# Vulnerable people and clinical trials. Reflexions in European law

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# Summary

*Who are vulnerable people? Why are they vulnerable in clinical trials? How are they protected by European law? These initial questions rapidly evolve into the formulation of an old dilemma that is constantly renewed by medical progress and increasing levels of human rights protection. Protection of individual participants' rights may conflict with the promotion of public health. Specifically, the challenge is to justify and organise the participation of people who are unable to defend their own interests in clinical trials and are essential not only to public health but also to the health of the group they represent.*

*The case of vulnerable people will serve both as the subject of interest and as a heuristic tool. Why are older adults not a category of vulnerable participants? Why assimilate pregnant women to people unable to defend their interests? Why can patients suffering from orphan diseases be classified as a vulnerable category in clinical trials? How should participants from developing countries be classified? Hence, by first clarifying the concept of vulnerability will it be possible to get a preliminary answer to this ethical dilemma. Then, by examining the different types of risks to which a person can be vulnerable will it be possible to distinguish between two emerging types of vulnerability in the field of clinical trials: vulnerability to risks of violation of autonomy in the decision making process of a (potential) trial participant, and vulnerability to risks of violation of health and safety when ingesting a potentially dangerous experimental medicine. The former case concerns decisional vulnerability, i.e. the inability to defend one's own interests and the resulting exposure to abuse and exploitation. The latter case, rarely apprehended through the notion of vulnerability, concerns the health vulnerability of the future patient, his medical condition, and the need for representation in clinical trials in order to avoid a medical weakness to be exacerbated via marginalisation from clinical trials, leading to the lack of research and reliable medical data.*

*Although very different, those two types of vulnerability are often conflated or assimilated with one another because they are frequently present in a single person, the best example being children, both legally incapacitated and physiologically different than adults. And yet the distinction is crucial in order to modulate the protection of vulnerable people depending on their different needs. In fact this distinction then allows to select vulnerability factors that are particularly relevant in the specific field of clinical trials. Only then is it possible to examine the factors of vulnerability for which protection is possible and for which a normative response can be ethically justifiable, legally feasible, and economically viable.*

*Without claiming to bring an ideal solution to these complex dilemmas, this thesis advances an ethical and critical perspective on European law. It stresses the considerable progress made in protecting vulnerable people, highlights the means and instruments that are most efficacious, and stimulates reflection on how to further ameliorate the protection of vulnerable people in clinical trials.*

# Foreword

*This PhD has taken place in "cotutelle" between the medical faculty of the University of Basel and the legal faculty of the University of Aix-Marseille.*

*Two different manuscripts have been prepared in order to meet the different requirements of each faculty. The present manuscript constitutes the thesis elaborated for the medical faculty of the University of Basel.*

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# Introduction

## 1 ORIGIN OF RESEARCH

1. The origin of this research was initially the question of clinical trials on elderly people as it raises two main problems. The first one is related to the difficulties in obtaining consent since older adults tend to suffer from cognitive limitations. The second problem revolves around the lack of clinical research with older persons, irrespective of whether it is within geriatric disease context or medicine in general. When examined jointly they reveal the challenge of finding a good balance between promoting health and quality medicines for older adults and protecting them from abusive recruitment practices in clinical trials.

2. However, it became obvious that these problems were not specific to older adults in clinical trials: it is also the case for children, pregnant women or in emergency situations. Hence it is as well the case for other people who are allocated a status of "vulnerable group" in European law relative to clinical trials. Although older adults are not a "vulnerable group" as such, they pose similar problems.

3. This dilemma raised the rather theoretical question of how to define vulnerability in general and in clinical trials, as well as the practical question of how vulnerable groups are protected in European law. Hence the research was expanded to the broader topic of vulnerable people in clinical trials in order to compare protections to those within this group and critically analyse them, but also to understand why older adults are not a "vulnerable group" under European law related to clinical trials.

4. Moreover, two supplementary reasons make the broadening of this topic particularly relevant in the context of European law. First, the explicit term "vulnerable" has recently penetrated European law on clinical trials with the 2014 reform in the European Union as we will see later on. Second, this same reform also permitted to bring closer the provisions on vulnerable populations in the two legal instruments in European law related to clinical trials[1].

[1] Regulation (UE) 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 (Hereafter "Regulation 536/2014") ; Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, CETS N°195, Strasbourg, 25 January 2005 (Hereafter "Additional Protocol").

# 2 OBJECT OF RESEARCH

## 2.1 VULNERABLE PEOPLE AND CONCEPT OF VULNERABILITY

5. Lists of vulnerable people in European law may differ according to the field of interest. Regarding clinical trials, there are two lists depending on the chosen source: 2005 Additional Protocol to the Oviedo Convention on biomedical research from the Council of Europe or Regulation 536/2014 on clinical trials from the European Union. According to the Additional Protocol on biomedical research, several groups deserve specific attention, namely: people who are not able to give consent (minors and incapacitated adults), pregnant and breast-feeding women, people in emergency situations and persons deprived of liberty (articles 15, 18, 19 and 20). Similarly, Regulation 536/2014 considers minors, incapacitated adults, pregnant and breast-feeding women and persons in emergency situations as vulnerable (article 10). Interestingly, a generic group has been added in comparison to the Council of Europe: "specific groups or subgroups" which we will develop further on. However, persons deprived of liberty are not among the list of Regulation 536/2014, but they are quickly mentioned in article 34 in order to allow Member States to consider them as vulnerable along with other groups: "persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions".

6. This work will challenge the relevance and accuracy of both these lists. This questioning is possible because it is inherent to the concept of vulnerability which can be paradoxical, ambiguous and malleable[2]. In fact, vulnerability is both universal and particular, it can concern anyone depending on the situation, it can change over time, some authors name it "existential vulnerability"[3]. Thus it is an inherently human characteristic, which is the very reason of elaborating human rights protection[4]. Lists of vulnerable groups can be very broad, can be different according to the topic, and sometimes they are not even explicit termed as such[5]. This

[2] "the difficulties in navigating between insufficient comprehensiveness and excessive broadness, if all are to be considered vulnerable, have fuelled a critique of using the concept of vulnerability at all". Hurst S., "Vulnerability in research and health care ; describing the elephant in the room ?", *Bioethics*, Vol. 22, n°4, 2008, p. 195 ; See also Levine C. *et al.*, "The limitations of 'vulnerability' as a protection for human research participants", *American Journal of Bioethics*, Vol. 4, n°3, 2004, p. 4 ; Fiechter-Boulvard F., "La notion de vulnérabilité et sa consécration par le droit", *in* Cohey-Cordet F. (ed.), *Vulnérabilité et droit. Le développement de la vulnérabilité et ses enjeux en droit*, Presses Universitaires de Grenoble, Grenoble, 2000, pp. 13-32; Fineman M. A., "The vulnerable subject : Anchoring equality in the human condition", *Yale Journal of Law and Feminism*, Vol. 20, n°1, 2008, pp. 1-23.

[3] Bielby P., *Competence and vulnerability in biomedical research*, International Library of Ethics, Law and the New Medicine, Springer, 2008, p. 53.

[4] Grear A., "Challenging corporate 'humanity' : legal disembodiment, embodiment and human rights", *Human Rights Law Review*, Vol. 7, n°3, 2007, p. 532 ; Morawa A. H. E., "Vulnerability as a concept of international human rights law", *Journal of International Relations and Development*, Vol. 6, n°2, 2003, pp. 139-155 ; Turner, S. T., *Vulnerability and human rights*, *Essays on human rights*, Pennsylvania State University Press, University Park, 2006, p. 25.

[5] Cour de cassation, Rapport annuel 2009. Les personnes vulnérables dans la jurisprudence de la Cour de cassation, La Documentation Française, Paris, 2009, p. 56.

malleability is thus both the strength and the weakness of the concept of vulnerability. It allows to unite, within one highly emblematic notion, all the different interpretations[6].

7. In this work, vulnerability refers to a "heightened state of vulnerability", when it exceeds a certain acceptable level or benchmark. This descriptive approach of vulnerability showing inequities between people gives the concept of vulnerability its practical and normative relevance[7]. Thus from an anthropological or descriptive concept, vulnerability can become a normative concept, be it ethical, moral or legal. In law especially, vulnerability corresponds to an abnormal inability to enjoy one's rights and freedoms[8]. Vulnerability is the sign of ineffectiveness of human rights protection[9], and the sign of the need for a more subtle protection guaranteeing to vulnerable people the means for their own resilience, taking inspiration from theories like ethics of care or capabilities[10]. In spite of all different interpretations of vulnerability, the societal responsibility of protecting vulnerable people seems to be outright[11].

### 2.2 CLINICAL TRIALS AND BIOMEDICAL RESEARCH

8. 2005 Additional Protocol to the Oviedo Convention from the Council of Europe examines "biomedical research" and not "clinical trials" like European Union 536/2014 Regulation. Biomedical research is a lot broader than clinical trials as it can include any type of research such as observational work, simple questionnaires or interviews without any clinical intervention[12]. 536/2014 Regulation only relates to clinical trials on medicinal products for human use, *i.e*. tests in human participants or experimental medicines in order to study their safety and efficacy in providing health treatment (article 2.2.1). It thus excludes observational studies in normal clinical practice, animal testing, as well as *in silico* trials[13]. As both legal

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[6] Faberon F., "Vulnérabilité et besoin dans le droit de l'aide et de l'action sociale", *in* Paillet É. & Richard P. (eds.), *Effectivité des droits et vulnérabilité de la personne*, Bruylant, Bruxelles, 2014, p. 52.

[7] "Most strands of literature agree that vulnerability is a useful (and measurable) concept only if it is defined as vulnerability to a measurable loss (the metric) below a minimum level (the benchmark). Without use of a benchmark, the term 'vulnerability' becomes too imprecise for practical use ». Alwang J., Siegel P. B. et Jørgensen S. L., « Vulnerability : a view from different disciplines", *Social Protection Discussion Paper Series,* n°0115, 2001, p. 29.

[8] Cour de cassation, Les personnes vulnérables dans la jurisprudence de la Cour de cassation, op. cit.

[9] Paillet É. & Richard P. (eds.), Effectivité des droits et vulnérabilité de la personne, Bruylant, Bruxelles, 2014, p. 4 ; Cour de cassation, Les personnes vulnérables dans la jurisprudence de la Cour de cassation, op. cit.; Rendtorff J. D., "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – towards a foundation of bioethics and biolaw", Medicine, Health Care and Philosophy, Vol. 5, n°3, 2002, p. 238.

[10] Nussbaum M. C., "Capabilities and human rights", *Fordham Law Review*, Vol. 66, n°2, 1997, p. 275 ; Maillard N., *La vulnérabilité. Une nouvelle catégorie morale ?*, Le champ éthique n°56, Labor et Fides, Geneva, 2011, p. 158.

[11] Goodin R., *Protection the vulnerable : a re-analysis of our social responsibilities*, London & Chicago, The University of Chicago Press, 1985, p. 39.

[12] Explanatory report to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, ETS N° 164, Oviedo, 4 April 1997, (Hereafter "Oviedo Convention"), § 17.

[13] Viceconti M., Henney A. et Morley-Fletcher E., "*In silico* clinical trials : how computer simulation will transform the biomedical industry", *International Journal of Clinical Trials,* Vol. 3, n°2, 2016, pp. 37-46 ; Gal J. *et al.,* "Optimisation du processus de développement d'un nouveau médicament par modélisation et simulation : état des lieux et enjeux", *Revue d'Épidémiologie et de Santé Publique,* Vol. 64S, 2016, pp. S117-S136.

frameworks will constantly be compared throughout this research, this study is limited to the more restrictive field of clinical trials.

9. Clinical trials take place in three main phases, and sometimes in a fourth one. Phase I concerns first-in-human trials, testing the safety of (the maximum dose of) the experimental medicine on a small number of healthy volunteers. Phase II tests the efficacy (and minimum dose for efficacy) of the drug on a bigger group of volunteers suffering from the condition which the experimental drug is supposed to diagnose, prevent or cure. Phase III, also called pivotal trials, consists in testing the drug on a large number of patients in order to precisely know the posology for instance in different age groups, and most of all in order to compare the safety and efficacy of the drug to the currently available treatment or to a placebo if necessary, and to prove the relevance and utility of its marketing.

10. If the new medicinal product is granted a marketing authorisation and is commercialised, pharmacovigilance begins: information is collected from patients and practitioners about the effects of the drug. Even with this surveillance, 197 000 deaths per year in the European Union would be related to adverse effects of medicinal products according to the European Medicines Agency[14]. In fact, many effects of a drug cannot be observed during phases I-III because they only appear rarely and thus only when used in a large number of people; because they only appear with long-term use; or because they only appear in certain groups of people who were not studied in clinical trials, which is the case for most vulnerable people[15]. Hence, there can be a phase IV clinical trial, which is different from simple pharmacovigilance.

11. Finally, there are three essential issues at stake with clinical trials. First, the goal is to promote public health through improvement of quality and security of a new drug, as well as their efficacy[16]. Second, clinical trials serve the purpose of benefiting the health of future patients, but not necessarily the health of its participants. This explains the consecutive international reactions, pleading for informed consent and further ethics principles which came after the barbaric Nazi experiments and many more abusive research conducted in Japan or in America[17]. Even with restrictions and safeguards, tragic events still happen, like the recent death of a healthy volunteer in France in January 2016 solely a few days after the start of a phase I

[14] EMA, Strengthening pharmacovigilance to reduce adverse effects of medicines, MEMO/08/782, London, 2008, p. 1.
[15] Directive 2010/84/EU of the European Parliament and of the Council of 15 december 2010, amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, Recital 2.
[16] Simon P., *Le médicament sous toutes ses coutures*, Éditions de Santé Coll. Polémiques, Paris, 2003, p. 73 ; For historical examples : Mattei J.-F. (ed.), *Questions d'éthique biomédicale*, Flammarion, Nouvelle Bibliothèque Scientifique, Paris, 2008, p. 321 ; Bouvenot G., "Problèmes éthiques posés par l'expérimentation humaine des médicaments", *in* Bouvenot G. et Vray M., *Essais cliniques : théorie, pratique et critique*, Flammarion médecine-sciences Coll. Statistique en biologie et en médecine, Paris, 2006, p. 162 ; European Parliament Resolution of 2 March 2017 on EU options for improving access to medicines, (2016/2057(INI)), P8_TA(2017)0061, Observation 11.
[17] Nuernberg Military Tribunals, "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", US Government Printing Office, Washington DC, 1949, Vol. 2, pp. 181-182 ; Delfosse M.-L. & Bert C., *Bioéthique, droits de l'homme et biodroit. Recueil de textes annotés internationaux, régionaux, belges et français*, Larcier, Brussels, 2005, p. 301.

trial[18]. Restrictions however can also be counterproductive and expose future patients to great dangers if drugs are not properly tested. This explains the slow transition towards an approach to participants' recruitment that is more considerate with equitably sharing benefits of research through patients' proper representation in clinical trials[19]. The third issue at stake in clinical trials lies in economic competitiveness of the pharmaceuticals' market. In fact, 61% of trials in the European Union are conducted by pharmaceutical companies trying to market new drugs to compensate the humongous costs of clinical trials as well as to make profits[20]. Market dynamics can have a beneficial impact on health protection[21], unfortunately as this work will show, this is rarely the case for vulnerable people.

# 3 SCOPE OF RESEARCH

## 3.1 EUROPEAN LEGAL FRAMEWORK(S)

12. Clinical trials and biomedical research are regulated at national levels, however adopting a European perspective is fundamental for this research work. First, recruiting enough participants for a clinical trial almost systematically obliges to cross a border: any trial of more than 40 participants conducted in Europe involves more than one Member State[22], and 67% of participants recruited in the European Union are part of a multinational trial[23], which is probably even more exacerbated regarding vulnerable participants who are more difficult to recruit, for instance in the case of rare diseases. Second, due to the European Union market and freedoms to circulate, the pharmaceutical market is highly dependent on European competitiveness[24] and is no exception to ethics tourism[25], then again confirming the importance of harmonised protection provisions. Third, the European perspective is relevant as both the Council of Europe

[18] Benkimoun P., "Essai clinique mortel de Rennes : la toxicité de la molécule en cause", *Le Monde,* 3 Novembre 2016, https://www.lemonde.fr/sante/article/2016/11/03/essai-clinique-mortel-de-rennes-la-toxicite-de-la-molecule-en-cause_5024450_1651302.html [24 January 2018].
[19] Delfosse M.-L. & Bert C., Bioéthique, droits de l'homme et biodroit, op. cit..
[20] EMA Website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f [10 May 2018].
[21] Bailleux A., "Les alliances entre libre circulation et droits fondamentaux. Le flou au cœur de la jurisprudence communautaire", *Journal de Droit Européen,* n° 160, 2009, p. 11 ; Brosset E. (ed.), *Droit européen et protection de la santé. Bilan et perspectives*, Bruylant, Brussels, 2015, p. 21.
[22] European Commission, Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC, VOLUME I, Document de travail des services de la Commission, SWD(2012) 200 final, Brussels, 17 July 2012, § 25.
[23] *Ibid*., § 24.
[24] Dubouis L., Blumann C., *Droit matériel de l'Union européenne*, 6th edition, Domat Droit public, Montchrétien, Paris, 2009, p. 184.
[25] For instance : Waligora M., "Failures in clinical trials in the European Union: Lessons from the Polish experience", *Science and Engineering Ethics*, Vol. 19, 2013, pp. 1087-1098.

and the European Union have provided for a legal framework on the topic which is important to compare[26] as well as to confront with research ethics instruments.

13. Instruments from the Council of Europe, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine or Oviedo Convention) as well as its Additional Protocol on biomedical research, adopt a human rights approach which is inherent to the international organisation. In addition to these two instruments specific to bioethics and research ethics, the Convention for the Protection of Human Rights and Fundamental Freedoms (European Convention on Human Rights or ECHR) does protect rights that are relevant to biomedical research, like article 2 on the right to life, article 3 on the ban of inhuman treatments or article 8 on the respect for private life, as well as many others. The advantage of using this more general instrument is sometimes to circumvent the fact that only 29 Member States have ratified the Oviedo Convention and 11 the Additional Protocol on biomedical research, and benefit from the protection of the Court.

14. The European Union on the contrary is rather focused on market considerations than on participants' protection, emphasising the fact that the latter falls within national competencies[27]. The issue of a clear receptivity of the European Commission to the lobbying of pharmaceutical companies is repeatedly raised[28]. Market considerations were the main scope for the initial Directive 2001/20/EC on clinical trials[29], and they were also the main reason for the reform and elaboration of Regulation 536/2014. As administrative and insurance costs were increasing unreasonably (administrative costs were at least multiplied by two, insurance costs by eight)[30], deadlines for evaluation of applications were expanding endlessly, and Member States had different interpretations of the directive… All these elements lead to 25% decrease in the number of clinical trials between 2007 and 2011[31], triggering the active elaboration of the new regulation. The main general change, outside the topic of vulnerable populations, lies in the creation of a unique European Union portal and database gathering all information and serving as platform for communication between clinical trials sponsors, Member States, the European

[26] Andorno R., "Regulatory discrepancies between the Council of Europe and the EU regarding biomedical research", *in* Andorno R. (ed.), *Principles of international biolaw. Seeking common ground at the intersection of bioethics and human rights*, Coll. Droit, bioéthique et santé, Bruylant, 2013, pp. 175-194.

[27] Regulation 536/2014, Recital 6.

[28] "it is difficult to shake the feeling that the voices of industry received more than due attention". Lidell K. *et al*., "Medical research involving incapacitated adults: implications of the EU Clinical Trials Directive 2001/20/EC", *Medical Law Review*, 2006, Vol. 14, n°3, p. 374.

[29] 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*, O. J*., 1.5.2001, L 121, pp. 34-44.

[30] European Commission, Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC*, op. cit.,* VOLUME II, p. 5; Delawi D. *et al*., "Conducting a European multi-center trial: First experiences with the new EU clinical trials directive from an academic perspective", *European Spine Journal*, Vol. 17, 2008, pp. 1113-1115.

[31] Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, COM(2012) 369 final, 2012/0192 (COD), Explanatory memorandum, p. 3.

Medicines Agency and the European Commission, but also as a transparency platform for the public. Regulation 536/2014 will be applicable once this Union portal will function, by the end of 2019[32]. Even if market related issues have led to this reform, it also brought considerable improvements in participants' protection that are clearly – even if not explicitly admitted[33] – inspired from the Council of Europe.

### 3.2 EUROPEAN RESEARCH ETHICS

15. Ethics is an ambiguous notion, especially when used in a legal setting. Historically, the first normative framework related to clinical trials is related to biomedical ethics and human rights[34]. The ambiguity between ethics and fundamental rights has remained since then as most legal literature demonstrating an ethical approach in law tend to do so by emphasising the value given to human rights[35]. But ethics is not exactly law. Rather, ethics is the balancing of competing values, the response to a dilemma for which no solution is satisfactory[36]. Thus, ethics provides a critical view on the pertinence and justice of the rules enacted by the law. Finally, ethics and soft law are often mistakenly conflated. However ethics refers to substantial, material rules whereas soft law refers to formal considerations, it refers to the type of legal instrument and its nonbinding nature. Often indeed, soft law is used to convey ethical content[37]: recommendations, good practices, opinions, notably from ethics committees (national ethics committees advising governments on general issues, clinical ethics committees advising physicians on actual cases or research ethics committees evaluating research protocols)[38]. As it is very difficult or even impossible in our pluralist societies to reach a consensus, ethics sometimes

[32] EMA Website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp [14 May 2018].

[33] Interestingly, this is not just a simple omission as parliamentary amendments had suggested to insert a reference. Willmott G., Committee on the Environment, Public Health and Food Safety (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012)0369 – C7 0194/2012 – 2012/0192(COD)), A7-0208/2013, Strasbourg, 7 June 2013, Amendment 32.

[34] "It is interesting to note that the first issue with which both new disciplines – modern medical ethics and human rights law – were confronted was precisely medical research on human beings". Andorno R., "Regulatory discrepancies between the Council of Europe and the EU regarding biomedical research", *op. cit*., p. 178 ; Duprat J.-P., "La portée des normes dans le domaine de la biomédecine", *Revue française des affaires sociales*, Vol. 3, n°3, 2002, p. 32.

[35] For instance : primacy of human beings, integrity and informed consent "constituent la base d'un droit éthique européen qui est fondé sur la Charte des droits fondamentaux de l'Union". Rage-Andrieu V., "L'apport du règlement 2017/745 à l'évaluation clinique des dispositifs médicaux", *RDSS*, Vol. 1, 2018, p. 50 ; Chassang G. *et al.*, "Les fondements de l'éthique de la recherche en droit communautaire", *International Journal of Bioethics*, Vol. 22, n°1-2, 2011, pp. 185-203 ; Sutour S. & Lorrain J.-L., Sénat, Rapport d'information sur la prise en compte des questions éthiques à l'échelon européen, n°67, Commission des affaires européennes, Ordinary session 2013-2014, 2013 ; "In this paper, I reflect on the parallel development and accidental divorce of bioethics and human rights to urge their reconciliation". Baker R., "Bioethics and human rights: A historical perspective", *Cambridge Quarterly of Healthcare Ethics*, Vol. n°10, 2001, p. 241.

[36] Vöneky S., *Recht, Moral und Ethik. Grundlagen und Grenzen demokratischer Legitimation für Ethikgremien*, Jus publicum. Beiträge zum Öffentlichen Recht, Mohr Siebeck, Tübingen, 2010, p. 24-26 ; Sutour S. & Lorrain J.-L., Rapport d'information sur la prise en compte des questions éthiques à l'échelon européen, *op. cit*., p. 19.

[37] Conseil d'État, *Étude annuelle 2013. Le droit souple*, La Documentation Française, Paris, 2013, p. 61.

[38] Monnier S., *Les comités d'éthique et le droit. Éléments d'analyse sur le système normatif de la bioéthique*, L'Harmattan Coll. Logiques Juridiques, Paris, 2005, p. 418

rather becomes procedural ethics[39]. That is a decision becomes "ethical" only if it has been discussed according to specific procedural rules like the presence of scientific experts as well as representatives from patients or from different religions[40].

16. Dealing with ethics in European law is in itself paradoxical as it conveys values that are intrinsic to national competencies[41]. However both the Council of Europe and the European Union have developed abundant legislations[42]. Most of all, each have created their own ethics committees. The Council of Europe set up in 1985 what has now become the Bioethics Committee or DH-BIO, composed of representatives of Member States who elaborated the Oviedo Convention - first internationally binding instrument in bioethics - and who are in charge of implementing it as well as developing it further. In the European Union, the European Group on Ethics in science and new technologies has been created in 1991. It is an independent, pluralistic and multidisciplinary ethics committee[43] in charge of advising the European Commission, often with concrete impact on European Union law[44].

17. In Europe, research ethics principles stem from two sources: European law itself and international research ethics guidelines, notably as they are conveyed in the European legal framework. The involvement of the DH-BIO of the Council of Europe is undoubtedly present as the Oviedo Convention and its Additional Protocol on biomedical research are inherently relevant to research ethics. The involvement of the European Union in research ethics is less obvious and rather perceptible through nonbinding and scattered reports or recommendations. For instance, the European Group on Ethics, the European Parliament and the European Medicines Agency have each drafted separate documents on research ethics in developing countries[45]. The European Commission has mandated an *ad hoc* committee to draft ethical

[39] Habermas J., *De l'éthique de la discussion*, Cerf, Champ Essais, 1992, 204 p ; Lanfranchi M.-P., "Le rôle des comités d'éthique dans l'élaboration et le suivi du droit international relatif au vivant humain", *in* Brosset E. (ed.), *Le droit international et européen du vivant. Quel rôle pour les acteurs privés ?*, La Documentation Française Coll. Monde européen et international, Paris, 2009, p. 55 ; Martinez É., "Comités d'éthique et démocratie (quelques réflexions sur l'exemple français)", *International Journal of Bioethics*, Vol. 18, n°1-2, 2007, p. 117.

[40] "Le mouvement consultatif exprime l'émergence d'un droit négocié consacrant le passage d'un droit autoritaire à un droit autorisé, qui utilise les opinions éclairées comme armes de persuasion". Martinez É., "Les enjeux de la 'recomposition' du droit de la bioéthique", *International Journal of Bioethics*, Vol. 15, n°2-3, 2004, p. 56.

[41] Hennette-Vauchez S. et Roman D., *Droits de l'Homme et libertés fondamentales*, 1st edition, Dalloz, 2013, p. 142.

[42] Council of Europe : Directorate General I – Human Rights Directorate, Bioethics Unit, Legal instruments of the Council of Europe in the field of bioethics, Strasbourg, 2014, Volume I, p. 2 & Volume II, p. 2 ; European Union : Chassang G. *et al.*, "Les fondements de l'éthique de la recherche en droit communautaire", *op. cit*., p. 195 ; Both : Sutour S. & Lorrain J.-L., Rapport d'information sur la prise en compte des questions éthiques à l'échelon européen, *op. cit*., p. 34.

[43] Sutour S. & Lorrain J.-L., Rapport d'information sur la prise en compte des questions éthiques à l'échelon européen, *op. cit*., p. 24.

[44] Dubos O., "Droit communautaire et bioéthique: Étude des internormativités à travers les avis du Groupe européen d'éthique", *International Journal of Bioethics*, Vol. 15, n°2-3, 2004, pp. 101-127.

[45] European Group on Ethics in Science and Technologies (EGE), Opinion N° 17 on ethical aspects of clinical research in developing countries, 2003 ; Schipper I., Directorate-General for external policies of the Union (DG-EXPO), European Parliament, Clinical trials in developing countries: How to protect people against unethical practices ?, EXPO/B/DEVE/2008/45 PE 406.974, Brussels, 2009 ; EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities, EMA/121340/2011, London, 2012.

recommendations for clinical trials in children[46], as well as academic experts to elaborate a textbook on research ethics[47]. Moreover, the legal framework itself conveys ethical issues and values, for instance when Directive 2001/20/EC obliged each Member States to put in place research ethics committees[48] or when provisions on informed consent became very precise in Regulation 536/2014[49] as was also highlighted by the European Parliament[50].

18. Finally, it is interesting to analyse the impact of international guidelines on research ethics in European law and bioethics, notably the World Medical Association's Declaration of Helsinki[51], the good practices from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[52] and the guidelines from the Council for International Organizations of Medical Sciences (CIOMS)[53].

19. 1964 Declaration of Helsinki stated ethics principles applicable to medical research involving human subjects, has become the main reference for research on a global level[54]. It has often been criticised as well for two reasons: first it is deemed to be very general and unprecise, leading to many interpretations, and second, as it is often updated, regulators are reluctant to give it binding force[55]. The instruments from the Council of Europe do not mention the Declaration of Helsinki, however the judges of the European Court of Human Rights have used it as supplementary argument grounding their reflexions in a few research ethics cases[56]. As for the European Union, Regulation 536/2014 does mention the Declaration of Helsinki but only in cases where the regulation would not be self-sufficient (Recitals 43 and 80).

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[46] These recommendations were drafted in 2008 but updated in 2017. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. Recommendations of the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, Final 2008 ; Updated version: Ethical considerations for clinical trials on medicinal products conducted with minors, Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) N° 536/2014 on clinical trials on medicinal products for human use, 18 September 2017, revision 1.

[47] European Commission, European textbook on ethics in research, EUR 24452 EN, Brussels, 2010.

[48] European Commission, Summary of the responses to the public consultation paper, Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC, SANCO/C/8/SF/dn D(2010) 380240, Brussels, 30 March 2010, p. 2.

[49] Regulation 536/2014, Article 29.

[50] "Justification: Compliance with the core elements of informed consent as set out in Chapter V should be assessed by the reporting Member State in Part I. While individual Member States are best placed to decide on certain cultural aspects, the core elements set out in Chapter V should also be considered in Part I". Willmott G. (ENVI), Report on the proposal for a regulation, *op. cit*., Amendment 96.

[51] WMA (World Medical Association), Declaration of Helsinki - Ethics principles applicable to medical involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

[52] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practices, E6(R1), Geneva, 1996.

[53] These guidelines have first been drafted and published in 2002, and recently updated in 2016. CIOMS (Council for International Organizations of Medical Sciences), International Ethical Guidelines for Health-related Research Involving Humans, in collaboration with the World Health Organization (WHO), Geneva, 2016 (Hereafter CIOMS Guidelines).

