations of vulnerability, the claim for a societal responsibility to protect vulnerable people seems to be outright.⁴⁸ Basing on normative theories like social justice,⁴⁹ capabilities,⁵⁰ notably when applied to the health sector,⁵¹ it can be argued in favour

⁴⁴ S. Nguengang Wakap *et al.*, 'Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database' *European Journal of Human Genetics* (2019).

⁴⁵ EMA Website, <https://www.ema.europa.eu/en/committees/working-parties-other-groups/pdco-working-parties-other-groups>, accessed 21 October 2019.

⁴⁶ *Ibid.*

⁴⁷ EMA, Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation, EMA/CHMP/458101/2016, 13 December 2018.

⁴⁸ R. Goodin, *Protection the Vulnerable: A Re-Analysis of Our Social Responsibilities* (Chicago: The University of Chicago Press, 1985) p. 39.

⁴⁹ J. Rawls, *A Theory of Justice* (Cambridge, MA: Belknap Press of Harvard University Press, 1971) 607 p.

⁵⁰ A. Sen, *L'idée de justice* (Paris: Flammarion Coll. Champs Essais, 2010) 286-287 ; M.C Nussbaum, *Creating capabilities. The human development approach*, (Cambridge, MA: The Belknap Press of Harvard University Press, 2011) 37.

⁵¹ N. Daniels, 'L'extension de la justice comme équité à la santé et aux soins de santé', *Presses de Science Po (PFNSP)* 2(34) (2009) 13; S. Venkatapuram, *Health and Justice: The Capability to Be Healthy* (Cambridge: Cambridge University Press, 2007) p. 53; J.P. Ruger, 'Toward a theory of a right to health: Capability and incompletely theorized agreements', *Yale Journal of Law and Humanities* 18 (2006) 318.

of the existence of a normative concept of health vulnerability. More specifically, we will insist on the importance of promoting an ethical claim to equitably represent vulnerable patients in health research. Such a claim is also supported by bioethics principles. Justice aspects emerge as the exclusion from clinical trials maintains and even worsens health disparities.⁵² Beneficence and non-maleficence⁵³ also justify such an obligation in order to prevent the dangers of the absence of treatment or of off-label use of drugs.⁵⁴

Key international research ethics instruments also have provisions supporting the claim to equitably represent vulnerable groups in research. The Declaration of Helsinki states that “groups that are underrepresented in medical research should be provided appropriate access to participation in research” (§13), and that research on vulnerable groups should focus on “the health needs or priorities of this group” in order for them “to benefit from the knowledge, practices or interventions that result from the research” (§§19-20). The 2016 CIOMS guidelines also have several relevant provisions. First, Guideline 1 mentions the “social value” of research, which cannot create unjust situations and has to be evaluated notably with the “significance of the health need”. Second, Guideline 3 urges all stakeholders to “ensure that the benefits and burdens of research are equitably distributed”, stating that “because categorical exclusion from research can result in or exacerbate health disparities, the exclusion of groups in need of special protection must be justified. (...) Groups that are underrepresented in medical research should be provided appropriate access to participate”. Finally, the International Bioethics Committee of the UNESCO released a report on big data and health that is emphasising on the “responsibilities of all stakeholders” regarding benefit sharing and big data being considered as “a common good for human kind”: “advancements and new opportunities provided by science and technology might help reduce and not deepen the inequalities that prevent many human beings from enjoying the highest attainable standard of health”.⁵⁵

The societal obligation to promote research and development of quality treatments for orphan diseases could thus be reinforced by reaffirming long recognised ethical principles and interpreting them through the lens of the concept of health vulnerability. The concrete consequences, benefits and risks, for orphan disease patients could also be strengthened if this normative principle would be translated into human rights.

4.2 A Human Rights Approach to the Vulnerability of Orphan Disease Patients

In law, vulnerability is sometimes described as an abnormal inability to enjoy one’s rights and freedoms.⁵⁶ Regarding orphan disease patients, several different and related rights are at stake.

A principle of equitable representation of vulnerable people, and of orphan disease patients, in research would correspond to existing obligations in international human rights law, e.g. Article 27 of the Universal Declaration of Human Rights in that it promotes a right “to share in scientific advancement and its benefits”.⁵⁷ Besides, the Universal Declaration on Bioethics

⁵² W. Rogers and A. Ballantyne, ‘Justice in health research: What is the role of evidence-based medicine?’, *Perspectives in Biology and Medicine* 52(2) (2009) 199.

⁵³ T.L. Beauchamp and J.F. Childress, *Principles of biomedical ethics* (New York: Oxford University Press, 2013) 459 p.

⁵⁴ H. Helmchen *et al.*, *From exclusion to inclusion. Improving clinical research in vulnerable people* (Berlin: Berlin-Brandenburgische Akademie der Wissenschaften (BBAW), 2014) p. 45.

⁵⁵ UNESCO, International Bioethics Committee, Report of the IBC on big data and health, Paris, 15 September 2017, p. 15, §§73-74.