[54] Human D. & Fluss S. S., "The World Medical Association's Declaration of Helsinki : Historical and contemporary perspectives", 24 July 2001, http://www.wma.net/fr/20activities/10ethics/10helsinki/draft_historical_contemporary_perspectives.pdf [23 August 2015].

[55] Schipper I. (DG-EXPO), Clinical trials in developing countries: How to protect people against unethical practices ?, *op. cit.*, p. 5 & p. 17.

[56] ECtHR, Grand Chamber, Case of Gillberg v. Sweden, Application n° 41723/06, 3 Avril 2012, §89 ; ECtHR, First Section, Case of Bataliny v. Russia, Application n°10060/07, 23 July 2015, §90.

20. The ICH guidelines are a set of scientific guidelines developed between Europe, Japan and the United States of America since 1990[57]. Although they are quite widespread and used in practice for instance in developing countries, their lack of concerns for ethical issues has often been deplored. Trying to compensate for this lack, they often refer to the Declaration of Helsinki, which unfortunate as the United States have explicitly rejected it in 2008[58]. The Council of Europe does not refer to ICH guidelines, but the European Union very often does, be it in article 47 of Regulation 536/2014 as well as in numerous work documents from the European Medicines Agency[59].

21. Last but not least, the CIOMS, created in 1949 by the UNESCO and World Health Organisation, elaborated first in 2002 and then updated in 2016, is a guideline for health related research involving human. This is probably the most detailed and thorough set of research ethics principles. Unfortunately, it is not mentioned at all in European law in spite of one attempt by European Union parliamentary members[60].

# 4 RESEARCH AIMS AND METHODOLOGY

22. The aim of this research is to highlight the main issues at stakes when referring to vulnerable people in clinical trials. The concept of vulnerability is too often restricted to problems related with autonomy and decision making, which would limit this work to examining the decisional vulnerability of clinical trials participants. However, it was chosen not to restrict the great potential of the concept of vulnerability and go further in the analysis in order to demonstrate that vulnerability is also related to the health of future patients (as opposed to participants), and that this vulnerability has to be protected and prevented starting from the design of clinical trials.

23. The methodology of this research is theoretical in nature as it consisted of gathering and critically analysing European law documents, from binding instruments to any relevant work from European institutions and its organs. This analysis was carried in the light of relevant international ethical guidelines in the field and applicable in Europe, as well as in the light of legal, medical and ethical literature that has been published on the related topic.

24. The following chapters will delve into these numerous issues. Chapter 1 will deal with the concept of vulnerability and how it should not be limited to decisional vulnerability as it leads to very different and even contradictory ways to protect vulnerable people. Chapter 2 will

[57] ICH, Website, http://www.ich.org/fileadmin/Public_Web_Site/ABOUT_ICH/Vision/Overview_of_ICH_Website_9Jul2015.pdf [24 August 2015].
[58] Schipper I. (DG-EXPO), Clinical trials in developing countries: How to protect people against unethical practices ?, *op. cit.*, p. 17.
[59] EMA Website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000227.jsp&mid=WC0b01ac05801df740 [20 May 2018].
[60] Willmott G. (ENVI), Report on the proposal for a regulation, *op. cit*., Amendment 149.

analyse more precisely the situation of two particularly complex groups of vulnerable persons: children and frail older adults because their “double” vulnerability often triggers the confusion between health vulnerability and decisional vulnerability. Thus, this chapter will analyse in detail the evolving ethical challenges related to paediatric research. Chapter 3 will build on chapter 2 by examining the possibility of integrating research advance directives in European law, which would be of particular interest for frail older adults as those do not constitute a “vulnerable group” *per se* in clinical trials. Interestingly, they are on the contrary one of the most vulnerable groups, both regarding medical needs and decision-making capacity (Chapter 4). In light of these different chapters, we will critically analyse in a thorough discussion section the status and protection in European law of vulnerable people in clinical trials.

# Chapter 1: Does the new EU Regulation on clinical trials adequately protect vulnerable research participants?


### ORIGINAL PUBLICATION

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### ABSTRACT

Vulnerable research participants deserve special protection because of their increased risks of being wronged. Yet, paradoxically, the conduct of trials involving vulnerable groups is sometimes inescapable to develop safe and efficient therapies suitable to these groups. The key question is therefore how to protect vulnerable research participants from harm and exploitation without excluding the populations they belong to from the benefits of research. The European Union faced this challenge in April 2014 when adopting the new Regulation on clinical trials, which will replace the currently applicable 2001 Clinical Trials Directive in 2016. In order to assess the protection of vulnerable persons in the new Regulation, this paper makes four suggestions: first, the need to adopt a risk-based approach to vulnerability in biomedical research; second, to better distinguish between decisional vulnerabilities and health-related vulnerabilities; third, to emphasise the need to preserve the freedom of consent of subjects with decisional vulnerability, who are more susceptible to undue influence; and finally to assert the need of actively promoting specific clinical trials involving people with physical or psychological vulnerabilities. In conclusion, this paper claims that the protection of vulnerable subjects still needs to be improved in the new EU Regulation.



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# 1 Introduction

25. All major international[61] and European[62] standards relating to biomedical research expressly stipulate that vulnerable research participants deserve special protection because they "may have an increased likelihood of being wronged or of incurring additional harm"[63]. Vulnerability is often described as the inability to protect one's own interest, but it is usually not defined more precisely, leaving the possibility of different understandings of this concept. Typically, the category of "vulnerable persons" in biomedical research includes, among others, children, people with mental disabilities, older frail persons, pregnant women, persons deprived of their liberty, and socially or economically disadvantaged people. It is not justified to conduct research with vulnerable groups if a research of comparable effectiveness can be obtained with non-vulnerable groups[64]. However, paradoxically, the conduct of clinical trials involving vulnerable participants is sometimes inescapable because of the need to develop safe and efficient therapies suitable for these specific groups. This paradox reflects the complexities that regulations about research including vulnerable groups have to address when defining the concept of vulnerability and the appropriate protections for vulnerable participants.

26. The various parliamentary committees of the European Union (EU) that were involved between 2012 and 2014 in the discussions for the elaboration of a new Regulation on clinical trials struggled to find appropriate regulatory responses to these difficulties. After almost two years of discussions, the EU Parliament and the Council adopted in April 2014 the new Regulation No 536/2014[65], which will replace in 2016 the currently applicable 2001 Clinical Trials Directive (CTD)[66]. The latter did not measure up to the hopes that had been placed in it and is deemed partly responsible for the significant increase in costs and delays for the conduct of clinical trials, and for the recent 25% decline of the number of clinical trials in the EU[67]. These

[61] CIOMS (Council for International Organizations of Medical Sciences), International Ethical Guidelines for Health-related Research Involving Humans, in collaboration with the World Health Organization (WHO), Geneva, 2002 (Hereafter "CIOMS Guidelines"), Guideline 13 ; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practices, E6(R1), Geneva, 1996.

[62] Peroni L. & Timmer A., "Vulnerable groups: The promise of an emerging concept in European human rights convention law", *International Journal of Constitutional Law*, Vol. 11, n°4, 2013, pp. 1056-1085 ; Rendtorff J. D., "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – towards a foundation of bioethics and biolaw", *Medicine, Health Care and Philosophy*, Vol. 5, n°3, 2002, pp. 235-244.

[63] WMA (World Medical Association), Declaration of Helsinki - Ethics principles applicable to medical involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 (Hereafter "Declaration of Helsinki"), §19.

[64] WMA, Declaration of Helsinki, §20.

[65] Regulation (UE) 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 (Hereafter "Regulation 536/2014") .

[66] 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 (Hereafter "Directive 2001/20/EC").

[67] Robinson K. & Andrews P. J., "'(more) trials and tribulations': The effect of the EU directive on clinical trials in intensive care and emergency medicine, five years after its implementation", *Journal of Medical Ethics*, Vol. 36, n°6, 2010, pp. 322-325.

problems were particularly exacerbated for multinational clinical trials – which concern almost any trials involving more than 40 research participants – because of the discrepancies between Member States in the transposition of the CTD into national law. Therefore, the objective of the new Regulation is to streamline the rules governing clinical trials and to provide a unique legal framework to be directly applicable and binding for all EU Member States by the end of 2016.

27. As the key objective of the adoption of a new regulation was to facilitate the conduct of clinical trials in Europe, several scholars were critical of the insufficient attention that the Draft Regulation paid to research participants' protection[68]. This particular issue is notably one of the most amended topics when comparing the 2012 Draft Regulation with the version that was finally adopted in 2014. Even if the new Regulation has been definitively passed, the implementation guidelines and recommendations are still being updated in order to fit the changes brought by the new regulatory framework[69].

28. With this important EU policy change as a background, this paper aims, first, to suggest the need to adopt a risk-based approach to vulnerability in biomedical research; second, to argue for the importance of distinguishing between two kinds of risks for vulnerable research participants: the risk of exploitation and the risk of physical or psychological harm; third, to claim that the protection of vulnerable subjects still needs to be improved in the new EU Regulation, and finally to make four suggestions in this direction.

# 2 A risk-based definition of vulnerable persons

29. The notion of vulnerability is omnipresent in bioethics but its utility is often challenged. Some argue that other principles give a sufficient protection to vulnerable persons[70], or that it is too difficult to conceptualize the notion of vulnerability[71]. This is why ethicists and lawmakers tend to adopt a so-called *labelling approach*: instead of giving an abstract definition

[68] Heringa J. & Dute J., "The proposed EU-regulation on clinical trials on medicinal products: An unethical proposal ?", *European Journal of Health Law*, n°20, 2013, pp. 347-362.

[69] Implementation guidelines and recommendations are provided by three main stakeholders: the European Commission, the European Medicines Agency, and the Clinical Trials Facilitation Group; http://ec.europa.eu/health/human-use/clinical-trials/information/index_en.htm#ct4 [9 March 2015]. Another option could be to adopt a specific regulation on vulnerable participants, having in mind the model of the Paediatric Regulation: Regulation (EC) N° 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Hereafter "Regulation 1901/2006").

[70] Hurst S., "Vulnerability in research and health care; describing the elephant in the room?", *Bioethics*, Vol. 22, n°4, 2008, pp. 191-202.

[71] Schroeder D. et Genefas E., "Vulnerability : Too vague and too broad?", *Cambridge Quarterly of Healthcare Ethics*, n°18, 2009, pp. 113-121.

of vulnerability, they give a list of populations who are considered vulnerable[72]. Yet, as we will see below, this approach leads to both an overprotection of persons belonging to a vulnerable group, and an under-protection of vulnerable persons who do not belong to a typical vulnerable group category.

30. All human beings are vulnerable at several points of their lives and in many different ways because vulnerability is inherent to human beings, which means that it belongs ontologically to the human condition[73]. However, this intrinsic human vulnerability is substantially greater when people are subject to medical interventions which do not aim to prevent or treat their condition, but merely –or mainly– to increase scientific knowledge. Due to a complex of varied circumstances, some individuals are particularly exposed to exploitation or harm in such a context. The complexity of factors that may increase susceptibility to harm or exploitation makes it very difficult to define in abstract terms who is "vulnerable". Instead, it seems preferable to first identify the different types of risks to which research participants are exposed, and then deduce which individuals might be particularly vulnerable to those risks. In this way, we argue that vulnerability results from the addition of two elements: an exposure to a specific risk, and a particular susceptibility of the exposed person to this precise risk.

31. For instance, cognitively impaired individuals are vulnerable when deciding to participate in a clinical trial because they might not fully understand or remember the implications and risks of trial participation. Nevertheless, these same persons will not necessarily be at greater risk of physical harm than healthy research participants. On the contrary, frail elderly persons who are free from cognition problems are not vulnerable in terms of the decision-making process, but only regarding their greater exposure to physical or psychological harm.

32. Consequently we will determine the persons who are vulnerable depending on the risks involved in clinical trials. Two types of risk are distinguishable: those of exploitation and those of health harm. The risk of exploitation is the risk of a subjects unduly consenting to participation, of their weakness to be abused at the benefit of research because of cognitive impairment, deprivation of liberty, socio-economic condition (for instance when trials are conducted in developing countries), hierarchical pressure, "therapeutic misconception", etc. The risk of health harm is the risk of greater negative health effects from the trial because of, for instance, disease, age, poly-medication, co-morbidity, pregnancy, etc.

33. Some persons can be categorized as vulnerable in terms of both risks. For example, minors are unable to give a valid consent but are also physically and psychologically more fragile than adults. Equally, older dementia patients are exposed to increased risks of exploitation

[72] Luna F., "Elucidating the concept of vulnerability: Layers not labels", *International Journal of Feminist Approaches to Bioethics*, Vol. 2, n°1, 2009, pp. 121-139.
[73] Fineman M. A., "The vulnerable subject: Anchoring equality in the human condition", *Yale Journal of Law and Feminism*, Vol. 20, n°1, 2008, pp. 1-23.

because of their cognitive impairment and because they are often not legally capable of taking decisions anymore. But they have also, due to their age, a physical frailty, which may impair the absorption or effects of drugs. As these combinations are frequent, scholars and lawmakers normally treat these two kinds of risks as a whole, which complicates the organisation of an appropriate protection for vulnerable research participants.

34. The legal and ethical literature usually does not distinguish between the risks of exploitation and those of health harm. However, this theoretical distinction has practical relevance as it justifies two contrasting legal responses. On the one hand, more persons should be considered at risk of exploitation and thus should be considered as vulnerable; on the other hand, more persons at risk of health harm should be systematically included in clinical trials, with the necessary safeguards, in order to facilitate the development of safe and efficient therapies for the specific population groups they represent. Where participants are both vulnerable to exploitation and to physical or psychological harm, the two different types of legal response have to be applied, which might necessitate some special arrangements.

# 3 Legal and ethical responses to vulnerability of research participants

## 3.1 DECISIONAL VULNERABILITIES: THE RISK OF EXPLOITATION

35. Theoretically, requiring free and informed consent to involvement in clinical trials protects participants against the risk of exploitation. The tendency is to consider as vulnerable only the persons who do not have legal capacity (minors and incapacitated), persons who *de facto* are unable to consent (unconscious persons in emergency situations), or sometimes persons who are deprived of liberty (like prisoners or residents of medico-social institutions) [74].

36. However, the understanding of decisional vulnerability in this article is wider than those typical examples being legally capable (or allowed) to give informed consent and being actually autonomous are two different things.

37. In addition, scholars as well as ethical guidelines, for instance the CIOMS Guidelines for Biomedical Research (Guideline 13) and the ICH Guidelines for Good Clinical Practice (§1.61) draw attention to "invisible"[75] vulnerable persons: those under hierarchical pressure, or socially

[74] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, ETS N° 164, Oviedo, 4 April 1997, (Hereafter "Oviedo Convention"); Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, CETS N°195, Strasbourg, 25 January 2005 (Hereafter "Additional Protocol").

[75] Stone T. H., "The invisible vulnerable: The economically and educationally disadvantaged subjects of clinical research", *The Journal of Law, Medicine & Ethics*, Vol. 31, n°1, 2003, pp. 149-153.

or economically or educationally disadvantaged[76]. In this sense, some scholars distinguish between "intrinsic vulnerability" and "relational vulnerability".[77] The inability to give a truly free informed consent does not only result from the intrinsic frailty of potential participants (e.g. their cognitive impairment or unconsciousness), but also from some external or relational factors. A current illustration for external factors is the fact that more and more trials are conducted in low-income countries[78], sometimes abusing from the lack of money, from the lack of education, the lack of health care, or the lack of ethics committees.

38. On the contrary, confusion arises when other vulnerable subjects are added to the list, as if they also had the same decisional vulnerability and needed the same protection. Why would a pregnant woman have decisional vulnerability? Why would she not be able to give free and informed consent to a clinical trial? Does the pregnancy affect her reason to the point where she cannot understand the medical information and cannot decide freely for herself? The real reason for her exclusion from trials is the risk of health harm, for her and for the future child, but not any risk of exploitation of her mental inability to give consent.

## 3.2 HEALTH-RELATED VULNERABILITY: THE RISK OF PHYSICAL OR PSYCHOLOGICAL HARM

39. Physically or psychologically vulnerable persons, like frail elderly people or those with chronic conditions like depression, are not formally categorized as "vulnerable participants" as long as they are legally able to consent to research participation. Yet they often do not match with the inclusion criteria to participate in clinical trials for several reasons indirectly related to the safety and reliability requirements. Investigators often choose to exclude them because their physical or psychological vulnerability can make it too difficult to protect their safety. Furthermore, in order to get reliable results, the groups of participants have to be homogeneous and it might also be difficult to gather a sufficient number of participants with the same vulnerability. The obstacles to conduct research with vulnerable subjects can lead investigators to recruit "healthy" participants. As a consequence, they may be collecting research results that could be inapplicable to physically and psychologically vulnerable patients. The general "marginalization of vulnerable populations"[79], which has been denounced, consists in an under-

[76] Denny C. C. & Grady C., "Clinical research with economically disadvantaged populations", *Journal of Medical Ethics*, Vol. 33, 2007, pp. 382-385.
[77] Bell E. *et al.*, "Beyond consent in research. Revisiting vulnerability in deep brain stimulation for psychiatric disorders", *Cambridge Quarterly of Healthcare Ethics*, Vol. 23, n°3, 2014, p. 364.
[78] European Medicines Agency (EMA), Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities, EMA/121340/2011, London, 2012.
[79] Rogers W. & Ballantyne A., "Justice in health research: What is the role of evidence-based medicine ?", *Perspectives in Biology and Medicine*, Vol. 52, n°2, 2009, p. 199.

representation in clinical trials, for instance of pregnant women[80], very elderly[81] or palliative care populations[82]. It was also the case for children, but since 2006 the problem of their under-representation has been recognized and partly solved by the EU Regulation on medicinal products for paediatric use (Paediatric Regulation), which aims to facilitate the development and availability of medicines for children[83].

40. Excluding physically or psychologically vulnerable research subjects from clinical trials has a negative impact on the safety of future patients having the same vulnerability, because the risks of the trial are only postponed to the pharmacovigilance phase, where medical surveillance is at its lowest in comparison to clinical trials. The principle of justice should play a role when conceptualizing the notion of "vulnerability"[84]. This principle obliges researchers to promote research benefitting persons who are particularly in need of suitable therapies because of their physical or psychological vulnerability[85]. Their inclusion in clinical trials should incorporate supplementary ethical requirements and additional medical surveillance.

# 4 The protection of trial participants in the new EU regulation on clinical trials

41. As mentioned above, the new Regulation on Clinical Trials was adopted in April 2014 by the European Parliament and the Council to replace the 2001 Clinical Trials Directive (CTD). According to Article 99 of the Regulation, it will not be applied before May 2016. The advantages of switching from a directive to a regulation are twofold: first, all Member States will now have exactly the same text, and second, this Regulation will be directly binding and applicable at the national level, without any need for an implementation process by domestic law. As we will see, the new Regulation improves the consideration of vulnerable populations in clinical trials in comparison to the CTD, but the protection is still lacking clarity and thoroughness.

[80] Lyerly A. D., Little M. O. & Faden R., "The second wave: Toward responsible inclusion of pregnant women in research", *International Journal of Feminist Approaches to Bioethics,* Vol. 1, n°2, 2008, pp. 5-22.
[81] Cherubini A. *et al.*, "Fighting against age discrimination in clinical trials", *Journal of the American Geriatrics Society*, Vol. 58, n°9, 2010, pp. 1791-1796 ; Hempenius L. *et al.*, "Inclusion of frail elderly patients in clinical trials: Solutions to the problems", *Journal of Geriatric Oncology*, Vol. 4, n°1, 2013, pp. 26-31.
[82] Keeley P. W., "Improving the evidence base in palliative medicine: a moral imperative", *Journal of Medical Ethics*, Vol. 34, 2008, pp. 757-760.
[83] Regulation 1901/2006.
[84] Eckenwiler L. A. *et al.*, "Hopes for Helsinki: Reconsidering 'vulnerability'", *Journal of Medical Ethics*, Vol. 34, n°10, 2008, pp. 765-766.
[85] Lange M. M. *et al.*, "Vulnerability in research ethics: A way forward", *Bioethics*, Vol. 27, n°6, 2013, pp. 333-340 ; Rogers W. & Lange M. M., "Rethinking the vulnerability of minority populations in research", *Am J Public Health*, Vol. 103, n°12, 2013, pp. 2141-2146.

## 4.1 AN IMPROVED BUT STILL UNCLEAR CONSIDERATION OF VULNERABLE POPULATIONS

42. In its first version of July 2012, the Regulation offered a surprisingly limited protection of vulnerable subjects with only three categories: minors, incapacitated adults and unconscious patients in emergency situations. Certainly it was a step further in comparison to the CTD with the addition of emergency situations. However, it was still unsatisfying compared to the previously mentioned European standards relating to biomedical research.

43. After almost two years of discussion and many amendments, the extent of vulnerable categories has been substantially increased. First, Recital 15 of the Regulation's Preamble alludes to the vulnerability of "frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders", which seems to correspond to what we call health-related vulnerability. Recital 31, without explicitly labelling them as vulnerable, refers to participants belonging to an "economically or socially disadvantaged group" or placed "in a situation of institutional or hierarchical dependency that could inappropriately influence" their decision to participate. This latter Recital corresponds, in part, to our decisional vulnerabilities and confirms the need for differentiated legal responses, depending on the type of vulnerability.

44. However, this distinction is not clear in the body of the Regulation. Article 10 provides that specific considerations shall be given to the assessment of applications for authorisation of clinical trials involving vulnerable populations, on the basis of expertise in the relevant disease and population. It includes minors, incapacitated subjects, pregnant and breastfeeding women, specific groups or subgroups and patients in emergency situations. It is unclear whether the expression "specific groups or subgroups" refers to all groups mentioned in Recitals 15 and 31 or only to some of them. Furthermore, in the specific considerations regarding the informed consent, several categories are benefiting from a special status: incapacitated subjects (Article 31), minors (Article 32), pregnant and breastfeeding women (Article 33), and patients in emergency situations (Article 35). But most interestingly, Article 34 gives the possibility for Member States to organize a further protection for certain subjects in a situation of institutional or hierarchical dependency likely to inappropriately influence their consent. However it does not mention economically or socially disadvantaged groups, and does not provide any specific protection for them. In a certain but incomplete way, their protection is concretized in the Regulation thanks to Article 25(5), which introduces the equivalence principle for the protection of trial participants outside of the EU. The latter thus also applies for the protection of vulnerable subjects, notably when recruited in developing countries, who are usually socially and economical disadvantaged in comparison to the developed countries conducting the clinical trials. Finally, there is no mention at all of the vulnerable groups -yet expressly mentioned as such in the Recital 15- of the "frail or older people, people suffering from

multiple chronic conditions, and people affected by mental health disorders" at any further provisions of the Regulation.

45. If the situation of vulnerable populations is herewith nonetheless considered more comprehensively than in the CTD, the category of "vulnerable participants" remains vague. The new Regulation does not clearly define who is considered as vulnerable and who deserves which type of protection. Protection is limited to some general considerations in the Preamble, a restrictive provision on vulnerable subjects and a wider range of specific protective measures related to informed consent. This is problematic since theoretical clarity of the concept of vulnerability in biomedical research is crucial because it has significant consequences on the quality of protection[86].

## 4.2 A LEGAL PROTECTION OF VULNERABLE PARTICIPANTS LACKING THOROUGHNESS

46. In order to evaluate the protection of vulnerable trial participants in the new EU Regulation, we again turn to the distinction between decisional vulnerabilities (risk of exploitation) and health-related vulnerabilities (risk of physical or psychological harm).

### 4.2.1 Decisional vulnerabilities

47. Many potential participants in clinical trials, because of their reduced cognitive capacities or freedom of choice, are at risk of being exploited for the benefit of scientific knowledge. First of all, subjects might be unable to give free and informed consent to research participation, be it *de jure* (minors and incapacitated adults) or *de facto* (unconscious patients in emergency situations). Second of all, other subjects might be at risk of being unduly influenced to accept to participate in clinical trials: socially, economically, financially and educationally disadvantaged groups, persons deprived of liberty or in medical institutions, persons in a situation of institutional, familial or hierarchical pressure etc. An excessive compensation or pressure could induce them to participate in clinical trials against their better judgment. In such cases, specific safeguards are needed to ensure that they have the ability to provide truly free consent to research participation.

48. Still, while the new Regulation requires "informed consent" in Article 28, only Recital 31 of the Preamble emphasises and explains the need for this consent to be given freely: "the investigator should take into account all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial".

[86] Rogers W., Mackenzie C., & Dodds S., "Why bioethics needs a concept of vulnerability", *International Journal of Feminist Approaches to Bioethics*, Vol. 5, n°2, 2012, pp. 11-38.

49. Certainly, Article 28.1.h sets as a condition for clinical trials that "no undue influence, including that of a financial nature, is exerted on subjects to participate in the clinical trial". However there is a big discrepancy between such a short reference and the reality of the exploitation, notably in developing countries, but not only as it should also emphasize, hierarchical, institutional, religious or familial pressure that can make a subject vulnerable to undue influence to participate.

50. Article 34 allows Member States to maintain additional measures regarding "persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions", but does not actually require States to provide special protection to those subjects regarding their free and informed consent. But even so, only allowing for additional protection is not protection *per se*.

51. Consequently, Recital 31 does not find a concrete nor complete implementation in the Regulation. Persons with decisional vulnerabilities are thus not sufficiently protected from the risk of exploitation in clinical trials.

### 4.2.2 Health-related vulnerability

52. Some patients (children, frail or older adults, pregnant women, people with multiple chronic diseases, etc.) present particular physical, physiological or psychological conditions that may have a negative impact on the safety and efficacy of treatments and might put them at greater risk of harm in comparison to non-vulnerable participants. These population groups need therapies or drug dosages adapted to their condition, which implies the conduct of specific trials, which must be accompanied by additional safeguards (closer medical surveillance, competence of the investigator) to palliate the greater risk of harm.

53. The new Regulation does consider physical and psychological vulnerability and calls for clinical trials involving those specific groups in Recital 15 of the Preamble: "medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups". However, this is the only allusion to health-related vulnerabilities in the Regulation.

54. Technically, research participants with health related vulnerabilities are allowed to consent to research participation, even when the trial does not offer any direct benefit to them, but only to the population they represent. This is possible either because they are not vulnerable according to the Regulation and fall under Article 28.1(a); or because although they are vulnerable according to the Regulation, they are still legally capable, like for instance pregnant women (Article 33(b)I and ii); or finally because, although legally incapable like minors and incapacitated, they have a specific provision allowing them, in restricted cases, to participate to research for the benefit of the group that they represent (Articles 31.1(g)ii and article 32.1(g)ii).

55. It is unfortunate that the strategy applied to minors in the above mentioned Paediatric Regulation of 2006 has not been implemented for other physically or psychologically vulnerable subjects. The latter promotes high quality research involving children through incentives directed to pharmaceutical companies. As we have seen before, children are physically and psychologically vulnerable, but are also vulnerable in relation to decision-making. The complexity of this double vulnerability might explain why they are the only subjects benefiting from a specific set of rules.

# 5 Four suggestions for a more accurate protection of vulnerable persons in the new EU Regulation on clinical trials

56. Despite making strides towards the protection of vulnerable groups, the new Regulation is still lacking clarity and thoroughness and continues using the labelling approach, which we consider inadequate. In this section we make four general suggestions to improve the situation of vulnerable research participants in the EU.

### *Suggestion 1: A risk-based definition of vulnerability*

57. The first suggestion is to adopt a risk-based definition of vulnerability. This would actually be in line with the ambition of the European Union to include and exclude participants more accurately according to the level of risk entailed in a trial (Preamble of the Regulation, Recital 11). This means, the more risks there are or the higher the risks are, the more demanding the participants' protection has to be, and vice-versa. In this regard, it is interesting to note that the Regulation has adopted a risk-based approach by creating a new category of trials: the "low-intervention clinical trials", which pose only "very limited additional risk to the subject compared to normal practice (…). They should be subject to less stringent rules (…)" (Recital 11).

58. It is important to stress that the risk-based approach of the Regulation only refers to the levels of the risk of harm, by classifying the medicines according to their potential dangerousness, *e.g*. between marketed medicines and investigational medicines. On the contrary the scope of this article is, as a first step, to identify the type of risk and not its level. The risk-based approach of the regulation will be applicable to health vulnerabilities (risk of harm), but not directly to decisional vulnerabilities (risk of exploitation).

### *Suggestion 2: A distinction between decisional and health related vulnerabilities*

59. The second suggestion consists of distinguishing between, on the one hand, decisional vulnerabilities, and, on the other hand, health-related vulnerabilities. This would help clarifying the concept of vulnerability in biomedical research as well as the specific health care needs of vulnerable groups. The provisions devoted to vulnerable subjects (Art. 10) and to informed consent (Arts. 31 to 35) mix those categories. However, this fundamental distinction is implied in the Preamble, in particular, in Recital 15, which corresponds to what we call health-related vulnerability (increased risk of physical or psychological harm) and in Recital 31, which corresponds to our decisional vulnerabilities (increased risk of exploitation).

### *Suggestion 3: A wider protection of consent against undue influence*

60. There are persons who have the legal capacity to consent to medical research, but who, mainly because of external factors are more vulnerable than others to undue influence (the poor, the unemployed, the dependent).

61. As mentioned above, the new Regulation includes the absence of undue influence on potential participants as one of the conditions for conducting clinical trials (Article 28.1.h). Nevertheless, only financial incentives are explicitly mentioned, leaving aside other external factors which are as important like for instance hierarchical, institutional, familial or religious pressures, like is emphasized in the ICH guidelines (§1.61)

62. Similarly, the Preamble explains that the investigator should take into account all certain circumstances which might "inappropriately influence" the decision of certain potential subjects (Recital 31). However, no criteria are provided to determine which influence is "undue" or "inappropriate", and there is no mention of the fact that this factor should be assessed by an ethics committee, as is done in the CIOMS Guidelines (Guideline 7).

### *Suggestion 4: An assertion of the need to organize clinical trials with physically or psychologically vulnerable participants*

63. As we have demonstrated before, the new Regulation does offer opportunities for vulnerable persons to be included in non-therapeutic research as long as it can benefit the group they represent (*Infra 4.2.2*). But as demonstrated, only offering the possibility might not be sufficient to protect future vulnerable patients of the same group. Incentives – as it has been done for children – would be welcome, provided that sufficient safeguards are guaranteed.

64. Consequently, our fourth suggestion is to promote a more inclusive policy to encourage investigators to include physically or psychologically vulnerable participants in clinical trials, with the necessary additional safeguards. This promotion could be done, for instance,

through governmental incentives allocated to researchers accompanied with specific ethical considerations for vulnerable subjects, following the example of the Paediatric Regulation.

# 6 Conclusion

65. Having defined vulnerability as the result of a correlation between a susceptibility and a corresponding exposure to a risk, we claim that two types of vulnerabilities within clinical trials should be distinguished: one related to the risk of exploitation (decisional vulnerability), the other related to the risk of physical or psychological harm (health-related vulnerability). The first risk demands the protection of people who are unable to give their consent or who might be unduly influenced to consent to research participation. The second risk requires protecting people who are more likely to suffer any harm as a result of the experimental treatment. This protection does not entail excluding them from trials, but instead by providing these participants with additional safeguards like specific ethical requirement and medical monitoring. When participants have both kinds of vulnerabilities, the two types of protection have to be combined. Still, it seems important to distinguish them in order to fully assess the quality of the protection.

66. The new EU Regulation adopts a wider understanding of vulnerable participants than the 2001 Clinical Trials Directive, but their protection remains unsatisfying for two reasons: firstly, the definition of vulnerability stays unclear and not conceptualized, secondly, this leads to a patchy protection of vulnerable subjects. In sum, we make four suggestions to protect the interests of vulnerable research participants: to adopt a risk-based definition of vulnerability, to clearly distinguish between, on the one hand, decisional vulnerabilities and, on the other hand, health-related vulnerability; to emphasise the need to ensure the freedom of consent of those persons who are more susceptible to undue influences (decisional vulnerability), and finally to assert the importance of actively promoting specific clinical trials involving people with physical or psychological vulnerabilities.

# Chapter 2: Paediatric Research under the New EU Regulation on Clinical Trials: Old Issues New Challenges

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### ABSTRACT

Regulating paediatric research means searching for the balance between two valuable goals: protecting children while ensuring they benefit from safe and efficient medicines. Different legal instruments were adopted in the EU in order to regulate clinical trials, foster paediatric research and promote European and international ethical guidelines. However a new Regulation on clinical trials was adopted in 2014, and might change the current framework of paediatric research. How does the new Regulation 536/2014 foster research on children taking into account both the EU Paediatric Regulation and the EU Ethical Recommendations? Does it live up to the standards of the Directive 2001/20/EC and does it represent a step forward in accordance with international ethical guidelines? This article shows that, despite the adoption of new rules, many clarifications are still needed. Stakeholders involved in paediatric research have to play a driving role in the implementation process of the new Regulation.

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# 1 Introduction

67. Regulating paediatric research means striking the right balance between two valuable goals: protecting children because they are vulnerable, and making sure they benefit from safe and efficient medicines. After the outrageous medical experiments performed on humans during the Second World War, there has been a tendency to exclude any vulnerable participants from clinical trials. With time, this well-intentioned reaction showed its limitations. Due to the fact that children's bodies could react differently to drugs as compared to adults but there has been a dearth of data regarding testing in children, many drugs were used off-label. Thus calls for safe and efficient medicines specifically for children arose.

68. The Directive 2001/20/EC[87], implementing ICH-GCP international guidelines, introduced for the first time specific provisions[88] aimed at favouring the conduct of ethically acceptable clinical trials in children[89]. These provisions were enhanced by the ICH-E11 specifically devoted to paediatrics[90]. In 2006, the Paediatric Regulation established "a system of both obligations and rewards and incentives"[91] with the aim of fostering paediatric research[92]. One key measure of this Regulation is the institution, at the European Medicines Agency, of the Paediatric Committee (PDCO), in charge of giving advice and examining Paediatric Investigation Plans (PIP)[93]. Finally in 2008, EU Ethical Recommendations were developed with the aim of implementing non-binding ethical guidelines for Directive 2001/20/EC in the paediatric population.

69. However, the European legal framework and especially the Directive 2001/20/EC was deemed partly responsible for a dramatic increase in bureaucracy, costs and delays for launching clinical trials in the EU, leading to a 25% decrease in trials[94] as well as to their off-

[87] 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 (Hereafter "Directive 2001/20/EC")

[88] Directive 2001/20/EC, Article 4.

[89] "Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied". Directive 2001/20/EC, Recital 3.

[90] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Clinical Investigation of Medicinal Products in the Pediatric Population, E11, Geneva, 2000 (Hereafter "ICH E11)".

[91] Regulation (EC) N° 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Hereafter "Regulation 1901/2006"), Recital 6.

[92] European Medicines Agency (EMA), Successes of the Paediatric Regulation after 5 years. August 2007-December 2012, EMA/250577/2013, London, 2013.

[93] Paediatric Investigation Plans are documents "upon which the development and authorisation of medicinal products for the paediatric population should be based". Regulation 1901/2006, Recital 9.

[94] European Commission, Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC, VOLUME I, Working Document Commission Services, SWD(2012) 200 final, Brussels, 17 July 2012, (Annexes), p. 9.

shoring to emerging countries[95]. Those problems led to the elaboration and adoption of the new EU Regulation 536/2014[96] on clinical trials, which repeals the Directive 2001/20/EC, and will be directly binding and applicable for all EU-Member States by 2016. The major changes are as follows: first, the application procedure will be simplified, notably for multinational clinical trials, thanks to a unique application submitted to a single submission portal[97]. Second, assessment of the application is split in two: one part for the Reporting Member State (RMS), the other one for each Member State concerned by the trial[98]. Third, a new category of clinical low-intervention trials was created in order to facilitate research, notably academic trials, when the drug being tested is already authorized and additional procedures involve only minimal risk and burden[99]. Finally, there are several provisions that could impact paediatric research. For example, there are new criteria for the representativeness of subjects' age and sex to be similar to that of future patients[100], the possibility to conduct trials with minors in emergency situations[101], and the status of the PDCO.

70. How does the new Regulation foster paediatric research, taking into account the framework set up by the EU Paediatric Regulation? Does it implement the EU Ethical Recommendations; live up to the standards of the Directive 2001/20/EC; and represent a step forward in accordance with international relevant legal texts and guidelines?

71. This article will deal with specific novelties that might require further attention regarding their implementation in paediatric research, such as the concept of minimal risk introduced in the new EU regulation as a requirement to authorise paediatric trials (2); the new category of low-intervention trials and its applicability (3); the role and expertise of Ethics Committees in paediatrics (4), the newly introduced possibility of secondary use of children's data (5), as well as other internationally recognised ethical standards relevant to paediatrics that necessitate some clarification in the implementation of the new EU Regulation on clinical trials (6).

[95] The 2013 EMA report shows that, between 2005 and 2011, only 38.1% of the patients in pivotal trials submitted in marketing authorization applications to the EMA were from the EU. EMA, Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency ; Overview of patient recruitment and the geographical location of investigator sites. Containing data from 2005 to 2011, EMA/INS/GCP/676319/2012, London, 2013, p. 9.

[96] Regulation (UE) 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 (Hereafter "Regulation 536/2014")

[97] *Ibid*., Article 5.

[98] *Ibid*., Articles 6 and 7. The whole process is submitted to strict timelines sanctioned by the tacit agreement principle. *Ibid.,* Preamble Recital 8.

[99] *Ibid*., Article 2.2(3).

[100] *Ibid*., Article 6.1(b)i.

[101] *Ibid*., Article 35.2(a).

# 2 Minimal Risk: A Key but Still Heterogeneous Concept to Authorize Paediatric Trials

72. Whereas Directive 2001/20/EC only required risks to be minimized for children, the new Regulation introduces the criteria of minimal risk and minimal burden that now must be assessed "in comparison to the standard treatment of the minor's condition"[102].

73. Except for the ICH-GCP[103], many ethical guidelines consider "minimal risk" as a prerequisite for paediatric research (*e.g.* Declaration of Helsinki[104], CIOMS guidelines[105], UNESCO Declaration on Bioethics and Human Rights[106], EU Ethical Recommendations[107]). This is also the case for legal instruments such as the Oviedo Convention of the Council of Europe[108] and its Additional Protocol on Biomedical Research[109], as well as most national laws in Europe (*e.g.* Austrian law[110], Danish law[111], French law[112], German law[113], Dutch law[114], or Spanish law[115]) and abroad (the US[116] and Canada[117]). However, most of these texts do not define what constitutes minimal risk. When definitions are provided, there is a lack of consistency among them. However, there exist two main interpretations of minimal risk: the US "absolute interpretation"

[102] Regulation 536/2014, Article 32.

[103] In the ICH guidelines, the requirement for conducting trials with persons who are not able to consent is that the foreseeable risks are low. ICH, Guideline for Good Clinical Practices, E6(R1), Geneva, 1996, § 4.8.14.b, p. 17.

[104] WMA (World Medical Association), Declaration of Helsinki - Ethics principles applicable to medical involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 (Hereafter "Declaration of Helsinki"), §28.

[105] "Minimal risk – that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination". CIOMS (Council for International Organizations of Medical Sciences), International Ethical Guidelines for Health-related Research Involving Humans, in collaboration with the World Health Organization (WHO), Geneva, 2002 (Hereafter 2002 CIOMS Guidelines), Guideline 10.

[106] United Nations Educational, Scientific and Cultural Organization (UNESCO), Universal Declaration on Bioethics and Human Rights, 2006, Article 7.b).

[107] Ethical considerations for clinical trials performed in children. Recommendations of the *Ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, final 2008, §11.1.

[108] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo, 4 April 1997, ETS n°164, (Hereafter "Oviedo Convention"), Article 17.2.

[109] Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25 January 2005, CETS n°195, (Hereafter "Additional Protocol"), Article 15.2.

[110] *Arzneimittelgesetz* (AMG), §42(2)2 ; as well as *Medizinproduktegesetz* (MPG), §51(2)2.

[111] Act on Research Ethics Review of Health Research Projects as updated on 9 October 2013, Section 19(3)3.

[112] Code de la Santé Publique (CSP), Article L 1121-7.

[113] AMG, §41(2)2.d).

[114] Act of 26 February 1998, containing rules on medical research involving human subjects (Medical Research Act), Section 4.1.

[115] Law 14/2007, of 3 July 2007, on biomedical research, Article 20.2)b). Royal Decree 223/2004, of 6 February 2004, Article 4.b).

[116] Code of Federal Regulations (CFR), Title 45, Section 46.404 Research not involving greater than minimal risk.

[117] Canadian Institute of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERCC), and Social Sciences and Humanities Research Council of Canada (SSHRCC), Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2010, Articles 3.7.a and 6.12.

(2.1) and the Council of Europe "relative interpretation" (2.2). The EU Ethical Recommendations introduce a third, compromise approach (2.3). Questions remain as to how the Clinical Trials Regulation 536/2014 interprets minimal risk criteria (2.4).

## 2.1 THE US ABSOLUTE INTERPRETATION OF MINIMAL RISK

74. In the Code of Federal Regulations (CFR), minimal risk means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests"[118].

75. This "absolute interpretation"[119], or "healthy child interpretation"[120], was first criticised because it could hinder valuable research by limiting acceptable risk to the very low risks that a healthy child faces in his daily life. Additionally, this interpretation, although restrictive in general, would not be protective enough in some cases. For example, healthy children might live in geographically or socially dangerous areas, which would lead to their inclusion in research of relatively high risk, which could still be minimal in comparison to their daily life[121]. Even if several suggestions exist as to how to interpret the absolute definition of minimal risk[122], ambiguities remain as well as a lack of consensus on what is "small", "moderate", or "serious" risk of harm or "considerable" discomfort[123]. The comparator of "daily-life" itself also has often been questioned[124].

76. This restrictive interpretation of minimal risk is balanced with possible exceptions. Specific conditions have been required in the CFR[125], but more importantly, a crucial role is given to the IRB in the assessment of risk and the approval of the trial in accordance with these conditions[126].

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[118] CFR, Section 46.102 (i); This is almost similar to the previously mentioned definition of the CIOMS, except that the 2002 CIOMS guidelines do not refer to the daily-life but only to medical and psychological examinations. 2002 CIOMS Guidelines, Guideline 10.

[119] Westra A. E. *et al.*, "How best to define the concept of minimal risk", *Journal of Pediatrics*, Vol. 159, n°3, 2011, p. 496.

[120] Binik A., "On the minimal risk threshold in children", *American Journal of Bioethics*, Vol. 14, n°9, 2014, p. 3.

[121] *Ibid*., p. 4.

[122] For instance: to "limit the comparison of risks in nontherapeutic research to the risks posed by activities in daily-life that are designed to benefit others". Wendler D., "Justice and nontherapeutic pediatric research", *American Journal of Bioethics*, Vol. 14, n°9, 2014, pp. 13-15; or to distinguish between minimal risk of discomfort and minimal risk of harm. Westra A. E. *et al.*, "How best to define the concept of minimal risk", *op. cit*., p. 497.

[123] *Ibid*., p. 500.

[124] *Ibid*., p. 497.

[125] CFR, Section 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. CFR, Section §46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. CFR, Section §46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

[126] In summary, "greater than minimal risk" is allowed when there is a prospect of direct benefit, if the balance risk/benefit is at least as favourable as that presented by available alternative approaches. But it can also be allowed without prospect of direct benefit to the child, if it is likely to yield generalizable knowledge about the subject's disorder or condition and if

## 2.2 THE COUNCIL OF EUROPE RELATIVE INTERPRETATION OF MINIMAL RISK

77. According to the Council of Europe[127], research is deemed to bear minimal risk if, "having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned"[128].

78. It is further specified that "minimal risk and minimal burden depend on the current state of knowledge and availability of procedures, and less invasive procedures should be utilised once they become available"[129]. Precise examples clearly show that the interpretation of minimal risk is relative, which means that it depends on each individual, his/her condition and treatment. This is the case, for instance, of taking small additional tissue samples "at the time when tissue samples are being taken, *i.e.* a surgical operation".

79. This interpretation is "relative"[130] because it has to be assessed on a case-by-case basis, for instance distinguishing between the daily risks of healthy children versus sick children[131]. It depends on the specific risks that the research subject faces in his/her daily life. Therefore this interpretation of minimal risk is called "subject of research interpretation"[132]. The advantage and danger of this interpretation is that it permits to conduct research with higher risks in sick children. It might promote knowledge about their disease, but it also results in weaker protection of yet particularly vulnerable children. Can illness be a legitimate reason for treating children differently[133]? In any case, in both its texts, the Council of Europe excludes trials for children with any increase over minimal risk. The Council of Europe specifies that "any

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the procedures involved in the research are "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations" (45 CFR 46.406). In this case, the risk has to represent a "minor increase over minimal risk", according to the IRB (Institutional Review Board) evaluation. Finally, it could be possible to carry out "research not otherwise approvable" if it presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of the child and if it will be conducted "in accordance with sound ethical principles" (45 CFR 46.407). In any case, adequate provisions have to be made for soliciting the assent of the children and permission of their parents or guardians.

[127] The Oviedo Convention does not exactly define the minimal risk for children, but provides a long list of examples in its Explanatory report. For instance: "obtaining bodily fluids without invasive intervention, e.g. taking saliva or urine samples or cheek swab; at the time when tissues samples are being taken, for example during a surgical operation, taking small additional tissue samples; taking a blood sample from a peripheral vein or taking a sample of capillary blood; minor extensions to non-invasive diagnostic measures using technical equipment, such as sonographic examinations, taking an electrocardiogram following rest, one X-ray exposure, carrying out one computer tomographic exposure or one exposure using magnetic resonance imaging without a contrast medium". Explanatory report to the Additional Protocol, §100.

[128] Additional Protocol, Article 17.1.

[129] Explanatory report to the Additional Protocol, §96.

[130] Westra A. E. *et al.*, "How best to define the concept of minimal risk", *op. cit*., p. 495.

[131] "However, for certain participants, even these procedures might entail risk or burden which cannot be considered minimal. Assessment on an individual basis must therefore be carried out". Explanatory report to the Additional Protocol, §100.

[132] Binik A., "On the minimal risk threshold in children", *op. cit*., p. 4.

[133] *Ibid*., p. 5.

consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden"[134].

## 2.3 THE EU ETHICAL RECOMMENDATIONS: A COMPROMISE APPROACH TOWARD MINIMAL RISK

80. The EU Ethical Recommendations allow research with children when there is minimal risk and a prospect of benefit for the individual or for the group with the same condition. A minor increase over minimal risk is permitted when there is a benefit for the individual or for the group, but only if the risk/benefit ratio is at least as favourable as that of available alternative approaches. Finally, the Recommendations allow a greater than minor increase over minimal risk, but only when there is a benefit for the participant, and only if the risk/benefit ratio is especially favourable in relation to available alternatives approaches for the individual condition.

81. The EU Ethical Recommendations for paediatric research released in 2008 tried to find a balance between the two existing approaches. They refer to the texts of the Council of Europe and use a relative interpretation of minimal risk as they compare it to the risks of the participant's condition and treatment[135]. However, without referring to risks in daily-life, the EU Ethical Recommendations also seem to be aligned with the US absolute interpretation. The EU Ethical Recommendations consider "minimal risk" in a literal way, *i.e.* as a risk that would be minimal in every possible situation, similar to interpretation by the CFR. This explains why the Recommendations' examples of minimal risk[136] are in sharp contrast to those from the Oviedo Convention and on the contrary, why the EU Ethical Recommendations define exceptions to minimal risk[137], similarly to the CFR.

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[134] Additional Protocol, Article 15.2 ii.

[135] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., 12.1.

[136] "No or minimal risk: history taking, clinical examination, auxological measurments, tanner staging, behavioural testing, psychological testing, quality of life assessment, venepuncture, heel prick, finger prick, subcutaneous injection, urine collection with bag, breath condensate collection, collection of saliva or sputum, collection of hair sample, collection of tissue removed form body as part of medical treatment, topical analgesia, stool tests, Bio-impedancemetry, transcutaneous oxygen saturation monitoring (pulse oxymetry), blood pressure monitoring, electroencephalography, electrocardiography, vision or hearing testing, ophthalmoscopy, tympanometry, lung function tests (peak flow, exhaled NO, spirometry), oral glucose tolerance test, ultrasound scan, digitally amplified chest or limb X-ray, stable isotope examination*)"*. Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., Annex 4, p. 30.

[137] "Minor increase over minimal risk: Urine collection via endoluminal or suprapubic catheter, Arterial puncture, Umbilical catheter, pH metry, Nasogastric tube insertion and use, Transcutaneous oxygen or carbondioxide tension monitoring, Electrophysiological measurements (using stimulation), Exercise testing (ergometry, spiroergometry), Raised volume pulmonary function testing (infants), Peripheral venous lines, Polysomnography, Fasting (≥ 1 meal), Spinal CSF tap, Bone marrow aspiration, MRI scan, X-ray other than digitally amplified chest or limb X-ray, CT scan*, X-ray DEXA bone density measurement, Use of contrast media, Paracentesis, Skin punch biopsy, Airways or skin hyperreactivity challenge test"; "Greater than minor increase over minimal risk: Heart catheterisation, Endoscopy, Biopsy, Surgery or modification of standard surgical procedure carried out as part of medical treatment, Sedation, Anaesthesia, Systemic analgesia,

82. As a consequence, European legal texts referring to the criteria of minimal risk are inconsistent: on the one hand there is the Oviedo Convention and its "relative interpretation" of minimal risk, while on the other hand, the EU Ethical Recommendations offer a compromise between this interpretation and the 'absolute interpretation' inspired by US regulations. This inconsistency can lead to differences in the assessment of paediatric trials and consequent approval of the same research protocol[138]. One example demonstrates that the EU Ethical Recommendations are not protective enough because of this possibility to authorise a minor increase over minimal risk[139], which is not even the highest risk that the document allows. The Oviedo Convention, supposedly more permissive with a relative interpretation of minimal risk, was on the contrary too restrictive and thus more likely to limit research.

## 2.4 MINIMAL RISK IN THE NEW EU REGULATION ON CLINICAL TRIALS

83. The new Regulation's formulation, referring to the standard treatment of the minor's condition, suggests that the interpretation of minimal risk will be relative because it depends on the minor's condition and treatment. Does it mean that the level of acceptable risk can vary according to each child? If so, does it mean that children who are exposed to more risks should be exposed to even higher risks? Or does the notion of minimal risk entail only risks that are minimal in comparison to any treatment? Unfortunately, the Regulation does not provide any further indication on how to define minimal risks in practice.

84. This seems to be quite surprising given that the notion of risk is part of a broader challenge: implementation of a risk-adapted approach to clinical trials[140]. Furthermore, the sole notion of risk causes implementation problems, as brought to the attention of the European Commission during the legislative process by the Bioethics Committee of the Council of Europe[141] as well as by EU Parliament members in their 2013 amendments[142].

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Hypoglycaemia test, Unstable isotope usage, PET scanning*".* Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., Annex 4, p. 30.

[138] Westra A. E. *et al.*, "Drug development for children : How adequate is the current European ethical guidance ?", *Archives of Disease in Childhood*, Vol. 95, n°1, 2010, p. 3.

[139] *Ibid*., p. 5.

[140] It consists in building a framework which strictness would be proportionate to the level of risk involved in the trial. Rid A., "How should we regulate risk in biomedical research ? An ethical analysis of recent policy proposals and initiatives", *Health Policy*, Vol. 117, n°3, 2014, pp. 409-420.

[141] Bioethics Committee (DH-BIO), "Commentaires sur la proposition de Règlement du Parlement européen et du Conseil relative aux essais cliniques de médicaments à usage humain et abrogeant la directive 2001/20/CE à la lumière de la Convention sur les Droits de l'Homme et la biomédecine et de son Protocole additionnel relatif à la recherche biomédicale", DH-BIO (2012) 24, 2012, , p. 4.

[142] Notably in order to distinguish between 1) risks for physical integrity, 2) risks for individual rights of the participants, and 3) risks for data integrity and public health (which are quite similar to the OECD recommendations). Willmott G., Committee on the Environment, Public Health and Food Safety (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012)0369 – C7 0194/2012 – 2012/0192(COD)), A7-0208/2013, Strasbourg, 7 June 2013, Amendment 274, p. 136.

85. Questions clearly remain and it is evident that the new Regulation could benefit from further clarifications or conceptualization on risk and minimal risk, especially if we consider that many other interpretations could serve as a guide for risk-adapted implementation of the Regulation 536/2014 such as those contained in the Canadian Tri-Council Policy Statement[143] or the recommendations of the Organisation for Economic Co-operation and Development (OECD)[144].

86. In this context, there is no doubt that heterogeneous interpretations of minimal risk, and more generally the vagueness of the notion of risk, could raise uncertainties with respect to evaluating trial protocols and assessing when a trial should be considered as low-intervention.

# 3 Low-Intervention Trials Notion and Applicability

87. One main novelty in Regulation 536/2014 is the introduction of a new category of clinical trials, the low-intervention trial. The Regulation aims to facilitate trials[145] with already authorised medicinal products either when used in accordance with their Marketing Authorization or their use is "evidence-based and supported by published scientific evidence"[146]. In any case, any additional diagnostic or monitoring procedures have to pose no more than "minimal additional risk or burden to the safety of the subjects compared to normal clinical practice"[147]. The low-intervention trial category could become a very useful tool in paediatric research in order to properly test drugs in children and report on, after marketing authorization, off-label uses of drugs in paediatric medicine's daily practice. This procedure, which is more flexible and yet less consuming in terms of time and money, could also motivate sponsors to invest in research that focuses more on the needs of children, particularly academic sponsors for which clinical trials are far too expensive otherwise.

88. However, the main problem with implementation of this new category is the interpretation of the notion of "normal clinical practice". Usually, trials in minors must entail only minimal risks and burden in comparison "with the standard treatment of the minor's condition" while for a low-intervention clinical trial, any additional risk or burden need to be

[143] The Canadian Tri-Council Policy Statement, define minimal risk as the risk in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research. CIHR, NSERCC, SSHRCC, "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans", 2010, Chapter 2, section B.

[144] The OECD suggested to compare the additional or incremental risk for the subject participating in a trial with the risk of non-participation, *i.e.,* "the risk of usual care for patients (or the risk of daily life for healthy volunteers)". Organisation for Economic Co-operation and Development (OECD), "OECD Recommendation on the Governance of Clinical Trials", 2013, p. 23.

[145] There will be more flexibility in the content of the application, traceability, and in damage compensation system, shorter timelines and sometimes even simplified informed consent. Regulation 536/2014, Articles 76.3 and 3.3.c.

[146] Regulation 536/2014, Article 2.2(3)b.

[147] *Ibid*., Article 2.2(3)c.

compared with "normal clinical practice". At first sight, standard treatment of a minor's condition has a greater likelihood to entail higher risks (*e.g.,* a standard treatment in paediatric oncology) as compared to normal clinical practice, when we understand normal clinical practice as "routine examination". Do the expressions "standard treatment" and "normal clinical practice" designate the same thing? If so, why do legislators use two different expressions? If not, what is the exact difference? Furthermore, should we consider normal clinical practice for a healthy or sick child? In the EU Regulation, normal clinical practice is defined as the "treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder". This notion is crucial because it determines an acceptable level of risk in low-intervention clinical trials[148].

89. It is understandable to harbour some doubts in relation to this notion, notably its vagueness. Does "normal" mean the statistically most frequent practice? If so, how are Ethics Committees going to gather empirical data on each type of practice? Or does "normal" mean the latest available treatment? The German Medical Association asserts that "the standard of care should be based on the most up-to-date scientific knowledge, not on normal clinical practice. The definition should be defined more precisely"[149]. In the same direction, the OECD recommendations distinguish between "standard of care" as the "treatment regimen or medical management based on state of the art participant care"[150] and "usual care" (which could be similar to the EU normal clinical practice definition) defined as the use of a medicinal product "in accordance with the marketing authorisation"[151]. Several associations also have concerns and suggest to instead employ the expression "best current evidenced-based intervention"[152]. An amendment was presented in the parliamentary report in 2013, suggesting that the notion required concrete implementation guidelines from the Commission in order to avoid contrasting interpretations from each Member State[153]. Unfortunately, the amendment was not adopted in the final version, and the notion was not more clearly defined. The assessment of low-intervention trials could be particularly complicated in paediatric research where the concept of normal clinical practice is even less clear, largely because of widespread "off-label" use of medicines in children.

[148] Regulation 536/2014, Article 2.2(2).
[149] German Medical Association (GMA), "Response to the European Commission on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM/2012/369)", 2012, p. 11.
[150] OECD, "OECD Recommendation on the Governance of Clinical Trials", 2013, p. 44.
[151] *Ibid*., p. 24.
[152] The term "best current proven intervention", defined as "the treatment regimen followed to treat, prevent, or diagnose a disease or a disorder according to current reliable scientific evidence" (amend Article 1(6) of the proposed Regulation), should replace the term "normal clinical practice" throughout the text. Association Internationale de la Mutualité (AIM) *et al*., Joint Analysis "New Proposal for a Regulation on Clinical Trials: - The protection of human subjects must be upheld - Citizens' right to information must be strengthened", 2013, p. 8.
[153] Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit*., Amendment 12, p. 12.

# 4 The Role and Expertise of Ethics Committees in Paediatric Research

90. Trial applications must undergo ethical review[154], as conducted by an Ethics Committee (EC). Risk/benefit evaluation is to be carried out, within stringent and compulsory timelines, by the Reporting Member State (RMS) (Part I of the assessment), whereas the assessment of ethical and local aspects (such as the informed consent…) is to be carried out by all the Member States acting individually (Part II of the assessment). Risk-benefit is thus assessed only by the RMS and not also by the Ethics Committee at national level. It means that, despite the existing international guidelines and literature, the risk-benefit assessment is *de facto* taken out of the "ethical domain". While the RMS's assessment and decision are valid to all other EU Member States[155], the new Regulation could lead to sponsors giving preference to some states over others[156]. This issue reflects the EU's general reluctance to address ethical issues in this regulation, such as the definition of ECs[157], harmonization of different ethical review systems[158], and practical and operational aspects of the assessment of part II[159]. This reluctance is just one of many issues that ECs face with respect to paediatric research, including the question of their

[154] Regulation 536/2014, Article 4.

[155] Members States can only opt-out from the trial, but without having any impact on the decision regarding the trial application. Regulation 536/2014, Article 8.2.c.

[156] The chosen RMS can only refuse this appointment if other Member States concerned manage to agree on one of them being appointed. Regulation 536/2014, Article 5.

[157]Regulation 536/2014, Article 2.2(11). An Ethics Committee is defined as "an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purpose of this Regulation, taking into account the views of laypersons, in particular patients or patients» organisations". This new definition seems to have undergone quite a few cuts, notably on the symbolic statement of the ECs role to "protect the rights, safety and wellbeing of human subjects" and "to provide public assurance of that participation" foreseen in Directive 2001/20/EC. Directive 2001/20/EC, Article 6.

[158] The European Commission released a proposal in 2012 which had deleted any reference to ethics except for the provision stating that it is not part of the competence of the EU and should therefore be at the discretion of national laws (European Commission, "Proposal for a Regulation 2012/0192 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, COM(2012) 369 final", Recitals 6 and 12.); Many reactions from the scientific and academic community lead to the reestablishment of the ECs thanks to parliamentary amendments. But as underlined, this reestablishment was only done half-heartedly; For more on the topic: Bioethics Committee (DH-BIO), "Commentaires sur la proposition de Règlement du Parlement européen et du Conseil relative aux essais cliniques de médicaments à usage humain", *op. cit*.; European Group on Ethics in Science and New Technologies (EGE), Statement on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM 2012) 369 final, 2012; Nys H., "New European rules regarding the approval of clinical trials, the role of ethics committees and the protection of subjects", *Archivum Immunologiae et Therapia Experimentalis*, n°60, 2012, pp. 405-414; Den Boer A. et Schipper I., "New EU regulation on clinical trials : The impact on ethics and safeguards for participants", *Indian Journal of Medical Ethics*, Vol. X, n°2, 2013, pp. 106-109; Heringa J. & Dute J., "The proposed EU-regulation on clinical trials on medicinal products : An unethical proposal ?", *European Journal of Health Law*, n°20, 2013, pp. 347-362; Global Research in Paediatrics (GRiP), Children matter: important amendments in the draft Clinical Trials Regulation, 2013; Westra A.E. *et. al*, "New EU clinical trials regulation needs a few tweaks before implementation", *BMJ*, Vol. 348, 2014, pp. 1-2.