⁵⁶ Cour de cassation, *Rapport annuel 2009. Les personnes vulnérables dans la jurisprudence de la Cour de cassation* (Paris: La Documentation Française, 2009).

⁵⁷ Universal Declaration of Human Rights, General Assembly of the United Nations, Resolution 217 A, adopted in Paris, 10 December 1948, Article 27§1.

and Human Rights⁵⁸ also aims to “promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits” (Article 2). Such a right is also repeated in the specific case of genetic diseases. Article 12.1 of the Declaration on the human genome and human rights⁵⁹ states that “benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual”. This provision could be particularly useful for orphan diseases as about 70% of those are genetic.⁶⁰

Such a principle of equitable representation in research also resonates with European fundamental rights. The Charter of fundamental rights of the EU promotes health (article 35), and the 2017 resolution of the European Parliament insists on access to quality medicines being part of the fundamental right to health protection and health care access.⁶¹ It also denounces the dangers of off-label use and drugs’ adverse effects.⁶² In particular, the Parliament is giving recommendations insisting on the need to promote better access to quality medicines for orphan drugs.⁶³

But most of all, the principle of equitable representation in clinical trials resonates with the law of the Council of Europe and its case law. Article 3 of the Council of Europe’s Oviedo Convention promotes the equitable access to health care of appropriate quality.⁶⁴ Yet it has been demonstrated that most orphan disease patients don’t have access to quality health care. In the Additional Protocol on biomedical research, such a claim could consist in strengthening the requirement of quality of research and scientific expertise (article 8), both of which imply that the objectives of research must be relevant and feasible and most of all important regarding unmet medical needs.⁶⁵

Finally, a few dispositions from the European Convention on Human Rights (ECHR) could be used to justify a claim by orphan disease patients for better access to health research benefits and quality health care. In fact, it has been thoroughly demonstrated that an outline of the “right to health” is growing in the ECHR case law, although still hesitantly.⁶⁶ But the European judges are imposing more and more demanding procedural obligations to Member States when having to justify the harms that citizens may have suffered from because of a poorly organised public health system.⁶⁷ Moreover, some authors dedicated a precise analysis of the ECHR case law within the pharmaceutical context, and claimed for an obligation for states to actively promote a reliable knowledge production system in the context of pharmaceutical product development, based notably on the right to health, the right to life, the

⁵⁸ Universal Declaration on Bioethics and Human Rights, adopted by the General Conference of UNESCO on 19 October 2005.

⁵⁹ Universal Declaration on the Human Genome and Human Rights adopted by the General Conference of UNESCO on 11 November 1997.

⁶⁰ S. Nguengang Wakap *et al.*, ‘Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database’, *European Journal of Human Genetics* (2019).

⁶¹ European Parliament Resolution of 2 March 2017 on EU options for improving access to medicines, (2016/2057(INI)), P8_TA(2017)0061, Recitals A & C. and Observation 3.

⁶² *Ibid.*, Observation 16.

⁶³ *Ibid.*, Recommendations 23; 64-70; 73; 109.

⁶⁴ Explanatory report to the Oviedo Convention, §§ 23, 26 and 27.

⁶⁵ Explanatory report to the Additional Protocol, § 37.

⁶⁶ ECHR, *Lopes de Sousa Fernandes v. Portugal* [GC], no. 56080/13, 19 December 2017, Partly concurring, partly dissenting opinion from Judge Pinto de Albuquerque; É. Paillissé, *Le droit à la santé dans la jurisprudence de la Cour européenne des droits de l’homme*, PhD thesis, Université de Perpignan Via Domitia, 2018, pp. 51 onwards.

⁶⁷ See for instance ECHR, *Elena Cojocaru v. Romania*, no. 74114/12, 22 March 2016, § 111; Paillissé, *supra* note 65, pp. 303-306;

prohibition inhuman or degrading treatment, but mostly on the right to information and the right to private life.⁶⁸

Even if this claim is only prospective and does not reflect the current status of the ECHR case law, it does not seem that far stretched, especially in situations of health vulnerability, like for orphan disease patients. The concept of vulnerability itself, as used by the judges of the ECHR, tends to limit the margin of appreciation of Member States and even sometimes to create new obligations towards them.⁶⁹ The use of this concept is not systematic in the judges' analysis and decision making, but the tendency is growing. Moreover, it is especially growing in the field of health where the identification of a situation of vulnerability allows the European judges to justify an intrusion in national law in a field (like public health policies) that would normally be kept exclusively to Member States.⁷⁰ Last but not least, vulnerability situations also permitted to impose obligations of prevention from Member States, notably regarding the right to information and the right to participation for instance in the law making or public health processes,⁷¹ always with the goal to promote equality and equity.⁷²

In that way, collective claims from a vulnerable group like orphan disease patients could very much reinforce the representation of their interests in the national health systems and especially be the base for a claim, both to a reliable and equitable knowledge production system in the research and development of medicines.