[159] The Part II data sent through the EU portal does not appear to include approval of ethical aspects by the EC, although it specifically concerns ethical aspects. Petrini C., "Regulation (EU) n° 536/2014 on clinical trials on medicinal products for human use : An overview", *Ann Ist Super Sanita*, Vol. 50, n°4, 2014, p. 320.

paediatric expertise (4.1), their collaboration (4.2), and interaction with Paediatric Committee (PDCO) PDCO (4.3).

## 4.1 PAEDIATRIC EXPERTISE OF ETHICS COMMITTEES

91. The new Regulation did not really change the requirement from Directive 2001/20/EC that ECs have paediatric expertise or take "advice in clinical, ethical and psychosocial problems in the field of paediatrics" for trials on children[160]. These provisions, however, were thoroughly supplemented by the EU Ethical Recommendations, by adding requirements for ECs' members to demonstrate proper documented education and experience in the various aspects of working in paediatrics[161]. This document gives precise indications of what constitute paediatric expertise which goes "beyond having professionally worked with children and could be defined on the basis of education, training and experience on the various aspects of child development, ethics and psychosocial aspects"[162]. It also recommends having a specialised EC in paediatrics "for the evaluation of trial protocols that are complex or in serious paediatric diseases"[163].

92. The new Regulation does not yet satisfy these recommendations as it does not consider any of these and instead, adopts the formulation of the Directive 2001/20/EC almost word for word[164]. One amendment had been suggested, emphasising the need of paediatric expertise of the EC when the trial involves children[165], but was not adopted in the final version. This is unfortunate and surprising, as a survey involving ECs in Europe demonstrates ECs' lack of knowledge on both legal and ethical aspects of paediatric research, and the need of training and education of ECs in paediatrics[166].

[160] Directive 2001/20/EC, Article 4.h.
[161] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §8.
[162] The rest of the recommendation gives examples of paediatric expertise: "Therefore, this would include i) physicians with paediatric qualification; ii) paediatric ethicists; iii) a paediatric pharmacologist, iv) qualified paediatric nurses or psychologists, etc", the experts also have to demonstrate and document their experience with children in addition to expertise. Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §8.1.
[163] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §8.
[164] Regulation 536/2014, Recital 19 and Article 10.1.
[165] "In cases of clinical trials involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise". Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit*., Amendment 64, §2, 10a (new).
[166] Altavilla A. *et al.*, "Impact of the new European paediatric regulatory framework on ethics committees: Overview and perspectives", *Acta Paediatrica*, Vol. 101, n°1, 2012, p. 5.

## 4.2 COLLABORATION OF EUROPEAN RESEARCH ETHICS COMMITTEES IN PAEDIATRICS

93. An EU-wide study identified networking among ECs as a fundamental tool for enhancing collaboration, experience and information exchange[167], especially on ethical issues including procedures and principles of ethical assessment. The need of a network or platform organized at the European level was suggested at multiple times[168] [169] [170]. Two amendments, submitted in 2013 for an organisation at the European level of a network of ECs, argue that it is the role of the Commission to set up a European Platform to bring consistency in ethical reviews by encouraging cooperation and sharing of best practices among ECs[171]. This proposal is particularly important if we consider that ethical and legal disparities among Member States are still a major concern, possibly leading to so-called "ethics shopping", as highlighted by different stakeholders and by the European Group of Ethics[172]. Unfortunately, none of those potentially helpful suggestions has been adopted during the legislative process of the new EU Regulation on clinical trials.

94. Actually a network (EUREC) bringing together national Research Ethics Committees (REC) associations, networks or comparable initiatives on the European level exist. It aims at promoting awareness of specific working practices of RECs across Europe, enhancing the shared knowledge base of European RECs[173]. Nevertheless, as clinical trials in children shows very distinct particularities and challenges, there is still a need for a specific network among ECs involved in paediatric research. To promote and foster their cooperation and improve their

[167] Altavilla A. *et al.*, "Impact of the new European paediatric regulatory framework on ethics committees: Overview and perspectives", *op. cit*., p. 5.

[168] European Commission, Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC. Summary of the responses to the public consultation paper, SANCO/C/8/SF/dn D(2010) 380240, 2010, p. 6.

[169] European Commission, Revision of the "Clinical Trials Directive" 2001/20/EC. Summary of the replies to the public consultation on the "Concept Paper", SANCO/D/3/PB/SF/ddg1.d.3(2011)816084, 2011, §38, p. 5.

[170] A quality and accreditation system could be established for all Ethics Committees so that all trials are reviewed by "competent" bodies playing a key role also in the "risk-benefit assessment". Westra A.E. *et. al*, "New EU clinical trials regulation needs a few tweaks before implementation", *op. cit*.

[171] "Currently, the ethical review procedure varies greatly between Member States, often with various bodies at national, regional and local levels, and multiple procedures leading to divergent assessments. This is a source of delays and fragmentation. In the interests of European patients and public health, the procedures and principles of ethical review should be better harmonised through the sharing of best practices between ethics committees. To this end the Commission should facilitate the cooperation of ethics committees". Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit*., Amendment 27, Recital 14b (new); See also: "The Commission shall facilitate cooperation of ethics committees and the sharing of best practices on ethical issues including the procedures and principles of ethical assessment". *Ibid*., Amendment 79, Article 4a (new) 2.

[172] EGE, Statement on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit*.

[173] EUREC is connected with the EURECNET Project that is a consortium of twenty European research facilities which has been established in March 2011 and is being funded by the European Commission under Framework Program 7 (FP7). It is coordinated by the German Reference Centre for Ethics in the Life Sciences (DRZE). Following already existing efforts, especially efforts within a previous project (EUREC), one of its primary objectives is to foster a sustainable infrastructure for European RECs. http://www.eurecnet.org/index.html.

expertise, best practice models of ethical evaluation of paediatric trials should be developed. A quality and accreditation system could be established for these Committees so that all trials are reviewed by "competent" bodies playing a key role also in the "risk-benefit assessment"[174] particularly complex for children.

## 4.3 INTERACTIONS WITH THE PAEDIATRIC COMMITTEE (PDCO)

95. However, at the European institutional level, the new Regulation confirms the importance of the role of the Paediatric Committee (PDCO) by expressly requiring the opinions of the latter to be taken into account in the assessment of anticipated therapeutic and public health benefits[175].

96. Still there remain uncertainties about the roles of ECs and their interactions with the RMS authorities and PDCO. Coordination between competent authorities and ECs will need to be carefully established, particularly when Part I and II are presented together and the two assessments are processed in parallel within the same national timetable[176]. What happens when the PDCO gives the approval to the Paediatric Investigation Plan but the RMS and/or the EC does not approve the protocol of the same trial? The decision of the EC will entail more than balancing risk/benefit because it takes into account the whole protocol. On the contrary, the protocol was not yet designed at the time of the PDCO's decision, which only concern the PIP. Nevertheless as you would expect, the PDCO has a paediatric expertise that the EC and the national authorities in charge of the protocols evaluation does not necessarily have. Whose decision should prevail over the other? Further clarification would be helpful regarding interaction with authorities involved in the protocol review, ethical review conducted at a national level, evaluation of PIPs by the paediatric experts of PDCO, as well as detailed criteria and ethical guidelines for systematic use in the assessment of protocols and PIPs[177].

# 5 Secondary Use of Data in Children

97. One novelty of the Regulation 536/2014 is the introduction of secondary use of data collected in children: "Without prejudice to Directive 95/46/EC, the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or

[174] Westra A.E. *et. al*, "New EU clinical trials regulation needs a few tweaks before implementation", *op. cit*.
[175] Regulation 536/2014, Article 6.1.b.i.
[176] Petrini C., "Regulation (EU) n° 536/2014 on clinical trials on medicinal products for human use : An overview", *op. cit*.
[177] Enpr-EMA has set up a Working Group to gather examples of "good practice when ECs consider trials related to children and young people" and to develop proposals to disseminate those examples. Enpr-EMA, Mandate of the Enpr-EMA working Groups, EMA/493016/2013Rev.1, 2014, p. 4.

her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative"[178].

98. This new provision seems to be helpful to avoid unnecessary replications of trials and develop useful epidemiological studies, especially for generating data on children[179]. However, this "broad consent", given in advance, will never be as precise and informed as a repeated informed consent procedure. Even if doing so proves to avoid additional risks to children, because the samples are already obtained, a broad parental consent deprives the child of the opportunity to exercise autonomy, by not allowing his/her ratification of the parental consent at a later date. This problem could be particularly relevant in longitudinal studies that imply a potentially lengthy period of involvement of children. Moreover, if the minor keeps the right to withdraw his/her consent, notably when becoming legally competent, he/she has to be able to exercise this right. This means that he/she has to be informed of the existence of a new study. Thus it implies that re-identification of his/her data must be possible.

99. Furthermore, different legislations have adopted different definitions to guarantee the confidentiality of personal data[180]. Terms such as "anonymization", "pseudonymisation", "codification", and "de-identification" are indiscriminately used in guidelines and legal texts to indicate similar concepts as different requirements and level of confidentiality protection have been identified taking into account the notion of "reversibility" within the data processing procedures[181]. That's why it is important to have clear definitions and frameworks, so that parents and minors know exactly what they consent to when they are told that their child's information will be coded or anonymized. Finally, specific requirements must be established with reference to specific data, such as genetic data, which can raise concerns in terms of equity and discrimination especially for children. Precise definitions and provisions need to be developed, guaranteeing transparency to minors and legal representatives, and assuring legal certainty. Perhaps the forthcoming reform of the EU data protection legal framework will bring some answers to these questions[182].

[178] Regulation 536/2014, Article 28.2.

[179] Regulation 1901/2006, Article 41; Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §19.

[180] Canadian guidelines differentiate between directly identifying information, indirectly identifying information, coded information, anonymized information and anonymous information. For more details: Centre of Genomics and Policy (CGP), Maternal Infant Child and Youth Research Network (MICYRN), Best Practices for Health Research Involving Children and Adolescents, 2012, p. 92.

[181] Global Research in Paediatrics (GRiP), Report on ethical and governance issues related to processing of healthcare data, D.2.04, 2015.

[182] European Commission Website, http://ec.europa.eu/justice/data-protection/review/index_en.htm.

# 6 Other Relevant Ethical Standards Impacting Paediatric Research

100. There are other issues that require attention towards paediatric research. All of these are included in the EU Ethical Recommendations, and often correspond to internationally recognised ethical and methodological standards. Here we address those issues that require specific mention within the framework of the new EU Regulation.

## 6.1 Assent/Dissent and Compensation: a step forward with need of clarification

101. The notion of assent, introduced by the Declaration of Helsinki[183] and mentioned in the WHO-CIOMS[184] and ICH-E11 guidelines[185], was introduced into the EU legal framework only with Regulation 536/2014[186]. Nevertheless, Member States still have a large margin within which to manoeuvre in applying this principle, again possibly leading to some disparities, especially with multinational trials.

102. The new Regulation is significantly progressive with respect to "dissent" of the child. While Directive 2001/20/EC notes that dissent of the child has to be "considered"[187], the new Regulation now expects it to be "respected": "the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator"[188].

103. Best-practice guidelines that take into account national legislations and are based on a well-sustained methodological approach should be developed. Specific requirements to obtain the child's assent, adapted to different age-ranges, provided in the EU Ethical Recommendations[189], as well as international provision related to the respect of refusal[190] could be an important starting point for the implementation of these guidelines. Regarding

[183] Declaration of Helsinki, §29.
[184] 2002 CIOMS Guidelines, Guideline 14.
[185] ICH E11, §2.6.3, p. 11.
[186] EU Member States may foresee, in their national law, that the «minor who is capable of forming an opinion and assessing the information given to him or her, should himself or herself assent in order to participate in a clinical trial». Regulation 536/2014, Recital 32 and Article 29.8.
[187] Directive 2001/20/EC, Article 4.c.
[188] Regulation 536/2014, Article 32.1.c
[189] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit.*, §5.7, §6.1, §6.4 and §7.
[190] Oviedo convention, Article 17.1.v; United Nations Commission on Human Rights (UNCHR), Convention on the Rights of the Child of 20 November 1989, Article 12.1.

compensation, the new Regulation changes the provision applicable in the EU, stating that "no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial"[191].

104. This provision is quite progressive compared to the Directive 2001/20/EC, which forbade financial incentives but allowed "compensation" without further detail on the nature and extent of this compensation[192]. The new Regulation implements and supplements the EU Ethical Recommendations[193]. The EU framework on clinical trials might now be stricter than the Council of Europe Conventions[194] and U.S. legislation[195].

105. However, questions remain concerning the definitions of "inducement" or "incentive"[196]. It is not clear what the two terms in the new Regulation really entail. Therefore, it is also not clear which exact elements ECs should examined when reviewing payments. What constitutes an undue influence can be very different depending on the age of the minor, familial background and his/her financial or social situation[197].

## 6.2 Measures to Minimize Pain, Risk Monitoring and Use of Placebos: Missed Chances for Improvement

106. Directive 2001/20/EC required trials with minors and incapacitated adults to be "designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage (…) Both the risk threshold and the degree of distress have to be specially defined and constantly monitored"[198]. With the new EU Regulation, this is now a general provision for all participants and not only children and incapacitated persons[199].

[191] Regulation 536/2014, Article 32.1.d).
[192] Directive 2001/20/EC, Article 4.d.
[193] The EU Ethical Recommendations are stating that this ban of financial incentives should concern not only the child but also the parents / legal representatives, and that compensation was only related to the time and expenses of the latter. Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §21.
[194] The Oviedo Convention only forbids in its Additional Protocol on Biomedical Research «undue influence, including that of financial nature» on the potential participant. Additional Protocol, Article 12.
[195] The CFR provides that the IRBs is responsible of assessing «the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence». 21 CFR 50.20
[196] Canadian guidelines give precise and clearly distinguished definitions of reimbursement, compensation, appreciation and incentive. According to those, reimbursement would concern transportation, parking, meals, lodging or babysitting whereas compensation would rather be for time and inconvenience. Appreciation could be toys, gift certificate, books, movie coupons etc. and finally incentive could take the form of a draw, lottery or community service credit. CGP & MICYRN, Best Practices for Health Research Involving Children and Adolescents, *op. cit.,* p. 114.
[197] Since an increasing proportion of clinical trials are conducted in developing countries, the prohibition of (hidden) remuneration is particularly important for the protection of participants, *i.e*. with socially and financially disadvantaged populations who hope either for health care or for payment when they take part in a clinical trial. Regulation 536/2014; A Altavilla A., "Ethical standards for clinical trials conducted in third countries: The new strategy of the European Medicines Agency", *European Journal of Health Law*, Vol. 18, 2011, pp. 65-75.
[198] Directive 2001/20/EC, Article 4.
[199] Regulation 536/2014, Article 28.

107. Yet the EU Ethical Recommendations give thoroughly detailed guidelines on how to minimise pain, distress and fear in children, taking into account age and condition-appropriate validated scales. Furthermore, the document underlines the requirement to limit investigations/interventions to the minimum necessary for obtaining valid data (*e.g.,* using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling). Surprisingly, the new EU Regulation does not mention any of these recommendations or even the fact that children deserve specific attention and care to prevent physical and emotional pain and distress.

108. Furthermore, whereas the EU Ethical Recommendations expressly recommend to monitor the level of risk especially for paediatric populations[200] and to use a Data and Safety Monitoring Board (DSMB), the new EU Regulation only requires investigators to monitor three elements[201], including risks but only indirectly[202]. Using a DSMB for paediatric research is not mentioned. However, it would be useful to expressly address monitoring of risks, instead of leaving it up to the sponsor to decide the extent and nature of that. It would also be useful to mention that monitoring of risks should be specific to vulnerable groups, including children. The constant update of risk/benefit evaluation, in light of scientific developments during research, should be particularly important for the paediatric population, particularly if we take into account the fact that children are constantly developing themselves.

109. Finally, regarding control groups and placebos, although Directive 2001/20/EC does not contain specific requirements, the EU Ethical Recommendations give precise guidelines on the use of placebos and paediatric control groups[203]. Placebo is not acceptable when it implies that an effective and available treatment be withheld, especially for life-threatening conditions. There might be some occasions where its use is permissible but must be discussed, and then harm and exposure to harm should be avoided or minimised as much as possible, and 'rescue treatments and escape procedures' organised. However, none of these recommendations were included or mentioned in the new Regulation, not even in a general manner, despite the fact that various institutions, like the EMA[204], and guidelines, such as the WHO-CIOMS guidelines[205] or the Declaration of Helsinki[206] require as much[207].

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[200] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §9.

[201] Monitoring of the objective and methodology, monitoring of low-intervention trials, and monitoring of the degree of deviation from normal clinical practice. Regulation 536/2014, Article 48.

[202] The monitoring of the "objective and methodology" does not necessarily include the monitoring of the risks. As for the other elements, one of them only concerns the monitoring of low-intervention trials, and only the last element could lead to monitoring the risks: "degree of deviation of the intervention from normal clinical practice". *Ibid*., Article 48.

[203] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §9.2.1.

[204] The EMA warned against the danger to justify the use of placebos when the standard treatment is not available in the country where the trial is conducted. EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities, EMA/121340/2011, London, 2012, §4.6, p. 26-27.

[205] By principle, the use of placebo is forbidden, and only acceptable by exception: "- when there is no established effective intervention; - when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; - when use of an established effective intervention as comparator would not

## 6.3 PROVISIONS FOR TRIALS CARRIED OUT OUTSIDE THE EU: INADEQUATE IMPLEMENTATION FOR PAEDIATRICS

110. The new Regulation, which confirms existing rules adopted at the international[208] and European[209] level, introduces an equivalence criterion and specifies that clinical trials conducted outside the EU shall be conducted in accordance with principles equivalent to those in the Regulation, with regard to the rights and safety of a subject and the reliability and robustness of data[210]. As with any type of clinical trial, paediatric trials performed in non-EU countries should be conducted in accordance to the laws and regulations of the country of conduct, most importantly, in accordance to all ethical standards and good clinical practice applicable in the European Union, regardless of any goal for obtaining a Marketing Authorization[211].

111. Nevertheless, as demonstrated, many aspects especially related to ethical and methodological standards for paediatric research are not clear and harmonised in Europe. Hence, the criterion of equivalence could be interpreted in various and broad ways leading to an increasing shift of paediatric trials outside Europe, especially in low-income and emerging countries that, as many reports show, are particularly attractive for sponsors[212].

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yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects". 2002 CIOMS Guidelines, Guideline 11.

[206] The Declaration of Helsinki only allows the use of placebo when there is no proven intervention available, when it is indispensable to assess the safety and efficacy of the trial, or when the use of placebo does not expose the participant "to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention". WMA, Declaration of Helsinki, §33.

[207] Regulation 536/2014, Recital 80.

[208] 2002 CIOMS Guidelines, Guideline 3.

[209] Directive 2001/83/EC, as amended by Directive 2004/27/EC, established that clinical trials performed in third countries (non-EU countries) and submitted in a Marketing Authorisation application in the EU should be conducted in accordance with the principles of Good Clinical Practice and the ethical requirements equivalent to the provisions of Clinical Trials Directive and should comply with Good Manufacturing Practices of EU countries. In this sense, the EMA Reflexion Paper, released in 2012, proposed that EU competent authorities should refuse to consider data obtained that is not in accordance with ethical standards. EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit*.

[210] Regulation 536/2014, Article 25.5.

[211] Recommendations of the *Ad hoc* group, Ethical considerations for clinical trials performed in children, *op. cit*., §23.

[212] Low-income and emerging countries are particularly attractive for sponsors because less stringent regulation and/or weak enforcement can result in a faster approval of protocols and recruitment of subjects, for which participation in a trial may be the only option for access to medication and treatments. For more see: Koski G. and Nightingale S. L., "Research involving human subjects in developing countries", *NEJM, V*ol. 345, 2001, pp. 136-138; Hawkins J.S. and Emanuel E.J., *Exploitation and Developing Countries. The Ethics of Clinical Research,* Princeton, NJ: Princeton University Press, 2008; I. Schipper and F. Weyzig, "Ethics for drug testing in low and middle income countries, considerations for European market authorisation", *SOMO*, 2008, p. 77 .

# 7 Conclusion

112. Regulating paediatric research in the European Union and implementing the Regulation 536/2014 represent a particularly difficult challenge that requires clarity, transparency and legal certainty. As underlined, many notions actually need to be clarified because current discrepancies will lead to uncertainties in the assessment of paediatric protocols, especially in multicentre trials and trials conducted outside of the EU. Particular clarity is needed for the concepts of minimal risk and low-intervention trials, but also for issues concerning the role and paediatric expertise of ECs and their interaction with the Paediatric Committee (PDCO), as well as the conditions for processing paediatric data (especially in the case of secondary use of data in children) and compliance with other internationally recognized ethical standards.

113. Furthermore, current uncertainties and disparities in the EU Regulation are not tempered by any reference to international ethical guidelines that could provide a basis for greater harmonisation. It is unclear as to what is the current status of the EU Ethical Recommendations for paediatric research since they were not repealed, but might still be obsolete because of their strong link to the provisions of Directive 2001/20/EC. All the relevant guidelines and recommendations are expected to be revised and updated so as to be in line with the changes and requirements of the Clinical Trials Regulation, but since ethical aspects are not adequately addressed in the Regulation and are instead left to national provisions, clarifications of those issues are necessary in order to ensure equal treatment of children across Europe. The Oviedo Convention and its Additional Protocol on Biomedical Research are not mentioned once in the whole text of the Regulation[213] and the legal status of the Declaration of Helsinki and the ICH guidelines is vague[214]. The revision process of paediatric ICH guidelines currently continues and an addendum will be developed including, among others, an enhancement of the ethical considerations in paediatric studies within a global context[215].

114. In the light of this analysis, we wonder if the new Regulation represents a step forward for paediatric research. Since further clarifications are needed, the implementation

[213] The Oviedo Convention has been ratified by 29 countries to this date, Website of the Treaty Office from the Council of Europe, http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=23/02/2015&CL=ENG. The Additional Protocol to the Oviedo Convention on Biomedical Research has been ratified by 9 countries to this date, Website of the Treaty Office from the Council of Europe, http://conventions.coe.int/Treaty/Com mun/ChercheSig.asp?NT=195&CM=8&DF=23/02/2015&CL=ENG [15 June 2018].

[214] Their status is vague whereas their clarification was one of the claims in the responses to the public consultations as well as in literature on the proposal for the Regulation released by the European Commission. European Commission, Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC. Summary of the responses to the public consultation paper*, op. cit*., p. 15.

[215] ICH Steering Committee, Final Concept Paper E11(R1): Clinical Investigation of Medicinal Products in the Pediatric Population, 2014.

process of the new Regulation, carried out under supervision of the European Commission, will be a crucial step. All main stakeholders engaged in paediatric trials must play a major role in this process with the aim to facilitate and foster ethically sound paediatric research.

# Chapter 3: Integrating Advance Research Directives into the European Legal Framework

### ORIGINAL PUBLICATION

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### ABSTRACT

The possibility of using advance directives to prospectively consent to research participation in the event of dementia remains largely unexplored in Europe. Moreover, the legal status of advance directives for research is unclear in the European regulations governing biomedical research. The article explores the place that advance research directives have in the current European legal framework, and considers the possibility of integrating them more explicitly into the existing regulations. Special focus is placed on issues regarding informed consent, the role of proxies, and the level of acceptable risks and burdens.

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# 1 Introduction

115. Over the past decade, significant efforts have been made in Europe to promote patients' self-determination. An important step in this direction was the explicit support given by the Council of Europe and several European countries to the use of advance directives to specify healthcare preferences in case of future incapacity[216]. In contrast, the possibility of using advance directives to prospectively consent to research participation remains largely unexplored in Europe. Moreover, legal instruments in the area are virtually silent. However, despite the current regulatory vacuum, the use of advance research directives (ARDs) is gradually drawing interest among scholars[217]. In addition, non-governmental organisations promoting the care of patients suffering from dementia have, in recent years, given their explicit support to the use of ARDs, provided that certain safeguards are in place[218].

116. ARDs can serve as a useful tool for patients in the early stage of dementia who are still capable of consenting to research participation. These documents allow them to express their preferences about their participation in future or ongoing clinical trials should they lose decision-making capacity. Without such directives, family members are placed in the difficult role of having to make a decision based on the presumed wishes of the patient or on the assessment of his or her best interests, which are not obvious when no direct benefit is expected. Several studies show that proxies cannot reliably guess patients' preferences: they are either too reluctant to authorise their enrolment in clinical trials, or consent to studies that do not really correspond to the preferences and values of the persons they represent[219].

117. The current situation is challenging since there is a crucial need to conduct research involving dementia patients to better understand the conditions that cause dementia (in particular Alzheimer's disease), and to develop more effective therapeutic or preventive measures. Dementia is at present one of the greatest global health challenges as the number of people suffering from this condition worldwide is estimated at 44 million and is set to almost

[216] Andorno R., Biller-Andorno N. & Brauer S., "Advance Health Care Directives. Towards a Coordinated European Policy?", *European Journal of Health Law*, Vol. 16, n°3, 2009, pp. 207-227; Negri S. (ed.), Self-Determination, Dignity, and End-of-Life Care. Regulating Advance Directives in National and International Law, Leiden: Brill Academic Publishers, 2012; Goffin T., "Advance Directives as an Instrument in an Ageing Europe", *European Journal of Health Law*, Vol. 19, n°2, 2012, pp. 121-140; Veshi D. & Neitzke G., "Advance Directives in Some Western European Countries: A Legal and Ethical Comparison between Spain, France, England, and Germany", *European Journal of Health Law*, Vol. 22, n°4, 2015, pp. 321-345.

[217] Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *European Journal of Health Law,* Vol. 13, n°3, 2006, pp. 235-261; Helmchen H., "Ethics of clinical research with mentally ill persons", *European Archives of Psychiatry and Clinical Neuroscience,* Vol. 262, 2012, pp. 441-452; Jongsma K. and van de Vathorst S., "Advance directives in dementia research: The opinions and arguments of clinical researchers – an empirical study", *Research Ethics,* 2014, published online 8 August 2014: doi: 10.1177/1747016114523422.

[218] Alzheimer Europe, Position paper on the use of advance directives, 2009, §31.

[219] Stocking C.B. *et al*., "Speaking of research advance directives: planning for future research participation'", *Neurology*, Vol. 66, n°9, 2006, pp. 1361-1366.

double by 2030[220]. Rates increase significantly with age, as dementia affects 5 per cent of the population older than 65 and 25-50 per cent of those older than 85[221].

118. The moral advantage of ARDs, if compared to the current practice of proxy consent, is that participants themselves, while still competent, provide their consent to research participation. This possibility can be regarded as a mechanism of empowerment[222]. Like advance directives for healthcare, advance directives for research can be justified on the grounds that they offer a tool for prospective self-determination to those individuals who anticipate incapacity: if autonomous choices regarding one's own healthcare can be applied beyond one's competence, why should it be different for participation in clinical trials? From a more practical perspective, ARDs have the advantage of helping to solve the problem posed by the lack of information about the willingness of dementia patients to be enrolled in clinical trials. ARDs can facilitate the task of proxies in making decisions, while ensuring a greater respect for the personal preferences and values of participants[223]. These documents also have the potential to increase the participation of dementia patients in clinical trials and consequently, contribute to the development of specific treatments for this group of people.

119. It should be noted that it is beyond the scope of this article to address the philosophical objection, sometimes levelled against advance directives, that there is no continuity of identity before and after the onset of dementia[224]. We assume, as legal norms do, that people affected by dementia should still be regarded as the same persons they were before the onset of the cognitive impairment, no matter how serious their loss of memory or cognitive capacities. This is to say that advance directives should not be automatically disqualified as legally invalid on the ground that they were made by a different person to the one who is now suffering from dementia.

120. The article begins by exploring the place that ARDs have in the European legal framework governing biomedical research. The discussion then proceeds to consider the possibility of integrating them more explicitly into the existing European norms. The central questions addressed in the article are: What is the legal status of ARDs in Europe? What possibilities does the European legal framework offer for using ARDs? In addressing these questions, special focus is placed on issues regarding informed consent, the role of proxies, and the level of acceptable risks and burdens.

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[220] Alzheimer's Disease International, World Alzheimer Report 2014, Dementia and Risk Reduction: An Analysis of Protective and Modifiable Factors, www.alz.co.uk/research/world-report-2014 [14 July 2015].

[221] Yudofsky S. and Hales R. (eds.), The American Psychiatric Publishing Textbook of Neuropsychiatry and Behavioral Neurosciences, Washington, DC, Psychiatric Publishing, 2008, p. 452.

[222] Pierce R., "A changing landscape for advance directives in dementia research", *Social Sciences and Medicine,* Vol. 70, 2010, p. 624.

[223] Abdoler E. and Wendler D., "Using data to improve surrogate consent for clinical research with incapacitated adults", *Journal of Empirical Research on Human Research Ethics*, Vol. 7, n°2, 2012, pp. 37-50.

[224] See for instance Dresser R., "Dworkin on Dementia: Elegant Theory, Questionable Policy", *Hastings Center Report,* Vol. 25, n°6, 1995, pp. 32-38.

# 2 European Legal Framework for ARDs

121. The concept of advance directives for research has been discussed in the US since the end of the 1980s[225]. Some American scholars have emphasized the potential utility of these documents to facilitate research involving people with mental disorders[226]. As a result of these discussions, several proposals for the regulation of ARDs have been made in the US[227]. In Canada, the regulations governing research involving human subjects make explicit mention of advance directives for research[228]. In contrast, no proposals for guidelines or legislation in this area have been brought forward in Europe, and the European literature on ARDs is almost non-existent. The legal frameworks on biomedical research adopted by European bodies, namely the Council of Europe and the European Union, are ambiguous in this respect[229]. Similarly, European domestic laws are virtually silent about the possibility of consenting to research participation in the event of future mental incapacity.

122. It is important to stress that research involving persons unable to consent is not per se prohibited in Europe, but subject to additional safeguards, such as the requirement that the research poses no more than minimal risk and minimal burden to participants in circumstances where no direct benefit to them is expected, that the legally authorised representatives give their consent, and that the research protocol is approved by an independent ethics committee. The legal basis for such safeguards can be found in the 1997 European Convention on Human Rights and Biomedicine[230], and in the 2014 EU Regulation on Clinical Trials[231], which will replace the currently applicable 2001 EU Clinical Trials Directive[232] in 2016.

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[225] Levine R., Ethics and Regulation of Clinical Research, Baltimore, MD: Urban and Schwarzenberg, 1986, pp. 270-274; National Institutes of Health, Consent Process in Research Involving Impaired Human Subjects, 1987, Clinical Center Policy and Communications Bulletin, n87-4; National Bioethics Advisory Commission (NBAC), Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Report and Recommendations, vol. I, Washington, DC: US Government Printing Office, 1998, chapter 3.

[226] Moorehouse A. and Weisstub D., "Advance directives for research: ethical problems and responses", International Journal of Law and Psychiatry, Vol. 19, n°2, 1996, p.107; Backlar P., "Anticipatory planning for research participants with psychotic disorders like Schizophrenia", Psychology, Public Policy, and Law, Vol. 4, n°3, 1998, pp. 829-853.

[227] Pierce R., "A changing landscape for advance directives in dementia research", *op. cit*., p. 624.

[228] Canadian Institutes of Health Research, National Science and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, December 2014, Articles 3.10 and 3.11, www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf [14 July 2015].

[229] Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *op. cit*.

[230] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo, 4. IV. 1997, ETS 164 (hereinafter "Oviedo Convention"), Article 17.

[231] Council Regulation 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, 2014 OJ (L 158) 1 (hereinafter "Regulation 536/2014"), Article 31.

[232] Council Directive 2001/20 on the Approximation of the Law, 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, OJ L 121/34 (2001) (hereinafter "Directive 2001/20/EC").

## 2.1. COUNCIL OF EUROPE

123. The Council of Europe's Convention on Human Rights and Biomedicine 1997 (hereinafter Biomedicine Convention) includes only one provision relating to advance directives, which stipulates that "[t]he previously expressed wishes relating to a medical intervention by a patient who is not, at the time of the intervention, in a state to express his or her wishes shall be taken into account"[233]. It is important to point out that this provision was exclusively developed in relation to advance directives for healthcare. The Convention's drafters did not have in mind the use of these documents for research purposes. This is clear not only from the Explanatory Report to the Convention, which in its commentary on Article 9 refers to the "patient" and the "practitioner"[234], but also from the fact that Section V of the Convention, which specifically deals with biomedical research, does not mention the possibility of making advance directives in this context. Interestingly, the Convention does not say anything about positive advance directives for research. But it can be argued that refusals to participate in research, made either before or after the onset of the mental incapacity, would be binding. This can be inferred from Article 17.1(v), which enumerates, among the conditions for conducting research involving persons unable to consent, that "the person concerned does not object"[235].

124. In comparison to the Biomedicine Convention, the Convention's Additional Protocol on Biomedical Research 2005 takes a step towards the recognition of ARDs. Article 15, 1.iv indirectly refers to ARDs stipulating that the consent of the legal representative must be given "taking into account the person's previously expressed wishes or objections". This means that although prior wishes -including written wishes and objections- are regarded by the Protocol as relevant, they are not accepted as a stand-alone requirement. Instead, a kind of double safeguard mechanism for the protection of incapacitated research subjects is suggested. Therefore, the previously expressed wishes have to be assessed by the proxy decision-maker, who can eventually overrule them (as they need only to be "taken into account", and not strictly followed). Indeed, these instructions seem to be considered as an element that might complete the consent given by the legal representative of the incapable person, as opposed to an independent basis for the decision, and not as instructions documents that can operate independently. When such documents exist, the decision of the legal representative cannot be exclusively based on his or her own personal opinion, but should be *guided* by the preferences expressed by the individual before the onset of the incapacity.

[233] Oviedo Convention, Article 9.

[234] Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research, Strasbourg, 25 I. 2005, ETS 195 [hereinafter Explanatory Report to the Additional Protocol], §62.

[235] Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *op. cit*., p. 243.

## 2.2. EUROPEAN UNION

125. At the level of the European Union, the 2001 Clinical Trials Directive refers only indirectly to ARDs. Article 5 reads: "In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if…" [the list of additional requirements follows]. Since advance consent to participation in research is only mentioned in passing as a negative condition for the application of the general rules for conducting research involving incapacitated persons, it is hard to draw from this norm any positive conclusion about the general conditions for making ARDs and about their efficacy. Therefore, it seems excessive to deduce from this provision that "the effect of a valid previously given informed consent or refusal is that the potential research participant is legally treated as a competent research subject and therefore, the additional safeguards listed in the latter part of Article 5 (including consent given by a legal representative) need not be applied"[236].

126. In April 2014, a new Regulation on Clinical Trials was adopted by the EU to replace the 2001 Clinical Trials Directive. The Regulation, which will become directly applicable to Member States no earlier than on May 2016, uses almost the same wording as the 2001 Directive to refer -indirectly- to ARDs in Article 31. The only novelty of the new Regulation in this regard concerns research in emergency situations and the need for the researcher to ensure that the potential participant has not previously expressed objections to participate in the clinical trial (Article 35, d). However, advance directives as envisaged by the Regulation, expressing a wish not to be involved in specific emergency trials, seems very unlikely. Therefore, it is difficult to draw from this provision any conclusions that could be applicable to advance consent to clinical trials in the event of mental incapacity.

127. In short, the current European legal framework neither explicitly mentions the possibility of using ARDs nor forbids them. Concerning domestic regulations, the Swiss Law on Research Involving Human Beings 2011 is, to our knowledge, the only legal instrument in Europe that explicitly refers to the possibility of using advance directives to prospectively consent to medical research[237]. The UK Mental Capacity Act 2005, covering England and Wales, mentions

[236] Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *op. cit*., p. 246.

[237] Article 24, §1 stipulates that "[r]esearch projects involving persons unable to consent which offers prospects of direct benefit to participants can be conducted if the following conditions are met: 1. the subjects have given their consent when they were still competent and the consent is evidenced by a document; 2. in the absence of a document evidencing the consent, the legal representative, a trustworthy person or their relatives gave a written informed consent; 3. the subjects do not express in an identifiable manner, verbally or by a particular behavior, their refusal to participate in the research project". Article 24, §2 provides that in the case of research not offering prospect of direct benefit to participants, two additional conditions must be met: "the risks and burden associated with the project are minimal" and "the project is

ARDs only as a means for objection to involvement in research, as it stipulates that research on incapacitated persons cannot be performed if, among other things, it is contrary to "an advance decision of his which has effect"[238]. The following section will discuss the conditions for integrating advance research directives into the European legal framework governing biomedical research.

# 3 Challenges for Integrating ARDs into the European Legal Framework

128. On the one hand, the need for some common European requirements for the validity of consent to research participation (including dementia research) is undeniable. Although only 24 per cent of all clinical trials applied for in the EU are conducted in more than one Member State, they involve approximately 67 per cent of all subjects enrolled in clinical trials. This is to say that in Europe the majority of trials involving a large number of research subjects (40 or more) are multinational[239]. On the other hand, when aiming at a regional consensus on the use of ARDs it should be acknowledged that these documents raise a variety of ethical and legal questions, especially regarding informed consent, the role of proxies, and the level of acceptable risks and burdens. These three topics are discussed in this section.

## 3.1 INFORMED CONSENT

129. In general, participation in clinical trials is subject to stringent conditions and additional safeguards that do not apply to healthcare. These specific requirements are understandable because clinical trials do not generally aim to improve the health of research participants, but are primarily conducted to gain scientific knowledge that can potentially benefit future patients. In giving their consent, it is important that potential research subjects understand the *altruistic* nature of their involvement. Obviously, this must also be understood by those who give consent in the form of an ARD. In this regard, it has been argued that, in such

expected to offer long-term benefit to people suffering from the same disease, or having a comparable health condition" (Article 24, §2).

[238] Mental Capacity Act 2005, s 33(2).

[239] European Commission, Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicine Products for Human Use, and Rrepealing Directive 2001/20/EC, Brussels, 17 July 2012, p. 2, http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf, [14 July 2015].

a context, the individual must, at least, be able to understand the distinction between being a "patient" and a "research subject"[240].

130. Rebecca Dresser has pointed out how demanding it is to ask people at risk of dementia to imagine how it would be to participate in research after the onset of cognitive impairment. She even notes that "it may be a rare person who can genuinely achieve this level of understanding"[241]. In addition, although therapeutic misconception is not the prerogative of only dementia patients, Dresser reports empirical results demonstrating how frequently potential dementia research participants misunderstand the proposed study, notably the fact that it is not another treatment option, but principally aims to produce generalizable knowledge[242]. This "therapeutic misconception" can be even greater if the same advance directives combine treatment and research purposes[243]. This kind of misunderstanding is more likely to happen if the research subjects are already mildly affected by dementia. The assessment of the decision-making capacity of such individuals poses a significant ethical and legal challenge[244], and should be exercised with caution, in order to prevent any misuse or deception of potential research subjects.

131. It is generally accepted that participants in medical research "must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study (…)"[245]. There are in principle no reasons for departing from these requirements in the case of prospective consent to dementia research. This is certainly the case for ongoing clinical trials, providing that there are no changes in the protocol. However, it should be noted that it may be more difficult when dealing with future clinical trials, the design of which are not finalized. In any case, it is crucial that ARDs are very specific about the procedures to which participants will be exposed (for instance, taking blood samples, monitoring blood pressure, testing new drugs, etc.), as well as about the risks and burdens associated with these procedures[246].

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[240] Backlar P., "Anticipatory planning for research participants with psychotic disorders like Schizophrenia", op. cit., p. 842; Alzheimer Europe, "The Ethics of Dementia Research", 2011, chapter 4, www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/Ethics-of-dementia-research [14 July 2015].

[241] Dresser R., "Advance directives in dementia research. Promoting Autonomy and Protecting Subjects", IRB. Ethics & Human Research, Vol. 23, n°1, 2001, p. 4.

[242] *Ibid*.

[243] Pierce R., "A changing landscape for advance directives in dementia research", *op. cit*., p. 624.

[244] Trachsel M., Hermann H., and Biller-Andorno N., "Cognitive Fluctuations as a Challenge for the Assessment of Decision-Making Capacity in Patients with Dementia", American Journal of Alzheimer's Disease and Other Dementias, Vol. 30, n°4, 2015, pp. 360-363.

[245] World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, 2013 (hereinafter "Declaration of Helsinki"), §26.

[246] Regarding the importance of the specificity of the consent, see Gevers S., "Dementia and the Law", European Journal of Health Law, Vol. 13, n°3, 2006, p. 217.

132. Even though ARDs are defendable as an initial authorisation for research participation, and are a valuable means to promote patients' autonomous decisions, other safeguards remain necessary to ensure the well-being of cognitively impaired participants. It has been pointed out that in practice, at any sign of distress, dissent or discomfort, incompetent participants are excluded from clinical trials[247]. Nevertheless, the protection of incapacitated subjects cannot merely depend on the good will of researchers but should be ensured by legal mechanisms. It is important to guarantee that the well-being of participants is constantly monitored from both the researchers' side and also from the participant's side (*i.e.* the proxy). Physicians, researchers and ethics committees, due to the regular assessment of any changes in the protocol and in the balance benefit/risk, have to make sure that the participation of incapacitated subjects is in conformity with the prior consent and with the legal requirements. Such consent should therefore not be understood as a simple authorisation at the start of the study, but as a continuous process throughout the trial[248]. This is why the involvement of a legal representative is crucial in terms of monitoring and accountability. The proxy, who is someone close to the participant and has no personal interest in the research, is in a good position to assess the burdens that may result from research participation, and evaluate the subject's willingness to continue participation in the trial.

133. Concerning the possibility of withdrawal from research trials by participants after the onset of their incapacity, it has been argued that ARDs can be revoked at any time, even when the individual has already lost his or her decision-making capacity[249]. This means that "the threshold for the capacity to revoke or refuse to participate should be lower than the capacity to consent"[250]. Similarly, Alzheimer Europe lists among the conditions for the implementation of ARDs that the person "does not show any sign of unwillingness to participate at the start of the research, *e.g.* refusing to take medication when offered, obvious distress when interviewed, etc., and that the participant does not display signs of unwillingness to continue participating and/or experience distress as a result of the research"[251]. These conditions are in conformity with the European Biomedicine Convention, which requires that the incompetent individual "does not object"[252]. Similarly, the 2014 EU Regulation on Clinical Trials expressly gives incapacitated persons the right to withdraw from trials, independently from the opinion of their legal representatives[253]. However, this right to withdraw is rather demanding in the Regulation, as the

[247] Jongsma K. and van de Vathorst S., "Dementia research and advance consent: it is not about critical interest", Journal of Medical Ethics, 2014, published online 19 September 2014; doi:10.1136/medethics-2014-102445.
[248] See Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 25.I. 2005 (hereinafter "Additional Protocol"), Article 24.2.
[249] Backlar P., "Anticipatory planning for research participants with psychotic disorders like Schizophrenia", op. cit., p. 842.
[250] Moorehouse A. and Weisstub D., "Advance directives for research: ethical problems and responses", op. cit., p. 133.
[251] Alzheimer Europe, Position paper on the use of advance directives, op. cit., §32.
[252] Oviedo Convention Article 17.1.v; Additional Protocol, Article 15 1.v.
[253] Regulation 536/2014, Article 31.

patient has to express an "explicit wish" and must be "capable of forming an opinion and assessing the information"[254].

134. The right to withdraw from research can be compared to the way in which advance treatment refusals operate. Incapacitated patients who ask for life-saving treatments, which they have refused in an advance directive, would probably be treated, even if they have already lost their decision-making capacity[255]. This is because priority is given to the least harmful alternative, which is non-refusal of life-saving treatments, and in the case of ARDs, non-participation in research, even when the risks and burdens are very low. In other words, the initial consent given by means of ARDs is not sufficient to continue research procedures when participants show clear signs of unwillingness to continue participating in the trial.

## 3.2 THE ROLE OF PROXIES

135. Legal instruments in Europe state explicitly that the consent of the legally authorised representatives or proxies is absolutely required to enrol incapacitated adults in research trials[256]. However, from a theoretical perspective one may wonder whether such consent is necessary when the patient had consented in advance to research participation at a time when he or she was still competent. In this regard, Pierce suggests that ARDs can operate without the involvement of a proxy[257]. She argues that there are individuals who do not wish to defer the decisions concerning their participation in research to a surrogate decision-maker[258]. Therefore, she claims that, for reasons of equality, ARDs should be available to all competent individuals who wish to prospectively consent to research, regardless of whether they appoint a proxy[259].

136. This proposal is problematic, at least for practical reasons. It is difficult to imagine how a cognitively impaired individual could participate in clinical trials without the assistance of a trusted, independent caretaker. It must be noted that the proxy does not necessarily have to be a family member but could be any trusted person, including the treating physician, insofar he or she does not have any direct interest in the clinical trial. Proxies are in a better position than researchers to detect any discomfort or adverse reaction that the demented person may experience as result of his or her participation in the trial. Furthermore, proxies can be consulted by researchers about the interpretation of the directives and about any possible change in the original protocol that may imply additional risks or burdens for participants.

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[254] Regulation 536/2014, Article 31.1.c.

[255] Lemmens T., "End-of-life decisions and demented patients. What to do if patient's current and past wishes are in conflict with each other?", European Journal of Health Law, Vol. 19, n°2, 2012, pp. 177-186.

[256] Oviedo Convention, Articles 6.3 and 17.iv; Regulation 536/2014, Article 31.1.a.

[257] Pierce R., "A changing landscape for advance directives in dementia research", *op. cit*., p. 627.

[258] *Ibid*., p. 627.

[259] *Ibid*.

137. A related question is whether the proxy should be allowed to override the advance consent of the participant. As Pierce has pointed out, there could be situations in which this would be acceptable, for instance, a change in protocol that results in an alteration in the research experience, a change in patient behaviour with assessment by an independent behavioural psychologist, or a change in risk exposure, either as a result of a change in protocol or in the participant's health condition[260]. Certainly, those changes have to be relevant enough to justify overriding the consent of the participant. This can be the case, for instance, if the changes in the protocol or in the health condition of participants create unanticipated burdens and risks for them, or if the subjects show clear signs of distress, fear or pain as a result of their participation in the trial. These situations show how important the involvement of an independent, trusted person to ensure the well-being of the incapacitated subject.

## 3.3. LEVEL OF ACCEPTABLE RISKS AND BURDENS

138. It has been pointed out that "perhaps one of the most complex issues in the use of ARDs is whether it should be acceptable to prospectively consent to the full spectrum of risk, including risky research"[261]. Some scholars claim that it is permissible to consent to more than minimal risk and minimal burden on the grounds that the advance directive reflects the autonomous decision of the individual at a time when he or she was still competent[262]. But it can also be legitimately argued that ARDs are subject to the general limit of minimal risk and minimal burden that applies to all research studies involving incapacitated subjects. The reason for this is that the participant is especially vulnerable when the research is conducted and therefore deserves special protection at the time of the trial, it being irrelevant whether he or she was competent when the advance directive was made.

139. The current European legal framework on biomedical research clearly follows this second position: incapacitated subjects can be enrolled in research that does not offer the prospect of direct benefit only when it poses minimal risk and minimal burden[263]. There is no exception to this rule based on the circumstance that the individual had previously made an advance directive and accepted levels of risk and burden higher than minimal. In the European regulations, the "minimal risk and minimal burden" limit seems to have the status of an *ordre public* rule, which means that it cannot be the subject of renunciation. In this respect, it must be mentioned that the Biomedicine Convention prescribes that some of the protective provisions it

[260] Pierce R., "A changing landscape for advance directives in dementia research", *op. cit*., p. 627.
[261] *Ibid*.
[262] See Buller T., "Advance consent, critical interests and dementia research", *Journal of Medical Ethics*, 2014, published online 12 August 2014, doi: 10.1136/medethics-2014-102024); Pierce R., "A changing landscape for advance directives in dementia research", *op. cit*., p. 628.
[263] Oviedo Convention, Article 17; Additional Protocol, Article 15; Regulation 536/2014, Article 31.

contains cannot be set aside by the states' domestic laws[264]. Interestingly, Article 17, which sets the "minimal risk and minimal burden" limit, is explicitly mentioned as one of those non-negotiable provisions[265].

140. In the past, several American experts have favoured the first position mentioned above. They have argued that an advance consent would be an acceptable basis for allowing the incompetent individual to be involved in research with higher risk than the one permitted for other incompetent subjects[266]. More recently, Buller claims that advance directives for research and for treatment are similar and therefore, the level of acceptable risks should be similar as well[267]. Based on the comparison with advance refusals of life-sustaining treatments, he argues that a person has the right to expose herself to high risks, including the risk of death. Therefore a person should equally be able to decide in advance to expose oneself to risky research, and not be limited to research involving minimal risk.

141. However, leaving aside the current legal obstacles to the use of ARDs for research involving risks higher than minimal, there are reasons to remain sceptical about this possibility. The analogy with advance directives for healthcare is not satisfactory. There is a crucial difference between prospectively consenting to treatment and to participation in research. Preferences regarding healthcare, including the refusal of treatments that the patient considers to be too burdensome or useless, are directly related to the well-being of that same patient who made the advance directive. On the contrary, research studies are normally not designed to benefit participants themselves, but to gain scientific knowledge that may eventually help future patients. The altruistic nature of research participation explains why research involving human beings is subject to conditions that do not apply to treatment, not even to treatment refusals. These additional safeguards concerning research need to be taken particularly seriously when participants are cognitively impaired at the time the research is carried out.

142. Moreover, from a practical point of view, there are reasons to believe that most individuals consenting to research participation by means of advance directives would prefer not to be exposed to risks higher than minimal. In this regard, it is interesting to note an empirical study in which patients were asked to complete a research advance directive and to express their preferences regarding participation in clinical trials[268]. Only 11 per cent of patients accepted to complete a research advance directive. The great majority of them (76 per cent) were not willing to be exposed to more than minimal risk, while 49 per cent were also willing to take part in research without direct benefit, but which only posed minimal risk. Only 9 per cent

[264] Oviedo Convention, Article 26.
[265] Oviedo Convention, Article 26.2.
[266] American College of Physicians (ACP), 'Cognitively Impaired Subjects. Position Paper', *Annals of Internal Medicine,* Vol. 111, n°10, 1989, p. 843; National Bioethics Advisory Commission (NBAC), *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*, *Report and Recommendations, op. cit.*, chapter 3.
[267] Buller T., "Advance consent, critical interests and dementia research", *op. cit*., p. 6.
[268] Muthappan P., Foster H., and Wendler D., ''Research advance directives: protection or obstacle?", American Journal of Psychiatry, Vol. 162, n°12, 2005, pp. 2389-2391.

of those who were in favour of making an ARD (that is, 1 per cent of the total of patients who were initially invited to complete an ARD) would accept to participate in research that would not help them and posed greater than minimal risk.

# 4 Conclusion

143. This article has sought to draw attention to the fact that the European legal framework for biomedical research, as well as most European domestic laws, are virtually silent about the use of advance directives for research purposes. At the same time, it has shown that these same norms do not explicitly exclude the possibility of prospective consent to research participation. Considering that ARDs are perfectly in line with the commitment of European institutions to support patients' self-determination, we think that these tools could be integrated into the existing European norms relating to biomedical research. However, essential questions remain to be explored in greater depth. These include questions around how detailed the trial information which is given to potential participants must be, the role of the proxy before and during the trial, and the level of acceptable risk and burden which should be permitted in the context of ARDs.

144. As mentioned above, the use of ARDs can be justified in moral terms on the grounds that they contribute to patients' self-determination. Besides, ARDs could help to increase the amount of clinical trials with dementia patients and facilitate the development of specific drugs for this population. On the one hand, ARDs could do more justice to the patient's prior wishes than proxy consent does. On the other hand, it is unlikely that ARDs without the appointment of a proxy can offer a stand-alone solution to the requirement of informed consent. The involvement of a proxy seems indispensable to implement the advance directives in the light of the complete information at the time the research is conducted. In addition, other safeguards are necessary to ensure the well-being of incompetent participants, for example the right to withdraw or to be withdrawn from the trial at any time. Another question concerns the level of risks that can be accepted by means of ARDs. From the legal point of view, current regulations clearly forbid exposing incompetent participants to more than minimal risk and minimal burden, regardless of whether they have consented to them in advance or not. But from an ethical point of view, the question remains open for discussion.

145. In conclusion, it is desirable to clarify the legal status of ARDs and the conditions for their use in Europe. This would not only help to satisfy the wish of potential participants in dementia research, but also benefit future dementia patients by developing more effective therapeutic or preventive measures. This clarification would also facilitate the task of researchers and ethics committees. In this regard, it would be appropriate for the Council of

Europe, for instance, to address the use of ARDs, at least in their Guide for Research Ethics Committees[269]. Similarly, the European Commission could include guidance on ARDs while revising and updating the current guidelines and recommendations on clinical trials in the light of the new Clinical Trials Regulation[270]. In the context of an increasingly ageing population, the incidence of dementia is expected to grow in the coming years. Therefore, the need for research with incapacitated elderly patients will become more and more pressing. In this scenario, ARDs could turn out to be a useful tool to both empower potential research participants and contribute to the development of more effective treatments for dementia.

[269] See Council of Europe's Steering Committee on Bioethics, *Guide for Research Ethics Committee Members,* Strasbourg: Council of Europe, 2012, www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en /guide/Guide_EN.pdf [14 July 2015].

[270] See European Commission, *Clinical Trials. General Information*, http://ec.europa.eu/health/human-use/clinical-trials/information/index_en.htm#ct4 [14 July 2015].

# Chapter 4: Les personnes âgées vulnérables dans les recherches biomédicales: quelles réponses du droit européen?

### ORIGINAL PUBLICATION

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### ABSTRACT

As the main medications consumers, elderly persons are estimated to represent up to 30% of the European population in 2050. Paradoxically there is a considerable lack of information about drug prescription in older persons, which is compromising the quality of treatments, and leaving to physicians the considerable responsibility of improvised prescriptions, which are potentially either dangerous or ineffective. In fact, the geriatric population is either excluded from clinical trials or represented by relatively healthy elderly persons who do not accurately represent real world patients. Despite repeated demonstrations of the need to include frail elderly persons in clinical trials in the medical literature, European law only offers disappointing responses to the problem. The frequent decline in older persons' cognitive capacities makes the task even more difficult (cognitive frailty, early dementia like Alzheimer's disease or psychiatric disorders). Many older persons have reduced decision making capacity without benefiting from legal protection yet. Surprisingly, ethics guidelines as well as European law are not very sensitive to the phases before legal incompetence, and do not consider alternative ways to obtain informed consent as suggested in medical and ethical literature. Although these questions fall under national competencies, the issue is common to Europe and solutions will necessarily have to go beyond state borders. Involving the European legislator is essential in order to at least act as an incentive for a better inclusion of frail elderly persons in biomedical research, and for a better promotion of their autonomy.

# 1 Introduction

146. Les recherches biomédicales permettent d'améliorer les traitements, de réagir aux nouvelles maladies[271], et de s'adapter aux évolutions globales de la société, tel le vieillissement de la population. Car en effet, les personnes âgées sont estimées représenter 30% de la population européenne d'ici 2050[272], alors qu'elles sont les principales consommatrices de médicaments[273]. Par personnes âgées, on entend habituellement les personnes de plus de 65 ans[274], sachant que le critère de l'âge a pu montrer ses limites. Pour le thème des essais cliniques, c'est plutôt la prise en compte de leur vulnérabilité qui va conditionner leur statut juridique. Et pourtant, le droit européen[275] relatif à la recherche biomédicale ne donne pas de définition de la vulnérabilité ni de la personne vulnérable, mais liste seulement les personnes considérées comme vulnérables[276]. De manière générale, une personne est vulnérable lorsqu'elle est en état de faiblesse et qu'elle est exposée à des risques accrus de souffrances[277]. En matière d'essais cliniques, nous classerons la vulnérabilité en deux types principaux : la vulnérabilité physique et mentale et la vulnérabilité décisionnelle[278]. La première désigne une vulnérabilité aux effets secondaires ou indésirables des essais cliniques, une vulnérabilité qui est donc liée à la condition ou à l'état de santé du participant (enfants, femmes enceintes, personnes âgées fragiles, malades…). Le second type de vulnérabilité, la vulnérabilité

[271] Elles permettent de « comprendre les causes, le développement et les effets des maladies et améliorer les interventions préventives, diagnostiques et thérapeutiques ». Association Médicale Mondiale (AMM), Déclaration d'Helsinki - Principes éthiques applicables à la recherche médicale impliquant des êtres humains, adoptée par la 18ème Assemblée générale à Helsinki (Finlande), en juin 1964 et telle qu'amendée lors de l'Assemblée général à Fortaleza (Brésil), en Octobre 2013, § 6.

[272] Site Web d'Eurostat, http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Population_structure_by_major_age_groups,_EU-28,_2014%E2%80%9380_%28%C2%B9%29_%28%25_of_total_population%29_YB15.png [14 août 2015], Figure 6.

[273] Berdeu D. *et al*., « Clinical trials in the elderly : Ethical and methodologic considerations », *La Revue de médecine interne*, Vol. 21, n°7, 2000, p. 616.

[274] Comme par exemple c'est le cas dans certaines lignes directrices internationales spécialisées sur les questions gériatriques ICH, Studies in support of special populations: Geriatrics E7, Conférence internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments à usage humain, 1993, p. 2 ; ou encore comme c'est le cas dans la prise en compte des personnes âgées par les études démographiques de l'Union européenne, Site Web d'Eurostat http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing [13 août 2015].

[275] Nous entendons par droit européen, le droit du Conseil de l'Europe et celui de l'Union européenne ainsi que les principales lignes directrices éthiques applicables en Europe.

[276] Union Européenne, Règlement (UE) n° 536/2014 du Parlement européen et du Conseil du 16 avril 2014 relatif aux essais cliniques de médicaments à usage humain et abrogeant la directive 2001/20/CE, J.O., L 158, 27 mai 2014, Article 10 ; La Convention d'Oviedo du Conseil de l'Europe n'inclut même pas l'expression « personne vulnérable » et se contente de protéger les personnes qui n'ont pas la capacité de consentir. Conseil de l'Europe, Convention pour la protection des Droits de l'Homme et de la dignité de l'être humain à l'égard des applications de la biologie et de la médecine : Convention sur les Droits de l'Homme et la biomédecine, STCE N°164, Oviedo, 4 avril 1997, Article 17.

[277] Sur la définition de la vulnérabilité : Fiechter-Boulvard F., « La notion de vulnérabilité et sa consécration par le droit », *in* Cohey-Cordet F. (dir.), *Vulnérabilité et droit. Le développement de la vulnérabilité et ses enjeux en droit*, Presses Universitaires de Grenoble, Grenoble, 2000, p. 14 ; Paillet É. et Richard P. (dir.), *Effectivité des droits et vulnérabilité de la personne*, Bruylant, Bruxelles, 2014, p. 2 ; Enfin et surtout : Bergouignan C., « Mesurer la vulnérabilité ? », *in* Paillet É. et Richard P. (dir.), *Effectivité des droits de l'homme et vulnérabilité de la personne*, Bruylant, 2014, p. 12.

[278] Gennet É., Andorno R. et Elger B., « Does the new EU Regulation on clinical trials adequately protect vulnerable research participants ? », *Health Policy*, 2015, n°119, 2015, p. 925-931.

décisionnelle, vise le risque d'exploitation, le risque pour les participants de donner leur consentement sous une influence indue. Si cette vulnérabilité décisionnelle peut être d'origine relationnelle[279] et circonstancielle[280], nous nous focaliserons ici sur son origine cognitive : les mineurs, les adultes incapables, mais surtout les personnes âgées atteintes de maladies psychiatriques, troubles cognitifs ou encore démences telles la maladie d'Alzheimer[281]. Il est fréquent que ces deux types de vulnérabilités – physique et décisionnelle – se croisent et donc soient présents chez une seule et même personne, en particulier chez les personnes âgées. Si ces doubles vulnérabilités sont fréquentes, il n'en est pas moins important de les distinguer d'un point de vue méthodologique et argumentaire, car les réponses normatives découlant des différents types de vulnérabilités auront, si ce n'est une issue différente, au moins des justifications différentes.