Nonetheless, however promising those new technologies are for improving availability and thus access to innovative orphan medicines, it is crucial to underline the new risks that those technologies bring with them, and the additional situations of vulnerability they might create for orphan disease patients. In fact, the use of data-driven technologies also comes with supplementary risks related to the processing of personal data, *e.g.* machine learning biases or automated decision-making. But most of all, the violation of orphan disease patients' right to privacy would be particularly serious. For all patients and minority groups, there is always a risk of violation of the confidentiality of their health data and consequent risks of discrimination and stigmatisation – be it as an individual or as a group. Yet the violation of privacy in case of an orphan disease is especially serious because of the particular sensitivity of the health data. The very definition of an orphan disease is to be life-threatening, seriously debilitating, chronic and incurable. Hence it is especially crucial for the confidentiality of the data to be respected, notably in such domains as banking, insurance or on the employment market. However, it is difficult if not impossible to maintain confidentiality in the case of orphan diseases. Because patients are rare by definition, only very few supplementary data and efforts will be necessary to identify individual orphan disease patients. In that aspect, pseudonymisation will most likely be an inefficient tool to protect patients' privacy.

As a consequence, using a human rights approach to the concept of “health vulnerability” could potentially base a claim for innovative orphan drugs while still drawing the attention on other sources of vulnerability for orphan disease patients regarding such rights as privacy and

⁶⁸ *Ibid.*, p. 367; T. Lemmens, ‘Pharmaceutical knowledge governance: a human rights perspective’, *Journal of Law, Medicine and Ethics* (2013) 163-184. The author takes as an example: ECHR, *Roche v. United Kingdom* [GC], no. 32555/96, 19 October 2005.

⁶⁹ Notably in relation to article 14 ECHR on non-discrimination, for instance: ECHR, *Chapman v. United Kingdom* [GC], no. 27238/95, 18 January 2001; For a thorough study of the impact of the concept of vulnerability in the ECHR case-law: L. Peroni and A. Timmer, ‘Vulnerable groups : The promise of an emerging concept in European human rights convention law’, *International Journal of Constitutional Law* 11(4) (2013) 1057.

⁷⁰ Paillissé, *supra* note 65, p. 113.

⁷¹ *Ibid.*, p. 425, p. 431 onwards.

⁷² Peroni and Timmer, *supra* note 68, p. 1057.

personal data protection, and following the European frameworks on the protection of health-related personal data, be it from the European Union⁷³ or from the Council of Europe.⁷⁴

5 Conclusion

The research and development of orphan medicines is already benefitting from a special status in the European legal framework. However, this framework is currently not enough to guarantee a significant improvement in patients' access to orphan medicines. Therefore, it has been suggested to link the promotion of the health of orphan disease patients to the growing concept of vulnerability and specifically, to a collective dimension of health vulnerability. Using this normative concept permits to embed the development of orphan drugs and the promotion of patients' access to quality orphan medicines in the protection of fundamental rights as opposed to a simple incentivising regime which implementation is highly dependent on an economic and political context.

The concept of health vulnerability would be all the more helpful than the very idea of having to protect the most vulnerable people is quite consensual in Europe even if the details of such protection can be debated. The notion of vulnerability appeals to individual rights and freedoms concerning their involvement in clinical trials but also their rights regarding data-driven innovative technologies that represent a considerable opportunity to improve access to orphan drugs. Yet vulnerability not only concerns the individual but also brings a collective sense of solidarity, equity and justice especially in the perspective of public health protection. Hence, the concept of health vulnerability could empower orphan disease patients in a claim for improved quality of their health care and improved availability of innovative orphan drugs.

Conversely, more than a burden, orphan diseases would be the very illustrative example of how vulnerability triggers innovation. In fact, this is only when confronted with the most complex and contradicting issues at stake that humans get creative and find rationalised processes;⁷⁵ and this is where innovation comes from. Reaffirming the societal responsibility to protect vulnerability and to actively promote the development of orphan medicines could be the opportunity to develop further some of the innovative data-driven solutions that palliate the biggest difficulties, like *in silico* trials, while still drawing attention on the importance of protecting orphan disease patients from new sources and risks of vulnerability especially regarding their highly sensitive personal data.

⁷³ Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR); European Parliament, Resolution of 14 March 2017 on fundamental rights implications of big data: privacy, data protection, non-discrimination, security and law-enforcement.

⁷⁴ Council of Europe, Convention for the Protection of Individuals with regard to automatic processing of personal data, ETS n°108, 28 January 1981; Recommendation CM/rec(2019)2 on the protection of health related data, adopted by the Committee of Ministers on 27 March 2019.

⁷⁵ S. Braun, 'La recherche sur les maladies rares, un modèle pour les autres maladies?', *Les Tribunes de la Santé* 62 (2019) 51-59 ; EURORDIS, EURORDIS' position on rare disease research, 2012.