147. Quels sont les enjeux de la participation des personnes âgées vulnérables aux recherches biomédicales et comment le droit européen y répond-il? Comment prend-t-il en compte l'avis des principaux acteurs intéressés comme les médecins, les industries pharmaceutiques ou tout professionnel de santé impliqué dans l'éthique ? Deux enjeux distincts sont ainsi à analyser : celui de promouvoir la qualité des soins de santé des personnes âgées vulnérables par une meilleure inclusion dans les essais cliniques (2), et celui de protéger et de promouvoir l'autonomie des personnes âgées vulnérables dans le cadre des essais cliniques (3).

# 2 La promotion de la qualité des soins de santé des personnes âgées vulnérables

148. Les patients âgés sont très souvent exclus des essais cliniques alors qu'il y a un important besoin d'information sur les effets des médicaments sur ce type particulier de patients. L'enjeu principal pour promouvoir la santé des personnes âgées vulnérables est donc de mieux les inclure dans les recherches biomédicales (2.1). Toutefois, la réponse du droit européen à ce besoin n'est que partiellement satisfaisante (2.2).

[279] Les relations avec le médecin ou la famille – notamment les enfants -, les traditions religieuses ou encore les relations hiérarchiques comme par exemple les étudiants ou les militaires. Gennet É., Andorno R. et Elger B., « Does the new EU Regulation on clinical trials adequately protect vulnerable research participants ? », *op. cit*., p. 927.

[280] Les classes socio-économiques défavorisées ou encore les personnes privées de liberté comme les détenus ou encore les personnes en institutions d'hébergement ou de soins. *Ibid*.

[281] Berr C., Wancata J., Ritchie K., « Prevalence of dementia in the elderly in Europe », *European Neuropsychopharmacology,* n° 15, 2005, pp. 463-471.

## 2.1 LE BESOIN D'UNE MEILLEURE INCLUSION DANS LES RECHERCHES BIOMÉDICALES

149. S'il est difficile de trouver un juste milieu entre protection des participants aux essais et promotion de la santé des futurs patients, la protection actuelle de la vulnérabilité physique des personnes âgées peut paraître trop stricte (2.1.1) si on la compare aux recommandations scientifiques, médicales et éthiques en matière d'essais cliniques (2.1.2).

### 2.1.1 Entre protection et surprotection de la vulnérabilité physique

150. La fragilité physique des personnes âgées oblige à les protéger des recherches biomédicales (2.1.1.1), mais cette protection est à double tranchant puisqu'elle surprotège et marginalise les personnes âgées fragiles (2.1.1.2).

#### 2.1.1.1 LA FRAGILITÉ PHYSIQUE DES PERSONNES ÂGÉES

151. Les personnes âgées présentent des différences notables par rapport à une personne jeune. Elles vont absorber, transporter et éliminer les médicaments différemment, subir un déclin général de leur condition physique, souffrir d'affections multiples voire de maladies qui leur sont propres[282]. Ces caractéristiques sont un véritable challenge pour les médecins prescripteurs, que ce soit dans le cadre du traitement comme de celui de la recherche, car le rapport bénéfice-risque d'un traitement (expérimental ou non) est peut varier chez les personnes âgées selon leur condition de santé. Elles vont réagir différemment aux effets indésirables, secondaires, aux interactions médicamenteuses, ou de manière générale à l'efficacité du médicament[283]. Il est indispensable de déterminer ce rapport bénéfice risque de manière différenciée pour les personnes âgées en bonne santé, ainsi qu'aux différents stades de la fragilité.

152. La fragilité est un concept de médecine gériatrique et une condition clinique qui regroupe ces symptômes principalement physiques[284], liés à la vieillesse et à un déclin général

[282] Certaines maladies cardiaques, osseuses ou mentales. EMA, ICH Topic E7. Studies in support of special populations: Geriatrics. Questions and answers., EMA/CHMP/ICH/604661/2009, Agence Européenne du Médicament, Londres, 2010, p. 2 ; Pour une explication claire et détaillée des problèmes associés aux changements physiologiques et maladies liés à la vieillesse, ainsi que les problèmes associés à la polymédication lire Piette F. et Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *Gérontologie et société*, Vol. 4, n°103, 2002, pp. 73-92, p. 80 et 81.

[283] Bortz W., « Understanding frailty », *J Gerontol A Biol Sci Med Sci*, Vol. 65, n°3, 2010, pp. 255-257.

[284] « Frailty was defined as a clinical syndrome in which three or more of the following criteria were present : unintentional weight loss (10lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity ». Fried L. P. *et al.*, « Frailty in older adults : Evidence for a phenotype », *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, Vol. 56, n°3, 2001, pp. M146-M157.

de l'état de la personne âgée[285]. S'il est tentant d'utiliser vulnérabilité et fragilité comme synonymes[286], il faut préciser que la fragilité se limite à un état de faiblesse intrinsèque avec des critères essentiellement physiques, biologiques voire cognitifs[287], là où la vulnérabilité inclut aussi des caractéristiques extrinsèques comme les circonstances économiques ou relationnelles. Ainsi, la fragilité physique est la faiblesse de la personne âgée qui, due à ses réserves physiologiques diminuées et lorsqu'exposée à un risque accru de dommage (des recherches biomédicales), la rend vulnérable et nécessite qu'on l'en protège.

#### 2.1.1.2. LA MARGINALISATION DES PERSONNES ÂGÉES PHYSIQUEMENT FRAGILES

153. Aux fins de protection, beaucoup de comités d'éthiques refusent les recherches incluant des personnes âgées fragiles car le risque pour leur santé est très élevé[288]. Pour les promoteurs, industriels comme académiques, non seulement l'approbation du comité d'éthique est très incertaine, mais en plus, l'inclusion de personnes âgées fragiles est complexe[289]. Mais le problème vient aussi en grande partie des investigateurs eux-mêmes. Ces derniers pêchent souvent par timidité et ne proposent pas de protocoles incluant des sous groupes de personnes âgées fragiles de peur d'essuyer un refus du comité d'éthique. Voire, c'est par stratégie que les investigateurs excluent les personnes âgées fragiles de leurs protocoles. Cela leur permet d'éviter les complications et investissements en temps et en argent, et de favoriser l'obtention de résultats favorables, homogènes, et ainsi en permettre une publication plus rapide. En effet, comme les personnes âgées constituent un groupe très hétérogène, il faudra beaucoup plus de participants afin d'avoir des groupes homogènes et générer des données fiables sur le médicament testé[290]. Ensuite, c'est la fragilité même qui pose des problèmes pour les résultats des essais cliniques qui, forcément compteront plus de cas d'effets indésirables, secondaires, ou d'inefficacité du médicament, diminuant les chances d'obtention d'une autorisation de mise sur le marché. Il est donc économiquement et statistiquement plus intéressant de mener des essais cliniques sur des patients jeunes « monopathologiques et monomédiqués », que sur le double

[285] Fried L. P. *et al*., « Frailty in older adults : Evidence for a phenotype », *op. cit*.; Voir aussi Clegg A. *et al.,* « Frailty in elderly people », *Lancet*, Vol. 381, n°9868, 2013, pp. 752-762 ; et Van Kan G. A. *et al*., « The assessment of frailty in older adults », *Clin Geriatr Med,* Vol. n°26, 2010, pp. 275-286.

[286] Clegg A. *et al.,* « Frailty in elderly people », *op. cit*.

[287] Michel H., « La notion de fragilité des personnes âgées : Apports, limites et enjeux d'une démarche préventive », *Retraite et société*, Vol. 62, n°1, 2012, p. 175.

[288] Quelques exemples non exhaustifs : Aapro M. S. *et al*., "Never too old ? Age should not be a barrier to enrollment in cancer clinical trials », *Oncologist*, Vol. 10, n°3, 2005, pp. 198-204 ; Kaźmierska J., « Do we protect or discriminate ? Representation of senior adults in clinical trials », *Reports of Practical Oncology & Radiotherapy*, Vol. 18, n°1, 2013, pp. 6-10.

[289] Par exemple : Ridda J. *et al*., « Difficulties in recruiting older people in clinical trials : An examination of barriers and solutions », *Vaccine*, Vol. n°28, 2010, pp. 901-906 ; Marcantonio E. R. *et al.*, « Maximising clinical research participation in vulnerable older persons : Identification of barriers and motivators », *Journal of the American Geriatrics Society*, Vol. 56, n°8, 2008, pp. 1522-1527 ; Townsley C. A. *et al*., « Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials », *Journal of Clinical Oncology*, Vol. 23, n°13, 2005, pp. 3112-3124.

[290] Piette F. & Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *op. cit*., p. 78.

de participants hétérogènes d'une population âgée fragile[291]. Et il est facile d'exclure les patients âgés des essais en instaurant des critères d'inclusion limitatifs, par exemple en exigeant des patients monopathologiques[292].

154. Or, leur exclusion a pour conséquence le manque de données adaptées sur la prescription de médicaments aux futurs patients âgés fragiles[293]. Les risques engendrés par un essai clinique seront les mêmes pour les patients âgés fragiles une fois le médicament commercialisé, mais sans la surveillance rapprochée d'un essai clinique, ce qui maintient voire aggrave la situation des patients âgés fragiles et les marginalise[294]. Lorsque les participants âgés ne sont pas exclus, ils sont très différents des patients réels des services de gériatrie : moins de 75 ans, aucune comorbidités, peu de traitements concomitants ou encore absence de problèmes cognitifs[295]. Ces patients même âgés ne représentent pas fidèlement les réels patients[296], et ne permettent pas non plus d'obtenir les informations nécessaires à une prescription éclairée par les médecins[297]. Seuls les gériatres sont spécialement formés sur ces questions de l'adaptation des posologies aux personnes âgées. Or le manque de gériatres, associé à la croissance rapide de la proportion de personnes âgées, fait que la majorité des patients âgés est traitée par des médecins non gériatres[298]. Ces derniers dénoncent les prescriptions improvisées par extrapolation des données disponibles[299]. Au lieu de pouvoir anticiper les effets indésirables, ils les découvrent au fur et à mesure de l'utilisation[300].

[291] Piette F. & Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *op. cit*., p. 79 ; Cherubini A. *et al*., « Fighting against age discrimination in clinical trials », *Journal of the American Geriatrics Society*, Vol. 58, n°9, 2010, p. 1792.

[292] Piette F. et Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *op. cit*., p. 84.

[293] Dudeja V. *et al*., « Guideline recommended gastric cancer care in the elderly : Insights into the applicability of cancer trials to real world », *Ann Surg Oncol*, Vol. 18, n°1, 2011, pp. 26-33.

[294] Par exemple : Davidoff A. J. *et al*., « Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria », *J Am Geriatr Soc*, Vol. 63, n°3, 2015, pp. 486-500 ; Cherubini A. *et al*., « The persistent exclusion of older patients from ongoing clinical trials regarding heart failure », *Arch Intern Med*, Vol. 171, n°6, 2011, pp. 550-556.

[295] Cherubini A. *et al*., « Fighting against age discrimination in clinical trials », *op. cit*., p. 1792.

[296] Par exemple : Lloyd-Williams F. *et al*., « Why are patients in clinical trials of heart failure not like those we see in everyday practice ? », *Journal of Clinical Epidemiology*, Vol. n°56, 2003, pp. 1157-1162.

[297] EMA, Geriatric Medicines Strategy, EMA/CHMP/137793/2011, Agence Européenne du Médicament, Londres, 2011, p. 3.

[298] Une piste en dehors du domaine de la recherche biomédicale pourrait également être celle de la formation continue des médecins de toute spécialité sur les questions de médecine gériatrique, difficile à imposer à un niveau européen.

[299] « Nous ne pouvons pas cautionner le scandale du décalage constaté actuellement. On ne peut pas en effet admettre que la prescription se fasse dans une attitude d'improvisation compassionnelle, parfois à des doses non validées pour 30% des patients ». Piette F. et Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *op. cit*., p. 83.

[300] Sur le long terme, cela pourrait également poser la question de la responsabilité des institutions qui émettent les autorisations de mise sur le marché de médicaments qui n'ont pas été suffisamment testés pour avoir des données fiables sur leur administration aux patients réels, l'EMA, mais aussi les agences nationales comme en France l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM).

## 2.1.2 Recommandations scientifiques, médicales et éthiques

155. La doctrine médicale (2.1.2.1) comme les lignes directrices éthiques (2.1.2.2) affirment le besoin, pour la promotion de la santé des personnes âgées, de mieux les représenter dans les essais cliniques.

### 2.1.2.1 LA DOCTRINE MÉDICALE

156. La recommandation majeure de la doctrine médicale à l'échelle européenne[301] est d'inclure plus systématiquement les personnes âgées fragiles dans les essais. Cette recommandation ancienne semble être aujourd'hui toujours et encore d'actualité[302], montrant ainsi la difficulté de la tâche[303]. Trois propositions plus modestes pourraient potentiellement être plus réalisables.

157. La première serait celle de l'élaboration d'une liste européenne médicaments potentiellement inappropriés (PMI) pour les personnes âgées, et de faire des suggestions d'adaptation des posologies ou de traitements alternatifs. Ces listes existent déjà au niveau national[304], et une liste européenne a même été débutée avec 7 États membres de l'Union européenne[305], mais dont le champ reste encore à élargir. Si les gériatres sont déjà sensibilisés à ces questions, il reste aussi à en diffuser les résultats aux médecins des autres spécialités amenés à prescrire des médicaments à des patients âgés. Il pourrait par exemple être pertinent, pour l'EMA ou les autorités nationales compétentes, d'imposer aux industries pharmaceutiques de fournir ces informations sur la notice du médicament.

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[301] Une étude a même été menée à l'échelle de 9 Etats de l'Union européenne afin de dénoncer le manque d'essai clinique sur les personnes âgées, et d'en analyser les causes et possibles solutions. Crome A. *et al*, « Exclusion of older people from clinical trials. Professional views from nine EU countries participating in the PREDICT study », *Drugs Aging*, Vol. 28, N°8, 2011, pp. 667-677 ; PREDICT, European charter for older people in clinical trials, 2010, http://ec.europa.eu/research/health/medical-research/human-development-and-ageing/projects/predict_en.html [6 août 2015].

[302] Piette F. et Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *op. cit*., p. 89 ; Cherubini A. *et al*., « Fighting against age discrimination in clinical trials », *op. cit*., p. 1791 ; Autres exemples non exhaustifs de doctrine dans ce sens : Blozik E. *et al*., « Prescription of potentially inappropriate medication in older persons in Switzerland : Does the dispensing channel make a difference? », *Risk Manag Healthc Policy*, Vol. 8, 2015, pp. 73-80 ; Büla C., « Médicaments et personnes âgées : S'indigner… et se réjouir », *Revue Médicale Suisse*, 2011, pp. 2163-2164 ; Dauerman H. L. *et al*., « Bridging the gap between clinical trials of antiplatelet therapies and applications among elderly patients », *Am Heart J*, Vol. 159, n°4, 2010, pp. 508-517 ; Fitzsimmons P. R. *et al*., « Older participants are frequently excluded from Parkinson's disease research », *Parkinsonism Relat Disord*, Vol. 18, n°5, 2012, pp. 585-589 ; Lang K. J. et Lidder S., « Under-representation of the elderly in cancer clinical trials », *British Journal of Hospital Medicine*, Vol. 71, n°12, 2010, pp. 678-681.

[303] Payne J. K. et Hendrix C. C., « Clinical trial recruitment challenges with older adults with cancer », *Applied Nursing Research*, Vol. n°23, 2010, pp. 233-237 ; Masoudi F. A. *et al*., « Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure », *Am Heart J,* Vol. n°146, 2003, pp. 250-257.

[304] Par exemple en Allemagne avec la liste PRISCUS : Holt S. *et al*., « Potentially inappropriate medications in the elderly : The priscus list », *Dtsch Arztebl Int*, Vol. 107, n°31-32, 2010, pp. 543-551 ; Hefner G. *et al*., « Side effects related to potentially inappropriate medications in elderly psychiatric patients under everyday pharmacotherapy », *Eur J Clin Pharmacol*, Vol. 71, n°2, 2015, pp. 165-172.

[305] Renom-Guiteras A. *et al*., « The EU(7)-PIM list: A list of potentially inappropriate medications for older people consented by experts from seven European countries », *European Journal of Clinical Pharmacology,* Vol. 71, n°7, 2015, pp. 861-875, p. 13.

158. La seconde proposition, plus ambitieuse, serait de systématiser la conduite d'essais cliniques additionnels et spécifiques aux personnes âgées pendant la pharmacovigilance. L'idée serait ici pour l'EMA de donner une autorisation de mise sur le marché soumise à la condition de la conduite de ces essais supplémentaires dans un certain délai. Cette proposition a le mérite de ne pas retarder inutilement la mise sur le marché[306], tant pour des raisons économiques, que pour des raisons de santé publique.

159. Enfin, la troisième proposition vise à systématiser la tenue de registres de patients âgés vulnérables, au lieu de s'en remettre aux seules obligations des professionnels de santé de déclarer les effets non mentionnés dans la notice aux autorités de santé. La systématisation de tels registres nécessiterait cependant l'intervention, notamment financière, des autorités publiques nationales, éventuellement en collaboration avec les industries pharmaceutiques.

#### 2.1.2.2 LES LIGNES DIRECTRICES INTERNATIONALES

160. La Déclaration d'Helsinki et les lignes directrices du CIOMS ne mentionnent pas directement la population gériatrique, mais prévoient des recommandations dans ce sens. Dans les deux cas, elles attirent l'attention sur les groupes sous représentés pour lesquels des recherches seraient bénéfiques, obligeant à une meilleure justification de leur exclusion[307].

161. En revanche, la Conférence internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments à usage humain (ICH) consacre aux recherches biomédicales sur la population gériatrique des travaux entiers depuis 1993[308]. Selon ces lignes directrices, les participants aux essais cliniques doivent représenter la population destinée à être traitée, notamment par groupe d'âge et y compris pour les personnes âgées[309]. Ces dernières doivent être incluses en proportion suffisante[310] voire majoritaire[311], si la maladie visée est directement liée au vieillissement (*e.g*. maladie d'Alzheimer), ou si la population à traiter inclut une grande proportion de personnes âgées (*e.g.* hypertension). Ces recommandations devraient s'appliquer aux nouveaux médicaments, comme à ceux déjà sur le marché[312].

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[306] Piette F. et Le Quintrec J.-L., « L'emploi d'un médicament nouveau chez les personnes âgées : Terra incognita », *op. cit*., p. 89.

[307] WMA, Déclaration d'Helsinki, *op. cit*., § 13 ; CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, élaborées par le Conseil des Organisations internationales des Sciences médicales (CIOMS) avec la collaboration de l'Organisation mondiale de la santé, Genève, 2002, Ligne directrice 12.

[308] ICH, Studies in support of special populations: Geriatrics E7, Conférence internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments à usage humain, 1993.

[309] *Ibid*., p. 1.

[310] En 1993, il avait été estimé qu'un nombre de 100 personnes âgées pourrait suffire à procurer des données fiables sur les effets d'un médicament sur les personnes âgées, mais ce nombre ne paraît plus adéquat à ce jour. ICH, Final concept paper E7(R1) : Studies in support of special populations: Geriatrics, Conférence internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments à usage humain, 2008, p. 1.

[311] ICH, Studies in support of special populations: Geriatrics E7, *op. cit*., p. 2.

[312] ICH, Studies in support of special populations: Geriatrics E7, *op. cit*., p. 1.

162. En 2008, cette ligne directrice a été actualisée, exposant les problèmes non résolus[313] et concluant par trois recommandations[314] : 1) mieux justifier le nombre, l'âge et la répartition des participants âgés selon l'indication du médicament expérimental ; 2) prévoir le développement de tests de sécurité sur la population gériatrique pendant la pharmacovigilance ; 3) indiquer des éléments précis à examiner spécifiquement dans le cas de comorbidités et de traitements multiples. Il y est précisé à plusieurs reprises qu'étant donnée la difficulté de la tâche, les essais peuvent être repoussés à après la mise sur le marché afin de ne pas retarder démesurément la mise à disposition des médicaments aux patients[315].

## 2.2 LES RÉPONSES DU DROIT EUROPÉEN

163. La notion de fragilité est une notion médicale et non juridique, mais qu'il serait utile de reconnaître en droit comme une condition qui nécessite l'inclusion des personnes âgées fragiles dans les essais cliniques. Là où le dynamisme de l'Union est inégal mais présent (2.2.1), le Conseil de l'Europe est en revanche étonnamment silencieux (2.2.2).

### 2.2.1 L'Union européenne : une réponse à deux vitesses

164. Si l'Agence européenne du médicament (EMA) est depuis 2006 très active dans la promotion de la recherche en gériatrie [316] (2.2.1.1), le nouveau Règlement 536/2014 relatifs aux essais cliniques n'offre que quelques timides concrétisations de l'activité de l'EMA (2.2.1.2).

#### 2.2.1.1 LE DYNAMISME DE L'AGENCE EUROPÉENNE DU MÉDICAMENT

165. L'EMA est une agence décentralisée de l'Union responsable de l'évaluation scientifique des médicaments en vue de leur mise sur le marché. Ses avis ne sont que consultatifs, et elle n'a pas de compétence propre pour remettre les autorisations de mise sur le marché, ni pour imposer des lignes directrices scientifiques ou éthiques relatifs aux médicaments[317]. Mais de par l'indépendance et l'expertise de ses membres[318], il paraît crucial d'étudier ses avis et conseils scientifiques.

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[313] ICH, Final concept paper E7(R1) : Studies in support of special populations: Geriatrics, *op. cit*., p. 1-3.
[314] *Ibid*., p. 3.
[315] *Ibid*., p. 3.
[316] L'EMA a effectivement organisé plusieurs workshops sur des questions plus précises des médicaments administrés sur les personnes âgées et surtout, elle avait réagi dès 2006 en publiant un rapport sur les lignes directrices relatives aux médicaments pour les personnes âgées. EMA, Adequacy of guidance on the elderly regarding medicinal products for human use, Doc. Ref. EMEA/498920/2006, Agence Européenne du Médicament, Londres, 2006 ; Si elle conclut à la conformité de la plupart des dossiers soumis à l'EMA aux lignes directrices ICH E7, elle conclut également que ces lignes directrices nécessitent, pour être plus utiles, d'être développées plus en profondeur, notamment pour opérer une distinction entre « personnes âgées » et « personnes très âgées ». *Ibid*., p. 2.
[317] Site Web de l'EMA, http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42 [20 août 2015].

166. Le dynamisme de l'EMA en matière de gériatrie a été particulièrement remarqué en 2011, avec la stratégie pour les médicaments gériatriques[319]. Elle vise à d'abord s'assurer que les médicaments administrés aux personnes âgées soient de haute qualité, et que leur usage chez ces dernières soit suffisamment étudié[320]. La stratégie vise aussi à améliorer les notices de médicament, qui devraient comprendre toutes les informations pertinentes à l'administration d'un médicament à la population gériatrique, y compris les limitations et carences, afin de promouvoir une prescription « éclairée » par les médecins[321].

167. Pour atteindre ses objectifs, l'EMA a défini deux domaines d'actions privilégiés. Le premier relève de l'expertise et du conseil, par la promotion des échanges scientifiques ; le but étant de procurer une assistance aux industries pharmaceutiques mais également d'identifier les points à améliorer dans la législation pertinente ou les lignes directrices en la matière[322]. Ce premier objectif implique aussi la création du Groupe Expert en Gériatrie (GEG) en 2011[323]. Il est chargé de conseiller l'EMA sur les problèmes liés aux personnes âgées, par exemple en donnant son avis sur les lignes directrices existantes, sur les aspects gériatriques du développement, de l'évaluation et de la pharmacovigilance des médicaments à usage gériatriques, et de manière plus générale aider à la mise en place de la stratégie et procurer son expertise lorsqu'il y en a besoin. L'EMA projette aussi d'élaborer des directives sur la sécurité et l'efficacité des médicaments sur les patients âgés fragiles[324]. Le second domaine d'action est plus concret puisqu'il vise à renforcer la sévérité des critères d'évaluation des demandes de conduite d'essai clinique. Les demandes devront présenter des données sur les personnes âgées qui soient fiables, en quantité suffisante, et présentées de manière claire et sans impasses[325].

168. En outre, l'EMA se réserve le droit de soumettre l'autorisation de mise sur le marché à des obligations spécifiques de pharmacovigilance pour compléter l'information concernant certaines comorbidités ou effets indésirables[326]. Pour le moment, seuls deux rapports d'activités relatent les conséquences précises de la stratégie encore en cours. Le premier décrit ainsi la révision des lignes directrices pertinentes qui, pour 93% d'entre elles, n'étaient pas conformes aux directives de la ICH E7[327]. Dans un second rapport, l'EMA rapporte que 75% des médicaments nouvellement autorisés ne procuraient pas suffisamment d'informations relatives

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[318] Site Web de l'EMA, http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000092.jsp&mid=WC0b01ac0580028a43 [20 août 2015].
[319] EMA, Geriatric Medicines Strategy, EMA/CHMP/137793/2011, Agence Européenne du Médicament, Londres, 2011.
[320] *Ibid*., p. 1.
[321] *Ibid*., p. 1.
[322] *Ibid*., p. 3.
[323] EMA, Mandates, objectives and rules of procedure for the CHMP Geriatric Expert Group (GEG), EMA/281009/2013, Agence Européenne du Médicament, Londres, 2013.
[324] EMA, Geriatric Medicines Strategy, *op. cit*., p. 2.
[325] *Ibid*., p. 3
[326] *Ibid*., p. 2.
[327] EMA, Report analysis of scientific guidelines. EMA Geriatrics Medicines Strategy, EMA/352591/2013, 2013, p. 2.

à l'usage sur les personnes âgées[328]. Les activités de recherches ont également permis l'élaboration d'un article sur la qualité des médicaments administrés aux personnes âgées[329]. À l'exception de ces rapports d'activité, il n'y a, à cette date, pas encore de bilan général des résultats de la stratégie.

#### 2.2.1.2 L'IMPLICATION TIMIDE DU NOUVEAU RÈGLEMENT 536/2014

169. Le nouveau Règlement 536/2014 étend considérablement la protection des personnes vulnérables en comparaison à la Directive 2001/20/CE[330]. Mais malgré les efforts de l'EMA, aucun engagement n'a été pris vis-à-vis des personnes âgées.

170. Et pourtant, les besoins des personnes âgées sont reconnus. L'alinéa 14 du Préambule indique que « sauf disposition dûment justifiée dans le protocole, les participants à un essai clinique devraient être représentatifs des catégories de populations, par exemple le sexe et le groupe d'âge, susceptibles d'utiliser le médicament faisant l'objet de l'investigation ». De même, l'alinéa 15 du Préambule soulève aussi la problématique : « Afin d'améliorer les traitements disponibles pour les populations vulnérables telles que les personnes de santé fragile ou les personnes âgées, les personnes atteintes de plusieurs maladies chroniques ou les personnes atteintes de troubles psychiques, il convient d'étudier intégralement et de façon adaptée les effets sur ces groupes particuliers de médicaments susceptibles de présenter un intérêt clinique significatif, notamment en ce qui concerne les exigences liées aux caractéristiques spécifiques de ces populations et à la protection de la santé et du bien-être des participants y appartenant ».

171. Par conséquent, le besoin d'inclusion des personnes âgées fragiles, n'a pas été oublié. Il est simplement regrettable que le nouveau Règlement ne fasse suite à ce constat du problème à aucun moment dans tout le reste de ses dispositions. On pourrait interpréter l'article 10.4 comme incluant implicitement les personnes âgées : « Si, conformément au protocole, un essai clinique prévoit la participation de groupes ou de sous-groupes spécifiques de participants, le cas échéant, la demande d'autorisation de cet essai clinique est évaluée de façon particulièrement attentive à partir des connaissance relatives à la population que représentent les participants concernés »[331]. Mais même si cela était le cas, l'article reste vague et dépendant

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328 *Ibid*., pp. 2-3.

329 EMA, Concept paper on the need for a reflection paper on quality aspects of medicines for older people, EMA/165974/2013, Londres, 2013, p. 2.

330 Union européenne, Directive 2001/20/CE du Parlement européen et du Conseil du 4 avril 2001 concernant le rapprochement des dispositions législatives, réglementaires et administratives des États membres relatives à l'application de bonnes pratiques cliniques dans la conduite d'essais cliniques de médicaments à usage humain, *J.O.,* L 121, 1er mai 2001, pp. 34-44. Si la directive protégeait les mineurs et les adultes incapables, la protection des personnes vulnérables s'étend désormais en outre aux personnes inconscientes en situation d'urgence (Article 35), aux femmes enceintes (Article 33), et selon les droits nationaux, elle peut également s'appliquer aux personnes en situation de dépendance institutionnelle ou hiérarchique (Article 34). Union Européenne, Règlement (UE) n° 536/2014, *op. cit*., pp. 32-34.

331 Union Européenne, Règlement (UE) n° 536/2014, *op. cit*., Article 10.4.

d'une prémisse majeure : le fait que des essais soient conduits sur un groupe de personnes âgées. Or, c'est exactement dans cette prémisse que réside le problème, comme nous l'avons exposé au début de cette partie, un nombre insuffisant d'essais cliniques sont menés sur les personnes âgées.

172. Cette timide implication est d'autant plus étonnante que les législateurs européens ont déjà, depuis 2006, poussé la réflexion et franchi le cap de la réglementation pour les enfants. Ils ont reconnu que leur exclusion des essais cliniques, à la fois par souci de protection mais aussi par manque d'attractivité du marché, avait comme conséquence l'absence de médicaments adaptés[332]. Le Règlement pédiatrique 1901/2006 met ainsi en place un système d'obligations et d'incitations afin de faciliter le développement et l'accessibilité de médicaments à usage pédiatrique[333], et ce, sur la base juridique du rapprochement des législations nationales pour le fonctionnement du marché intérieur[334]. Le Parlement européen a d'ailleurs élaboré une résolution spécifique sur la maladie d'Alzheimer en 2011 témoignant du besoin des recherches, et notamment pour cela d'une « collaboration transnationale »[335]. En outre, il « insiste » pour que la problématique des essais thérapeutiques pour les patients atteints d'Alzheimer « trouve son prolongement dans la révision de la directive européenne portant sur les essais cliniques de médicaments (2001/20/CE) »[336], en vain.

## 2.2.2 Le silence étonnant du Conseil de l'Europe

173. L'unique disposition pertinente dans la Convention d'Oviedo[337] concerne les personnes juridiquement incapables, pour lesquelles il existe, par exception, la possibilité de mener des recherches[338]. Cependant, les personnes âgées fragiles ne sont qu'indirectement concernées car elles ne sont pas nécessairement incapables. Fragilité physique ne veut pas nécessairement dire troubles cognitifs ni démence. Le Protocole additionnel à la Convention d'Oviedo relatif à la recherche biomédicale prévoit les mêmes règles[339]. Bien qu'il mentionne des

[332] Règlement (CE) N° 1901/2006 du Parlement européen et du Conseil du 12 décembre 2006 relatif aux médicaments à usage pédiatrique, modifiant le règlement (CEE) n° 1768/92, les directives 2001/20/CE et 2001/83/CE ainsi que le règlement (CE) n° 726/2004, J.O., L 378, 27 décembre 2006, pp. 1-19, Préambule, Considérants 2 et 3.
[333] *Ibid*., Préambule, Considérants 4 et 6.
[334] Règlement (CE) N° 1901/2006, *op. cit*., Considérant 1..
[335] Union européenne, Résolution du Parlement européen du 19 janvier 2011 sur une initiative européenne pour faire face à la maladie d'Alzheimer et aux autres démences (2010/2084(INI)), P7_TA(2011)0016, §14, §20, §22 et §52.
[336] *Ibid*., §64.
[337] Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*., Chapitre V.
[338] Si cela peut lui procurer un bénéfice direct (Article 17.1), ou exceptionnellement si la recherche ne comporte pas de bénéfices potentiels directs, l'essai clinique peut être effectué si cela va améliorer les connaissances sur cette condition en question et sur ce type de patient particulier (Article 17.2.ii). *Ibid*.
[339] Conseil de l'Europe, Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, STCE N°195, Strasbourg, 25 janvier 2005, Article 15.

groupes vulnérables supplémentaires[340], là encore, aucune mention des personnes âgées fragiles.

174. Cette absence quasi totale de reconnaissance du besoin des personnes âgées vis-à-vis des recherches biomédicales est d'autant plus surprenante que le domaine des droits fondamentaux des personnes âgées est en plein développement[341]. Malgré tout, le dernier texte en date, une recommandation du Comité des Ministres adoptée le 19 février 2014 à propos de la promotion des droits de l'homme des personnes âgées[342] ne fait aucune mention de leur vulnérabilité vis-à-vis du défaut d'information sur l'usage des médicaments, ni du manque d'essai clinique qui est à l'origine de ce défaut d'information. Là encore, pareillement à l'Union européenne, cette absence même de reconnaissance par le Conseil de l'Europe du manque d'information sur les personnes âgées fragiles est paradoxale car il reconnaît ce besoin pour les enfants[343].

175. Ainsi, la phase d'élaboration du médicament, la phase de recherche biomédicale, est sous-estimée par le droit européen dans l'appréhension des enjeux de santé des personnes âgées. Elle est sous-estimée pour toutes les raisons que nous venons d'exposer, mais également car s'ajoute fréquemment un obstacle supplémentaire : l'obtention du consentement. L'obstacle est plus souvent contourné qu'affronté, remettant en cause la promotion de l'autonomie des personnes âgées vulnérables.

# 3 La promotion de l'autonomie des personnes âgées vulnérables

176. L'autonomie est un principe omniprésent en éthique clinique[344] qui oblige à respecter les choix du patient, et donc à respecter son droit à l'autodétermination[345]. Le respect du principe d'autonomie exige donc que le patient (ou le participant à une recherche) donne son

[340] Conseil de l'Europe, Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, *op. cit.* : Personnes privées de liberté (Article 20 du Protocole), personnes en situation d'urgence (Article 19 du Protocole), et enfin les femmes enceintes ou allaitantes (Article 18 du Protocole additionnel).

[341] Rien qu'au niveau du Conseil de l'Europe : Résolution 1793 (2011) de l'Assemblée parlementaire « Pour une longévité positive : valoriser l'emploi et le travail des seniors » ; Recommandation 1796 (2007) sur la situation des personnes âgées en Europe, Recommandation 1591 (2003) sur les défis de la politique sociale dans les sociétés européennes vieillissantes, Recommandation 1619 (2003) sur les droits des migrants âgés…

[342] Conseil de l'Europe, Recommandation CM/Rec(2014)2 sur la promotion des droits de l'homme des personnes âgées du Comité des Ministres aux États membres, adoptée le 19 février 2014.

[343] Même si, au contraire de l'Union, il n'est pas allé jusqu'à élaborer d'instrument ni même de régime spécifique aux enfants. Conseil de l'Europe, Rapport explicatif au Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, Strasbourg, STCE N°195, 25 janvier 2005, §90 et §92.

[344] Lamau M.-L., « Le recours au principe d'autonomie en éthique clinique », *Revue d'éthique et de théologie morale,* Vol. 2, n°234, 2005, pp. 63-70.

[345] Le Coz P., « Les principes éthiques reconnus à l'échelle internationale », *in* Mattei J.-F. (dir.), Questions d'éthique biomédicale, Flammarion Coll Nouvelle Bibliothèque Scientifique, Paris, 2008, p. 77.

consentement. Mais surtout, ce consentement soit libre et éclairé, ce qui suppose que la personne soit en mesure de comprendre et d'évaluer les enjeux de sa décision, et qu'elle soit également en mesure de faire ce choix librement, sans mesure coercitive extérieure[346]. Or, l'obtention de ce consentement de la part de personnes âgées vulnérables pose de sérieux défis (3.1) qui ont pour le moment encore peine à trouver réponse dans le droit européen (3.2).

## 3.1 LES DÉFIS DE L'OBTENTION DU CONSENTEMENT ÉCLAIRÉ

177. Lorsque la personne âgée vulnérable n'est que partiellement autonome, des mécanismes sont mis en place pour la protéger, mais cette protection peut parfois devenir surprotectrice (3.1.1). Divers moyens sont utilisés dans la pratique médicale pour promouvoir leur capacité de décision, mais ces moyens ne sont ni harmonisés ni même reflétés dans les recommandations scientifiques et éthiques (3.1.2).

### 3.1.1 Entre protection et surprotection de la vulnérabilité décisionnelle

178. La fragilité cognitive des personnes âgées constitue un réel obstacle à l'obtention du consentement éclairé (3.1.1.1), de sorte que la prudence des médecins et chercheurs est contre-productive lorsqu'elle marginalise les personnes âgées en les excluant soit des essais, soit du processus de consentement (3.1.1.2).

#### 3.1.1.1 LA FRAGILITÉ COGNITIVE DES PERSONNES ÂGÉES

179. C'est sur la vulnérabilité cognitive que nous nous attarderons en ce qu'elle affecte la capacité de donner une décision éclairée par la personne âgée juridiquement capable. C'est le cas par exemple des maladies psychiatriques ou neurologiques, mais aussi d'une condition très fréquente chez la personne âgée : la fragilité cognitive[347]. Elle est un syndrome clinique hétérogène de troubles cognitifs entraînant une confusion chez les personnes âgées, qui est

[346] Le Coz P., « Les principes éthiques reconnus à l'échelle internationale », *op. cit.,* p. 78.
[347] Hazif-Thomas C., Thomas P. et Walter M., « Motivation sociale, fragilité cognitive et assomption de la vieillesse », *La Lettre du Psychiatre*, Vol. VII, n°5-6, 2011, pp. 148-151..

causé par leur (pré-)fragilité physique[348], et qui se distingue de démences telles la maladie d'Alzheimer ou maladies associées[349].

180. En d'autres termes, la fragilité cognitive n'est que « vieillissement physiologique »[350] qui ralentit les capacités de compréhension et de mémorisation de l'information. Et ceci constitue un obstacle de taille pour obtenir le consentement éclairé des participants âgés. Une étude a rapporté que seule la moitié des participants âgés – jugés d'intelligence normale – avaient compris l'information qui leur avait été fournie à propos d'un protocole de recherche[351]. Et lorsqu'à la fragilité cognitive s'additionne une maladie neurologique ou psychiatrique, les résultats sont encore plus alarmants. Une étude a par exemple démontré que 70% des participants potentiels d'un essai clinique pour la maladie d'Alzheimer n'avaient été jugés que partiellement compétents[352], et les illustrations sont nombreuses dans la littérature[353].

#### 3.1.1.2 LA MARGINALISATION DES PERSONNES ÂGÉES COGNITIVEMENT FRAGILES

181. Plus qu'une protection de l'autonomie, le processus du consentement éclairé est parfois un défi car il se perd entre les documents administratifs et le vocabulaire médical. Il découragerait parfois la recherche sur les personnes âgées, et d'autant plus si la personne âgée est atteinte de fragilité cognitive[354], de dépression, maladie psychiatrique ou encore de la maladie d'Alzheimer ou autre démence[355].

182. Il relève du devoir des médecins de s'assurer au cas par cas que la personne est capable de prendre une décision[356]. Mais une tendance souvent dénoncée est de systématiquement considérer les personnes âgées comme trop vulnérables pour donner un consentement. On va alors, *dans leur intérêt*, les exclure de la recherche, faire appel à un

[348] EMA, Proposal for the development of a points to consider for baseline characterisation of frailty status, EMA/335158/2013, Agence Européenne du Médicament, Londres, 2013 ; Robertson D. A., Savva G. M. et Kenny R. A., « Frailty and cognitive impairment – a review of the evidence and causal mechanisms », *Ageing Research Reviews*, Vol. 12, 2013, pp. 840-851.

[349] Qingwei R. *et al*., « Cognitive frailty, a novel target for the prevention of elderly dependency », *Ageing Research Reviews*, Vol. 20, 2015, p. 4 ; Kelaiditi E. *et al*., « Cognitive frailty : rational and definition from an (IANA/IAGG) international consensus group », *The Journal of Nutrition, Health and Aging*, Vol. 17, n°9, 2013, p. 731.

[350] Ce vieillissement physiologique induit un « ralentissement du traitement de l'information ainsi qu'un déclin attentionnel ». Krolak-Salmon P., « Cognition et fragilité chez la personne âgée », *Les Cahiers de l'Année Gérontologique*, Vol. 4, n°13, 2012, p. 14.

[351] Krolak-Salmon P., « Cognition et fragilité chez la personne âgée », *op. cit*., p. 13 ; Berdeu D. *et al*., « Clinical trials in the elderly : Ethical and methodologic considerations », *op. cit*., p. 618.

[352] Bayer A. et Fish M., « The doctor's duty to the elderly patient in clinical trials », *Drugs Aging*, Vol. 20, n°15, 2003, p. 1093.

[353] *Ibid*., p. 1092 à 1094 ; Ou encore Dunn L. B. et Misra S., « Research ethics issues in geriatric psychiatry », *Psychiatr Clin North Am*, Vol. 32, n°2, 2009, p. 4.

[354] Barron J. S. *et al*., « Informed consent for research participation in frail older persons », *Aging Clin Exp Res*, Vol. 16, n°1, 2004, p. 79.

[355] Pour des résultats d'études empiriques en la matière, voir Dunn L. B. et Misra S., « Research ethics issues in geriatric psychiatry », *op. cit*., p. 4.

[356] Bayer A. et Fish M., « The doctor's duty to the elderly patient in clinical trials », *op. cit*., p. 1091 ; Meulenbroek O. *et al*., « Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent », *European Geriatric Medicine*, n°1, 2010, p. 58 ; Bayer A. et Fish M., « The doctor's duty to the elderly patient in clinical trials », *op. cit*., p. 1092 ; Bielby P., *Competence and vulnerability in biomedical research*, International Library of Ethics, Law and the New Medicine, Springer, 2008, p. 140.

représentant légal, ou bien limiter leur décision à ce que le comité d'éthique estime comme raisonnablement dans leur intérêt, ce qui est souvent très limitatif[357]. Cette tendance porte cependant atteinte à leur autodétermination par une ingérence surprotectrice[358]. Au contraire, il relève aussi du devoir du chercheur de tout mettre en œuvre pour l'optimiser et l'entretenir en faisant participer la personne au maximum[359] car la capacité de décision doit être vue comme une qualité dynamique et développable, et non comme une caractéristique fixe[360].

## 3.1.2. Recommandations scientifiques, médicales et éthiques

183. Là où la doctrine médicale propose des solutions pour promouvoir l'auto-détermination des personnes âgées (3.2.1), ces propositions ne sont pas reflétées par les lignes directrices internationales majeures (3.2.1).

### 3.2.1 LA DOCTRINE MÉDICALE

184. S'il existe des grilles générales d'évaluation de la capacité de décision[361] voire des instruments scientifiquement développés[362], les pratiques diffèrent grandement selon les chercheurs et selon les types de patients. La doctrine réclame des instruments qui soient harmonisés et spécifiques par exemple à une démence légère[363].

185. Ensuite, il s'agit de surmonter d'éventuelles faiblesses dans la capacité de décision et promouvoir l'autonomie des personnes âgées. Par exemple, certains proposent toute une série de moyens comme les vidéos ou outils interactifs, la lecture à haute voix, une écriture plus grande, ou encore l'usage régulier de quizz pour vérifier la compréhension et la mémoire avant et pendant l'essai[364]. Cependant, ces recommandations alourdissent encore le processus

[357] Lacour C., « La personne âgée vulnérable : Entre autonomie et protection », *Gérontologie et société*, Vol. 4, n°131, 2009, p. 192.
[358] Barron J. S. *et al.*, « Informed consent for research participation in frail older persons », *op. cit.*, p. 79.
[359] *Ibid.*, p. 81.
[360] Bielby P., Competence and vulnerability in biomedical research, op. cit., p. 142.
[361] Cinq critères majeurs guident généralement l'analyse : 1) la capacité à recevoir et à comprendre les informations ; 2) la capacité à les analyser ; 3) la capacité d'évaluer la situation et ses conséquences ; 4) la capacité de mettre en balance les bénéfices, risques et alternatives ; et 5) la capacité de prendre une décision et de l'exprimer. Meulenbroek O. *et al.*, « Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent », *op. cit.*, p. 58 ; Voir aussi les 4 capacités de Dunn : 1) comprendre l'information, 2) appliquer l'information à sa situation personnelle, 3) analyser l'information de façon rationnelle, 4) exprimer un choix clair et cohérent. Dunn L. B. et Misra S., « Research ethics issues in geriatric psychiatry », *op. cit.*, p. 2.
[362] Dunn L. B., Nowrangi M. A., Palmer B. W., Jeste D. V. et Saks E. R., « Assessing decisional capacity for clinical research or treatment : a review of instruments », *American Journal of Psychology*, n°163, 2006, pp. 1323-1334.
[363] Barron J. S. *et al.*, « Informed consent for research participation in frail older persons », *op. cit.*, p. 82.
[364] Bayer A. et Fish M., « The doctor's duty to the elderly patient in clinical trials », *op. cit.*, p. 1087 et p. 1093 ; Dans le même sens, voir Berdeu D. *et al.*, « Clinical trials in the elderly : Ethical and methodologic considerations », *op. cit.*, Tableau I, p. 619 ; Dunn L. B. et Misra S., « Research ethics issues in geriatric psychiatry », *op. cit.*, p. 5.

d'obtention du consentement sans même de garantie de stabilité. C'est pourquoi les efforts doctrinaux portent plus souvent sur l'encadrement du rôle des représentants[365].

186. Lorsque la capacité de décision n'est pas suffisante, il sera fait appel à un représentant pour autoriser la participation[366]. Mais les personnes vulnérables, *de facto* incapables, ne sont pas nécessairement sous protection juridique. Pour une démence telle l'Alzheimer, la protection juridique n'est que rarement déjà en place à cause de la rapidité d'évolution de la maladie. Et lorsqu'il y a représentant, d'autres problèmes se posent car ce dernier a le pouvoir de soumettre la personne aux risques liés à la recherche sans jamais vraiment savoir de ce que la personne aurait décidé[367]. En outre, son opinion peut aussi être biaisée[368], tout comme il peut présenter une vulnérabilité décisionnelle liée au vieillissement et à la fragilité cognitive[369], par exemple s'il s'agit du conjoint.

187. Enfin, une autre possibilité trop peu explorée est celle des directives anticipées. En matière de soins, elles servent aux patients à exprimer leurs souhaits en avance, pour un moment futur dans lequel ils ne seront plus capables de décider ou de s'exprimer. Elles pourraient être utiles avec les patients âgés pendant les stades précurseurs d'une démence[370] afin de leur donner un moyen supplémentaire de jouir de leur droit à l'auto-détermination. Mais plusieurs questionnements demeurent quant à leur éventuelle utilisation en matière de recherche : à quel point l'information doit-elle être détaillée ? À quel point la directive doit-elle être détaillée ? Les directives anticipées devraient-elles valoir consentement (si oui dans quelles conditions), ou ne devraient-elle être qu'un support pour les représentants légaux[371] ?

### 3.2.2 LES LIGNES DIRECTRICES INTERNATIONALES

188. Les instruments éthiques internationaux n'offrent que peu de recommandations spécifiques au consentement éclairé des personnes âgées. Il faut donc se tourner vers les mécanismes communs.

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[365] Bielby P., *Competence and vulnerability in biomedical research*, *op. cit*., p. 158 ; Lacour C., « La personne âgée vulnérable : Entre autonomie et protection », *op. cit.*, p. 188.

[366] Barron J. S. *et al*., « Informed consent for research participation in frail older persons », *op. cit*., p. 82 ; Dunn L. B. et Misra S., « Research ethics issues in geriatric psychiatry », *op. cit*., p. 2 ; Meulenbroek O. *et al*., « Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent », *op. cit*., p. 60.

[367] Meulenbroek O. *et al*., « Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent », *op. cit*., p. 58.

[368] Bayer A. et Fish M., « The doctor's duty to the elderly patient in clinical trials », *op. cit*., p. 1095; Dunn L. B. et Misra S., « Research ethics issues in geriatric psychiatry », *op. cit*., p.7; Beattie B. L., « Consent in Alzheimer's disease research : Risk/benefit factors », *Can J Neurol Sci*, Vol. 34, Suppl 1, 2007, p. S27.

[369] *Ibid*., p. S28.

[370] Jongsma K. et van de Vathorst S., "Advance directives in dementia research : The opinions and arguments of clinical researchers – an empirical study", *Research ethics*, publié en ligne le 8 août 2014: doi: 10.1177/1747016114523422 ; Helmchen H., « Ethics of clinical research with mentally ill persons », *Eur Arch Psy Clin*, Vol. 262, 2012, p. N441 ; Pierce R., « A changing landscape for advance directives in dementia research", *Soc Sci Med*, Vol. 70, 2010, p. 623 ; Alzheimer Europe, Position paper on the use of advance directives, 2009, http://www.alzheimer-europe.org/Policy-in-Practice2/Our-opinion-on/Advance-directives [22 mars 2015], § 31.

[371] Andorno R., Gennet É., Jongsma K. et Elger B., « Integrating Advance Research Directives into the European Legal Framework », *European Journal of Health Law*, Vol. 23, 2016, pp. 49-64.

189. Pour commencer, les trois lignes directrices éthiques majeures reconnaissent que la vulnérabilité va bien au-delà de la seule incapacité juridique. Elles définissent ainsi la vulnérabilité par ce que nous appelons ici la vulnérabilité décisionnelle, c'est-à-dire la difficulté de défendre ses intérêts et le risque accru de subir des influences extérieures qui modifieraient la décision de consentement[372]. Seules les lignes directrices du CIOMS mentionnent spécifiquement les personnes âgées vulnérables, en associant par exemple leur vulnérabilité à leur placement en institution ou au diagnostic d'une forme de démence[373], sans plus de détails.

190. En ce qui concerne l'évaluation de la capacité de décision et les moyens de l'améliorer, les lignes directrices restent générales. Globalement, elles exigent du médecin qu'il s'adapte aux besoins des participants potentiels[374], sans préciser les moyens d'évaluation et d'adaptation.

191. Si le consentement est donné par un représentant légal, la Déclaration d'Helsinki, les lignes directrices du CIOMS et de la ICH exigent le recueil de l'assentiment du participant[375]. Seuls le CIOMS et la Déclaration d'Helsinki précisent que toute objection du participant doit être respectée[376]. Le CIOMS met en garde contre les problèmes de partialité des membres de la famille ou amis mais ne donne pas de directives en la matière[377].

192. Pour finir, aucune des lignes directrices internationales ne traite explicitement de la possibilité d'utiliser des directives anticipées en matière de recherches biomédicales.

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[372] Les personnes vulnérables sont celles qui ont « une plus forte probabilité d'être abusés ou de subir un préjudice additionnel » et qui ont donc besoin d'une « protection adaptée » (§19). AMM, Déclaration d'Helsinki, *op. cit*. ; Les sujets vulnérables sont les individus dont la volonté de participer à un essai clinique est susceptible d'être influencée à tort par l'espoir, qu'il soit justifié ou non, de bénéfices associés avec la participation, ou bien de représailles de la part de supérieurs hiérarchiques en cas de refus de participer. ICH, Final concept paper E7(R1) : Studies in support of special populations: Geriatrics, *op. cit*., §1.61, p. 8 ; Les personnes vulnérables sont « celles qui sont relativement (ou totalement) incapables de protéger leurs propres intérêts. Plus précisément, leur pouvoir, leur intelligence, leur degré d'instruction, leurs ressources, leur force ou autres attributs nécessaires pour protéger leurs intérêts propres, peuvent être insuffisants ». CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, *op. cit*., Ligne directrice 13, Commentaire, p. 49.

[373] CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, *op. cit*., Ligne directrice 13, Commentaire « Autres groupes vulnérables », p. 50.

[374] ICH, Directive de bonne pratique clinique E6(R1) de la Conférence internationale sur l'harmonisation des exigences techniques pour l'enregistrement des médicaments à usage humain (ICH), 10 juin 1996, §4.8.12, p. 17 ; La Déclaration d'Helsinki exige du médecin engagé dans la recherche médicale qu'il protège, entre autres, le droit à l'autodétermination des participants, (§ 9), supposant aussi de s'adapter aux éventuels besoins spécifiques des personnes pour comprendre l'information (§ 26). WMA, Déclaration d'Helsinki, *op. cit*. ; Les lignes directrices du CIOMS mettent en garde contre les difficultés de compréhension du participant qui dépendent aussi « de la capacité et de la volonté de l'investigateur de communiquer avec patience et sensibilité ». CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, *op. cit*., Ligne directrice 4, Commentaire « Langue », p. 23.

[375] WMA, Déclaration d'Helsinki, *op. cit*., §29 ; CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, *op. cit*., Ligne directrice 15, Commentaire « Consentement de la personne », p. 54 ; ICH, Directive de bonne pratique clinique E6(R1), *op. cit*., §4.8.12, p. 17.

[376] WMA, Déclaration d'Helsinki, *op. cit*., §29 ; CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, *op. cit*., Ligne directrice 15, Commentaires, p. 54.

[377] CIOMS, Lignes directrices internationales d'éthique pour la recherche biomédicale impliquant des sujets humains, *op. cit*., Ligne directrice 15, Commentaire « Consentement de la personne », p. 54.

## 3.2 LA RÉPONSE DU DROIT EUROPÉEN

193. La protection de la vulnérabilité décisionnelle ne paraît en pratique que peu compatible avec la protection duelle classique des personnes capables et incapables. Il serait nécessaire de déterminer une catégorie intermédiaire afin de mieux adapter la protection des personnes dans ce cas, y compris des personnes âgées. Cependant, Union européenne comme Conseil de l'Europe semblent avoir une vision manichéenne de la capacité de consentir car les dispositions protectrices de la vulnérabilité décisionnelle, hors incapacité juridique, ne sont que marginales (3.2.1). Par conséquent, les dispositions applicables au consentement éclairé de la personne âgée vulnérable sont très limitées et seulement prospectives (3.2.2).

### 3.2.1 Une reconnaissance marginale de la vulnérabilité décisionnelle

194. L'éventuelle détermination d'une catégorie intermédiaire de capacité de décision des personnes relèverait des compétences nationales des États. Cependant, la reconnaissance de la vulnérabilité décisionnelle en tant qu'objectif éthique gagnerait à être ne serait-ce que reconnu au niveau européen afin d'inciter les États à mettre en place des dispositions spécifiques. Dans les développements suivants, nous exposerons dans quelle mesure l'Union (3.2.1.1) et le Conseil de l'Europe (3.2.1.2) reconnaissent la vulnérabilité décisionnelle.

#### 3.2.1.1 UNION EUROPÉENNE

195. Le Préambule fait clairement référence à des cas qui relèvent de la vulnérabilité décisionnelle - les catégories socioéconomiques défavorisées et les personnes en situation de dépendance institutionnelle ou hiérarchique[378] - mais sans les reprendre dans l'article dédié aux personnes vulnérables[379]. La spécificité de la situation des personnes âgées vulnérables n'est explicitement mentionnée à aucun moment du texte.

196. Seule la vulnérabilité des personnes en établissement de soins est reconnue[380] et pertinente pour les personnes âgées, mais elle ne suffit pas et ce, à plusieurs égards : d'une part, seule une partie des personnes âgées sont placées en établissement, d'autre part, le Règlement ne prévoit qu'une possibilité pour les Etats de mettre en place des dispositions supplémentaires, sans les y obliger pour autant[381]. Cette disposition risque donc de laisser libre court à une double

[378] Union Européenne, Règlement (UE) n° 536/2014, *op. cit*., Préambule, Considérant 31.
[379] En effet, l'article 10 traitant des personnes vulnérables mentionne les mineurs, les majeurs incapables, les femmes enceintes, les groupes ou sous-groupes spécifiques de participants, et enfin les personnes inconscientes en situation d'urgence. *Ibid*., Article 10.
[380] *Ibid*., Article 34.
[381] Ibid.

inégalité : inégalité entre les personnes âgées à domicile et les personnes âgées placées en établissement au sein même des États ; mais aussi une inégalité entre les personnes âgées placées en établissements dans des États différents, selon qu'ils auront mis en place ou non des dispositions plus protectrices. Laisser les États membres libres sur cette question risque donc de rendre encore la recherche biomédicale avec des personnes âgées vulnérables encore plus difficile, surtout lorsque les essais seront multinationaux.

197. Et pourtant, le Parlement européen avait attiré l'attention des États membres et du Conseil dans sa résolution de 2011, les encourageant à « promouvoir une réflexion et une démarche éthique par rapport aux malades pour garantir la permanence et le respect de la personne humaine, et à lancer une réflexion sur le statut juridique de la personne souffrant de maladies neurodégénératives afin d'encadrer juridiquement le champ de la privation de liberté et de la protection juridique du malade »[382], là encore, en vain.

#### 3.2.1.2 CONSEIL DE L'EUROPE

198. Outre les majeurs incapables et les mineurs[383], le Conseil de l'Europe reconnaît, dans le cadre des soins, une situation intermédiaire pour les personnes capables souffrant d'un trouble mental[384]. Pour pouvoir traiter la personne sans son consentement, il faut qu'il y ait altération des facultés mentales, que l'intervention ait comme but de traiter précisément ce trouble mental, et que l'absence de traitement soit préjudiciable à sa santé[385]. Ainsi, même s'il était techniquement possible de conduire des recherches sur des personnes souffrant d'un trouble mental sans leur consentement, ces cas se borneraient aux situations rares dans lesquelles les essais cliniques constituent la dernière option de traitement possible pour améliorer la santé du patient. En outre, cette option n'est que spéculative puisque la Convention d'Oviedo ne prévoit pas de dispositions spécifiques pour les personnes capables souffrant d'un trouble mental dans le cadre des recherches. Par conséquent, s'il l'on s'en tient au chapitre V de la Convention d'Oviedo sur la recherche scientifique, il n'est pas certain de savoir dans quelle catégorie classer les personnes âgées vulnérables.

199. Le Protocole additionnel sur la recherche biomédicale fait référence à la « personne en situation de faiblesse »[386] pour laquelle « des pressions très légères suffiront à vaincre sa volonté et à lui donner le sentiment qu'elle a l'obligation de donner son accord, même si tel n'est pas son souhait »[387]. Il distingue ainsi les personnes en situation de faiblesse des

[382] Union européenne, Résolution du Parlement européen du 19 janvier 2011, *op. cit*., §59.
[383] Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*., Articles 6 et 17.1.
[384] *Ibid*., Article 7.
[385] Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*., Article 7.
[386] *Ibid*., Article 12.
[387] Conseil de l'Europe, Rapport explicatif au Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, *op. cit*., Article 12, § 62.

« personnes vulnérables ou en état de dépendance »[388]. Malheureusement encore, cette vulnérabilité n'est pas reconnue jusqu'au point de mentionner les vulnérabilités dues à des troubles cognitifs ou à des maladies psychiatriques ou neurologiques, ni au point pour les personnes âgées vulnérables de se voir reconnaître un statut spécifique. L'omission de cette particularité de la majeure partie des personnes âgées est d'autant plus étonnante que les législateurs européens ont en revanche pris le soin d'ajouter des catégories de personnes qui bénéficient d'une protection spécifique : les femmes enceintes, les patients en situation d'urgence et les personnes privées de liberté[389].

## 3.2.2 Le traitement prospectif du consentement de la personne âgée vulnérable

200. Le droit de l'Union européenne comme celui du Conseil de l'Europe énoncent les règles essentielles qui entourent le régime du consentement éclairé, mais les conditions précises de son obtention relèvent des compétences nationales des États. L'étude du consentement de la personne âgée vulnérable n'y est ici donc que prospective. En effet dans un premier temps, nous étudierons les seules dispositions indirectement transposables à la situation des personnes âgées vulnérables (mais capables) : celles relatives à la promotion de l'auto-détermination du participant incapable (3.2.2.1). Dans un second temps, nous étudierons le statut d'éventuelles directives anticipées utilisées en matière de recherche (3.2.2.2).

### 3.2.2.1 L'AUTO-DÉTERMINATION DU PARTICIPANT INCAPABLE

201. Le participant incapable est dépendant de la décision de son représentant légal[390], mais les textes européens imposent parfois de le faire participer puisqu'il doit « dans la mesure du possible »[391] être associé à la procédure, et son refus doit être respecté[392]. Toutefois, la formule apparaît trop vague pour pouvoir guider les États membres vers une harmonisation des

[388] Cependant en lisant le rapport explicatif, on constate que la distinction entre vulnérabilité et état de dépendance n'est pas bien établie, la définition donnée de la vulnérabilité semblant englober l'état de dépendance, tout en en étant explicitement séparée. *Ibid*., Article 12, § 67 et – 69.

[389] Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*., respectivement les articles 18, 19 et 20.

[390] Union Européenne, Règlement (UE) n° 536/2014, *op. cit*., Article 31; Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*. Article 17. NB : Cependant, selon le Conseil de l'Europe, l'avis du médecin prévaudrait sur celui du représentant légal s'il estime la décision contre l'intérêt du patient incapable. Il reviendrait aux États de prévoir des recours appropriés pour ces situations. Rapport explicatif à la Convention sur les Droits de l'Homme et la biomédecine, *op. cit*.,, Article 6, § 48.

[391] Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*. Article 6.3 ; Voir aussi Conseil de l'Europe, Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, *op. cit*., Article 15.1.iii ; Union Européenne, Règlement (UE) n° 536/2014, *op. cit*., Article 31.3.

[392] Conseil de l'Europe, Convention sur les Droits de l'Homme et la biomédecine, *op. cit*. Article 17.1.v ; Voir aussi Conseil de l'Europe, Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, *op. cit*., Article 15.1.v ; Union Européenne, Règlement (UE) n° 536/2014, *op. cit*., Article 31.1.c.

législations, notamment sur la manière dont on évalue si la personne est en mesure de participer à la décision et de se forger une opinion, laissant peu d'indices sur la marche à suivre avec des patients capables mais atteints de fragilité cognitive ou de démence.

202. Le Conseil de l'Europe donne un peu plus de détails que l'Union en la matière. Par exemple le rapport explicatif de la Convention d'Oviedo indique que le participant incapable doit donner son consentement s'il est dans une phase d'amélioration de sa condition[393]. Cela pourrait être utile notamment pour les maladies psychiatriques, mais aussi et surtout pour les troubles cognitifs où les phases de lucidité alternent avec des phases de confusion. Malheureusement cette interprétation ne trouve aucun écho explicite dans le texte même de la Convention, notamment aucune obligation de réévaluer la capacité de décision du patient incapable. En revanche, le Protocole additionnel oblige implicitement à s'adapter aux capacités des participants en exigeant une information « adéquate, sous une forme compréhensible », exigence à laquelle le rapport explicatif du Protocole semble donner une dimension supérieure. Ainsi, sans figurer explicitement dans le Protocole additionnel, est amplement décrite dans le rapport explicatif toute une série de moyens pour pallier à diverses lacunes et faiblesses des participants potentiels comme l'usage de technologies audio-visuelles, l'allongement des délais de réflexion, l'adaptation aux troubles sensoriels ou au manque d'éducation[394]… Il est cependant dommage que les troubles cognitifs ne soient pas traités, laissant encore sans réponse la question de la protection pratique de la vulnérabilité décisionnelle de la plupart des personnes âgées.

#### 3.2.2.2 LES DIRECTIVES ANTICIPÉES

203. Harmoniser les législations européennes sur ce point paraît presque impossible au vu des divergences entre droits nationaux sur ce sujet – par exemple en matière de fin de vie – et de l'absence de compétence du droit européen en la matière. Par conséquent, la position des institutions européennes reste floue. Ni le Conseil de l'Europe, ni l'Union n'autorisent explicitement les directives anticipées en matière de recherches. Pis encore pour le Conseil de l'Europe, le représentant légal n'a même pas l'obligation de respecter les « souhaits précédemment exprimés » par le participant, mais seulement de les « prendre en compte »[395].

204. Quant au nouveau Règlement UE 536/2014, il n'exclue pas explicitement les directives anticipées : « Dans le cas de participants incapables qui n'ont pas donné leur consentement éclairé ou qui n'ont pas refusé de le faire avant la survenance de leur incapacité,

[393] Rapport explicatif à la Convention sur les Droits de l'Homme et la biomédecine, *op. cit*., Article 6, § 43.
[394] Conseil de l'Europe, Rapport explicatif au Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, *op. cit*., Article 13, § 72.
[395] Conseil de l'Europe, Protocole additionnel à la Convention sur les Droits de l'Homme et la biomédecine, relatif à la recherche biomédicale, *op. cit*., Article 15.1.iv.

un essai clinique ne peut être conduit que si (…) »[396]. Si on peut aisément conclure qu'une directive anticipée négative aurait valeur de refus opposable au représentant légal, la question d'une directive anticipée positive pose plus de problèmes[397]. En outre, il resterait à déterminer quel régime s'appliquerait alors : celui des participants capables ou incapables, puisque le sujet devenu incapable a consenti à la recherche en tant que personne capable[398].

# 4 Conclusion

205. Réglementer la recherche biomédicale sur les personnes âgées vulnérables implique des complexités pratiques auxquelles les textes européens ne sont pas encore adaptés. Afin de promouvoir la qualité de leurs soins de santé, la doctrine médicale et éthique démontre que les personnes âgées physiquement fragiles doivent – au lieu d'en être exclues – être incluses systématiquement dans les recherches biomédicales, avant et/ou après la mise sur le marché du médicament. Or le droit européen offre des réponses très inégales à ce besoin. Le droit du Conseil de l'Europe est totalement silencieux en la matière, tandis qu'en droit de l'Union européenne, les discussions au sein de l'Agence européenne du médicament n'ont pas suffit à faire intégrer de mesure spécifique aux personnes âgées dans le nouveau Règlement. Quant à la promotion de l'autonomie des personnes âgées, c'est surtout la doctrine médicale qui va alerter sur les challenges particuliers que représentent la fragilité cognitive, les maladies psychiatriques ou les démences comme la maladie d'Alzheimer. La plupart du temps, les personnes âgées ont une capacité de décision réduite sans encore bénéficier de protection juridique. Étonnamment, les lignes directrices éthiques ainsi que le droit européen sont plutôt manichéens et peu sensibles aux stades qui précèdent l'incapacité juridique. Une grande part de participants potentiels se trouve exclue de fait, là où des procédés intermédiaires pourraient encore être établis.

206. Les solutions à apporter à ces deux problématiques devront être liées : favoriser voire inciter l'inclusion des personnes âgées fragiles dans les essais cliniques nécessite d'aménager des solutions pour le consentement des personnes âgées atteintes de fragilité cognitive, de la maladie d'Alzheimer, autres démences ou maladies psychiatriques, que ce soit par l'assistance et la promotion de leur capacité de décision, ou par des directives anticipées. Si ces questions relèvent des compétences nationales des États, la problématique est commune à l'Europe et la réunion d'un nombre suffisant de participants âgés pour des tests cliniques

[396] *Ibid*., Article 31.1.
[397] Andorno R., Gennet É., Jongsma K. et Elger B., « Integrating Advance Research Directives into the European Legal Framework », *op. cit*.
[398] Certains auteurs disent que c'est le cas : Lötjönen S., « Medical research on patients with dementia – the role of advance directives in European legal instruments », *European Journal of Health Law,* Vol. 13, n°3, 2006, p. 246.

présente un caractère nécessairement transfrontière[399]. L'implication du législateur européen est indispensable pour, si ce n'est imposer des règles communes, au moins donner une impulsion dans le sens d'une meilleure inclusion des personnes âgées dans les recherches biomédicales, et d'une meilleure promotion de leur autonomie.

[399] Par exemple pour la maladie d'Alzheimer et autres démences, le Parlement européen énonce : « Considérant qu'il s'impose désormais de plus en plus clairement à l'esprit que l'incidence de maladies neurodégénératives sur la population européenne est d'une ampleur telle qu'aucun État membre n'est capable d'y faire face seul, et qu'il est donc nécessaire de renforcer puissamment dans les États membres et dans l'Union européenne la coopération et la coordination des efforts de recherche clinique innovante et pluridisciplinaire portant sur les causes, la prévention et le traitement de la maladie d'Alzheimer, ainsi que le partage de l'information et le niveau d'investissement financier dans ce domaine, afin de lutter contre les maladies neurodégénératives, en particulier la maladie d'Alzheimer, devenues un défi majeur pour les sociétés européennes ». Union européenne, Résolution du Parlement européen du 19 janvier 2011, *op. cit*., §J et §M.

# Discussion

207. Instead of using lists of vulnerable categories or of factors of vulnerability, we are suggesting here to use another approach or at least to use it as a complement. A helpful perspective is to focus on the type of risks[400] or on the type of damage the vulnerable person is exposed to[401]. Although it has not been often interpreted as such in the literature, this approach is actually suggested in the Declaration of Helsinki which evokes an "increased likelihood of being wronged or of incurring additional harm"[402]. It is further suggested in the CIOMS guidelines which emphasise the fact that consent violation is not the only type of harm vulnerable participants are exposed to[403]. This approach would allow clarification and systematisation of the definition of a vulnerable person and still allow adaptation to a specific area like clinical trials. Thus as outlined before, two main types of risks are emerging: risks to privacy (autonomy and private life) and risks to health[404]. The protection against those risks will tend to differ depending on the perspective of the trial participant (Section I) and of the future patient (Section 2).

## Section I: Vulnerable people and participation in clinical trials

208. Being unable to defend one's own interests creates a situation of vulnerability when the person is exposed to the risk of making a decision against her will. The extreme form of decisional vulnerability is legal incapacity (minors or incapacitated adults). However there are many other forms of decisional vulnerability, what we call *de facto* incapacity which includes persons in a coma, persons deprived of liberty, for which the European law foresees a specific

[400] "Each discipline reviewed tends to view vulnerability in a slightly different manner. Each uses different outcomes as its primary focus and is concerned with different forms of risk". Alwang J., Siegel P. B. & Jørgensen S. L., "Vulnerability: a view from different disciplines", *Social Protection Discussion Paper Series,* n°0115, 2001, p. 4; Bergouignan C., "Mesurer la vulnérabilité ?", *in* Paillet É. & Richard P. (eds.), *Effectivité des droits et vulnérabilité de la personne*, Bruylant, Brussels, 2014, p. 12.

[401] Hurst S., "Protéger les personnes vulnérables: Une exigence éthique à clarifier", *Revue Médicale Suisse*, Vol. 9, 2013, pp. 1054-1057.

[402] WMA (World Medical Association), Declaration of Helsinki - Ethics principles applicable to medical involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 (Hereafter "Declaration of Helsinki"), §19.

[403] CIOMS Guidelines, Guideline 15, Commentary.

[404] Schroeder D. & Genefas E., "Vulnerability: Too vague and too broad?", *Cambridge Quarterly of Healthcare Ethics*, n°18, 2009, p. 119 ; Hurst S., "Vulnerability in research and health care ; describing the elephant in the room ?", *Bioethics*, Vol. 22, n°4, 2008, p. 198 (Figure 2).

status and protection (1). Decisional vulnerability also concerns persons who are less visibly vulnerable, who are unable to defend their interests, but whose vulnerability seems to not attract the attention it deserves, leading to neglected protection in European law (2).

# 1 The strong protection of the autonomy of participants who are vulnerable because of their legal or *de facto* incapacity

209. Interestingly enough the lists of vulnerable people in the European legal frameworks surrounding biomedical research and clinical trials are quite restricted in comparison to other legal areas. This is because the frameworks are limited to persons who have a legal or *de facto* incapacity (1.1). Vulnerable participants who are explicitly designated as such in European law now benefit from a strong protection regime thanks to the progressive harmonisation of the two European legal frameworks: the Additional Protocol on biomedical research from the Council of Europe and Regulation 536/2014 from the European Union (1.2).

## 1.1 Restrictive vulnerable categories in clinical trials: legal and *de facto* incapacity

210. The lack of theorisation of vulnerability at the beginning of its use may have led to partial or under-use of the protection that vulnerability should have entitled a person or a group (1.1.1). In fact, there are a lot of different risks that one can be vulnerable to, however, the protection in response is mainly focussed on restricted types of decision making vulnerabilities (1.1.2).

### *1.1.1 The scattered use of the notion of vulnerability in European law and research ethics*

211. The notion of vulnerability can take several forms and in most cases, including clinical trials, normative instruments prefer having lists of vulnerable people than defining what constitutes vulnerability.

212. In the legal framework of the European Union, the use of the explicit term “vulnerable” is very new. The former directive 2001/20/EC was protecting minors and incapacitated adults but without using the explicit term (articles 4 and 5). Regulation 536/2014 now protects more groups of persons explicitly called “vulnerable” (article 10), including of course minors and incapacitated participants but also pregnant women, persons in emergency situations and “groups and subgroups of participants” which we will develop later on.

213. The legal framework of the Council of Europe does not refer to “vulnerable” groups explicitly but it does offer a special status to similar groups: persons who are no able to consent (*i.e*. minors and incapacitated), pregnant women, persons in emergency situations and persons

deprived of liberty (articles 15, 18, 19 and 20 of the Additional Protocol on biomedical research). Interestingly enough, the same instrument does use the term "vulnerable" in a slightly different context, in article 12 emphasising on the need for ethics committee members to possible undue influences on consent, and giving a very long list of vulnerable people in that specific situation in the explanatory report which we will come back to.

214. As specified above, the use of vulnerability is scattered as it can be implicit and most of all, there can be a "double" use of vulnerability for instance as observed in the Additional Protocol. It is also the case in the CIOMS guidelines: some groups benefit from a special status because of their special need of protection, and an unrelated article mentions other groups as "vulnerable", including some of the groups that already benefit from a special status, but not all of them… This is quite confusing and indeed, the CIOMS guidelines even explicitly specify that pregnant women are not vulnerable, but are still devoting a special status to their protection (Guideline 15).

215. The problems of using lists of different categories of vulnerable groups are numerous: stigmatisation, one size fits all protection, poor reflection of the complexity and variety of vulnerability situations, restricted access to protection, and slippery slope. Many authors in the literature as well as the CIOMS guidelines[405] have sought to solve these problems by suggesting a different approach: defining the factors of vulnerability rather than vulnerable people[406]. However, this approach is not satisfying either. Even though it gives a better understanding and allows to efficiently improve protection, it does not help in defining vulnerability specifically for biomedical research or clinical trials.

### *1.1.2 The partial use of the notion of vulnerability, mainly related to decision making*

216. Having clarified the type of risks vulnerable participants are exposed to, and before moving on to analyse the actual protection dedicated to them, it is evident that the European legal frameworks are making the risk of violation of autonomy, the determining criteria to designate the groups labelled as "vulnerable". In law, designation of vulnerable groups is unfortunately often limited to the identification of those who will have difficulties in giving a valid consent[407], be it legally or *de facto*: minors, incapacitated adults, people who are

[405] "A traditional approach to vulnerability in research has been to label entire classes of individuals as vulnerable. The account of vulnerability in this Guideline seeks to avoid considering members of entire classes of individuals as vulnerable", CIOMS Guidelines, Guideline 15, Commentary.
[406] Luna F., "Not the usual suspect : addressing layers of vulnerability", *Bioethics*, Vol. 27, n°6, 2013, pp. 325-332.
[407] For instance: Commission Nationale Consultative des Droits de l'Homme (CNCDH), Avis sur le consentement des personnes vulnérables. Plenary Assembly of 16 Avril 2015, *J.O.*, n°0158, 10 July 2015, Text n°126.

unconscious but in an emergency situation, persons deprived of liberty etc. Only the "usual suspects" as Florencia Luna would say[408].

217. On the contrary, persons who are "only" vulnerable to health risks are not among vulnerable groups whereas the list could be long: patients with orphan diseases, chronic disease, frail elderly patients to mention a few. There is only one exception which reflects the incoherence of legislators' choices: pregnant and breast feeding women. Even if this could be deemed as protection of legal incapacity of the foetus, embryo or breast-feeding children for obvious reasons, categorising pregnant women as vulnerable seems inconsistent with the rest, unless one would dare to say that pregnancy affects rationality[409]. The CIOMS guidelines even clearly state in their 2016 updated version that pregnant women are not to be considered as vulnerable because they can protect their interests[410], showing once again the tendency for literature and legislators to link vulnerability to only decisional vulnerability. This confusion between vulnerability and decisional vulnerability is frequent and also present in European law as we just showed, but it is also the case in the guidelines from the European Medicines Agency[411], in the CIOMS guidelines on vulnerability[412] and as well as in the ICH guidelines: "vulnerable subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced"[413].

## 1.2 THE STRONG PROTECTION OF PARTICIPANTS FOR THEIR LEGAL OR *DE FACTO* INCAPACITY

218. The protection of vulnerable participants has a strong base in the general regime applicable to all participants that we will present here (1.2.1) before examining the specific rules for vulnerable categories (1.2.2).

### *1.2.1 The general regime applicable to all participants*

219. Most rules from the general regime are similar between the legal frameworks of the Council of Europe and of the European Union. Pursuant to our suggestion to develop vulnerability through the different types of risks or damages, this work will distinguish between

[408] Luna F., "Not the usual suspect: addressing layers of vulnerability", *op. cit*.
[409] Coleman C. H., "Vulnerability as a regulatory category in human subject research", *The Journal of Law, Medicine & Ethics*, Vol. 37, n°1, 2009, p. 12.
[410] CIOMS Guidelines, Guideline 15, Commentary.
[411] EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities, EMA/121340/2011, London, 2012, p. 24.
[412] CIOMS Guidelines, Guideline 15.
[413] 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

risks for health and safety of participants and risks for privacy, and thereafter move to some additional guarantees thanks to procedural obligations.

220. Against risks for health and safety, several principles are applicable in European law and research ethics. First, primacy of individual has to be respected: their interests must prevail over those of science or society[414]. Second, no other alternative to clinical research should be possible before carrying out the research with human participants[415]. The third principle concerns the need of scientific quality of the research protocol and expertise of the investigators[416]. Last but not the least, there is a balance to be found between risks involved in the research and potential benefits[417]. The European Union does not distinguish between therapeutic and non-therapeutic research, direct and indirect benefits, but the Council of Europe does: risks should not be "disproportionate" regarding direct benefits, and they should not be "inacceptable" when no direct benefit is foreseen[418]. This distinction has been criticised because it is difficult to apply in practice[419], leading to its withdrawal from the Helsinki Declaration in 2000[420].

221. Against risks for privacy we can also find common general rules between European law and research ethics. Protection against risks for private life and confidentiality exists both in the law of the Council of Europe and the European Union, but is not specifically adapted or strengthened for vulnerable people. Rather, specific protection against risks to privacy for vulnerable people is focused on strengthening the protection of autonomy, thanks to the obligation to obtain informed consent from each participant[421]. First, this consent has to be free, it has to be voluntary and free from undue influences[422] and it has to be continuous, *i.e.* the participant can reconsider any time[423]. Second, this consent has to be informed, which implies that the participant received comprehensive but comprehensible information, including for instance when the person does not speak the same language or cannot read[424].

222. Finally, some other obligations are additional procedural guarantees that make sure all previously mentioned safeguards are actually respected. First of all, the previous approval of

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414 Regulation 536/2014, Article 3, Article 28.1.e., Article 28.1.f ; Oviedo Convention, Article 2 ; Additional Protocol, Article 3, Article 21.1, Article 23.1.

415 Oviedo Convention, Article 16.i ; Additional Protocol, Article 5.

416 Regulation 536/2014, Article 28.1.f ; Additional Protocol, Articles 8 et 21.2 ; Oviedo Convention, Article 4.

417 Regulation 536/2014, Article 28.1.a

418 Additional Protocol, Article 6.

419 "When we evaluate entire protocols as either therapeutic or nontherapeutic, as required by the Declaration of Helsinki, we end up with what I call the 'fallacy of the package deal'. Those who use this distinction typically classify as "therapeutic research" any protocol that includes one or more components that are intended to be therapeutic; therefore, the nontherapeutic components of the protocol are justified improperly according to the more permissive standards developed for therapeutic research", Levine R. J., "Some Recent Developments in the International Guidelines on the Ethics of Research Involving Human Subjects", *Annals of the New York Academy of Sciences,* Vol. 918, 2000, p. 172.

420 Poisson D., "Déclaration d'Helsinki. Quelles nouveautés ?", *Laennec,* Vol. 1, n°50, 2002, p. 48.

421 Oviedo Convention, Article 16.v ; Regulation 536/2014, Article 28.1. & Article 29.1

422 Regulation 536/2014, Article 28.1.h et Article 28.3 ; Additional Protocol, Article 12, Article 13.3, Article 14.2.

423 Additional Protocol, Article 13.3.

424 Oviedo Convention, Article 16.iv ; Additional Protocol, Article 13.1 et 13.2 ; Explanatory report to the Additional Protocol, § 72 ; Regulation 536/2014, Article 29.

the research protocol by an ethics committee is now an obligation in research ethics as well as in European law[425]. And although there has been some criticism on the differences of status, composition as well as functioning of ethics committees between and even within European countries, this is quite an undisputed requirement. Second, there are also specific obligations related to transparency, for instance with regular mandatory reports, notifications of adverse events or any event worthy of mention and in relevance with the scientific or ethical acceptability of the clinical trial[426]. Member states can thus suspend or even completely stop a clinical trial according to the continuous updates they receive[427]. Finally, Regulation 536/2014 of the European Union foresees inspections to be organized by Member States, all being coordinated by the European Medicines Agency[428]. These inspections are another way to make sure rights and well-being of participants are being respected, quality and integrity of data is being guaranteed and good clinical practices as well as ethics principles are being safeguarded[429]. Those inspections can take place before, during or after the clinical trial, with or without previous warning[430].

### *1.2.2 Stricter safeguards for vulnerable participants in European law*

223. The rules of protection of vulnerable participants are similar to those in the general regime, mainly just reinforced. The distinction between types of risks is important to present the specific regime applicable to vulnerable populations: risks to health and safety as opposed to risks to autonomy. For the sake of clarity, we will present those provisions in two separate tables which depict the double comparison: a comparison between each vulnerable group, and a simultaneous comparison between the frameworks of the Council of Europe and of the European Union. Table I is thus dedicated to provisions on the protection of vulnerable participants regarding health and safety risks of clinical trials, whereas Table II is dedicated to risks for autonomy. Regarding risks for privacy, the focus, for vulnerable participants, is on autonomy and not privacy in general. This is mainly because there are no stricter or specific rules on confidentiality for vulnerable categories. Their specific protection regarding privacy thus mainly concerns the protection of their autonomy during decision making.

224. There are a few significant elements to point out from these tables. The main element to highlight is the tremendous improvement of the legal framework of the European Union and its increasing harmonisation with the Council of Europe. The former European Union

[425] Oviedo Convention, Article 16.iii ; Additional Protocol, Article 7 ; Regulation 536/2014, Article 4 ;
[426] Additional Protocol, Article 24 ; Regulation 536/2014, Article 77.1.
[427] They inform other Member States concerned via the Union portal. Regulation 536/2014, Article 77.3.
[428] Regulation 536/2014, Article 78, Recitals 64 & 72 ; Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council (Hereafter Regulation 2017/556), Article 6 & Article 7.
[429] Regulation 2017/556, Article 6.
[430] Regulation 2017/556, Article 2 et 8.

instrument, Directive 2001/20/EC, was for instance only protecting minors and incapacitated adults, and was not obliging investigators to "respect" but only to "consider" their opinion. It was also only requiring risks to be minimised, which is a lot less protective than the current new formulation of "minimal risk". The new regulation is definitely inspired by the Additional Protocol on biomedical research from the Council of Europe, as is visible in the tables.

225. On some issues, Regulation 536/2014 even seems more protective, for instance on questions related to direct benefit needing to "outweigh" the risks whereas they need only to not be disproportionate according to the Additional Protocol. Moreover, Regulation 536/2014 is more restrictive regarding trials in emergency situations, which has been criticised for blocking innovative medicines[431].

226. In sum, vulnerability if viewed as a normative notion is meant to protect a lot of different aspects in a person's life, including health and autonomy. Similarly, legal and ethical frameworks of clinical trials are also meant to protect health and safety of participants as well as their autonomy. Although European law does protect both of these aspects for all participants including vulnerable ones, it looks like the decisive criteria to be part of a "vulnerable group" lies in a lack of autonomy. However, it does not mean that all participants lacking autonomy are adequately protected in European law as will be developed further in §2.

[431] "applying this derogation to trials which pose only a minimal risk is too restrictive and would be a backward step for some Member States. In practice, this would rule out many forms of research relating to resuscitation and innovative products". Willmott G., Committee on the Environment, Public Health and Food Safety (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012)0369 – C7 0194/2012 – 2012/0192(COD)), A7-0208/2013, Strasbourg, 7 June 2013, Amendment 91.

**Table I : Comparative table of the protection of vulnerable participants in the law of the Council of Europe and of the European Union regarding health and safety risks in clinical trials**

NB : In European Union regulation 536/2014, Article 10.4 mentions "specific groups and sub-groups" among vulnerable populations, but does not provide for a corresponding specific protection except for the need of expertise.

| Vulnerable group | **Incapacitated** Oviedo, Article 17 Protocol, Articles 15 et 16 | **Incapacitated** R 536/2014, Articles 10.2 & 31 | **Minor** Oviedo, Article 17 Protocol, Articles 15 & 16 | **Minor** R 536/2014, Articles 10.1 32 | **Pregnant woman** Protocol, Article 18 | **Pregnant woman** R 536/2014, Articles 10.3 & 33 | **Emergency** Protocol, Article 19 | **Emergency** R 536/2014, Articles 10.5 & 35 | **Deprivation of liberty** Protocol, Article 20 |
|---|---|---|---|---|---|---|---|---|---|
| Expertise/ special care | | Expertise or advice on "clinical, ethical and psychosocial questions" regarding the disease or the group | | "Paediatric expertise" or advice on "clinical, ethical and psychosocial questions" in paediatrics. | "Particular care shall be taken to avoid any adverse impact on the health of the child" | "Expertise in the relevant condition and patient population" | Research has been approved specifically for emergency | "Specific consideration shall be given to the circumstances of the conduct of the clinical trial" | |
| No alternative | No comparable effectiveness on others | - No comparable data validity on others<br>- Trial is "essential" for the group<br>- The participant suffers from the tested medical condition | No comparable effectiveness on others | - The condition is only paediatric or has already been tested on adults<br>- The minor participant suffers from the tested medical condition **OR** trial can only be done on minors | No comparable effectiveness on others | Condition of no alternative if no perspective of direct benefit | No comparable effectiveness on others | - The trial can only happen in emergencies<br>- The participant suffers from the tested medical condition which is serious, sudden or life threatening (and creates the emergency) | No comparable effectiveness on others |
| Direct benefit | Direct benefit | Direct benefit **outweighing** risks and burdens | Direct benefit | Direct benefit **outweighing** risks and burdens | Direct benefit | Direct benefit **outweighing** risks and burdens including for the (future) child | Direct benefit | Direct benefit **AND** Minimal risk compared to standard treatment | Direct benefit |
| No direct benefit Indirect benefit | - Significant improvement in the scientific understanding of the individual's condition<br>- Benefit for the group | - The participant suffers from the tested life-threatening or debilitating medical condition<br>- Benefit for the group<br>**Without prejudice to more stringent national rules prohibiting trials without direct benefit** | - Significant improvement in the scientific understanding of the individual's condition<br>- Benefit for the group | - The participant suffers from the tested medical condition<br>- Benefit for the group | Benefit for the group, for knowledge on reproduction, or for the (future) child | - Benefit for the group, for knowledge on reproduction, or for the (future) child<br>- No comparable effectiveness on others | - Significant improvement in the scientific understanding of the individual's condition<br>- Benefit for the group | **Impossible** | Benefit for the group |
| Risks | - Minimal risk and burden<br>- **No additional benefits shall be used to justify any increased level of risk or burden** | Minimal risk and burden **in comparison to standard treatment** | - Minimal risk and burden<br>- **No additional benefits shall be used to justify any increased level of risk or burden**. | Minimal risk and burden **in comparison to standard treatment** | Minimal risk and burden | Minimal risk and burden | Minimal risk and burden | | Minimal risk and burden |

## Table II : Comparative table of the protection of vulnerable participants in the law of the Council of Europe and of the European Union regarding risks for autonomy in clinical trials

NB : In the Additional Protocol on biomedical research from the Council of Europe, there is no specific provision for pregnant women, nor for persons deprived of liberty but article 12 on undue influences applies to them.

NB : In Regulation 536/2014 from the European Union, the only additional provision for pregnant women is the same as for minors and incapacitated adults on incentives or financial inducements.

| Vulnerable group | **Incapacitated**<br>R 536/2014, Article 31 | **Incapacitated**<br>Oviedo, Article 17 Protocol, Articles 12, 15 & 16 | **Minor**<br>Oviedo, Article 17 Protocol, Articles 12, 15 & 16 | **Minor**<br>R 536/2014, Article 32 | | **Emergency**<br>Protocol, Articles 12 & 19 | **Emergency**<br>R 536/2014, Article 35 |
|---|---|---|---|---|---|---|---|
| Information | Subjects received information "in a way that is adequate in view of their capacity to understand it" | - Information of the legal representative according to normal regime; as well as of the participant "unless not in a state to receive the information"<br>- Adequate, understandable and written information<br>- Information : Aim, plan, risks and benefits, opinion of the ethics committee, participants' rights especially right to refuse or withdraw without retaliation | | Information of the minor by investigators "who are trained or experienced in working with children" | | - Information of the person or legal representative « as soon as possible » | - Impossible to give information and obtain consent of the person or the legal representative in time<br>- Informed consent should be sought "without undue delay" and information given "as soon as possible" |
| Consent/ authorisation | - Informed consent of the legal representative<br><br>- Unless the incapacitated has not already given informed consent or refused to give it | - Specific written authorisation by the legal representative<br><br>- The legal representative is "taking into account the person'spreviously expressed wishes or objections". | | Informed consent of the legal representative | | "Consent or authorisation for continued participation shall berequested as soon as reasonably possible" | - The investigator certifies not to be aware of any objections previously expressed by the subject<br><br>- Incapacitated subjects and minors : Informed consent from the legal representative should be sought "without undue delay"<br><br>- Informed consent should be sought from the legal representative or the participant, "whichever is sooner", the participant has to consent as soon as capable of doing so.<br><br>- If the participant or representative refuses to continue, they have to be informed of their right so object to use of the data obtained |
| Participation to decision making | - "The subject shall as far as possible take part in the informed consent procedure"<br><br>- "The explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information (…) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator" | Incapacitated<br><br>- "shall as far as possible take part in the authorisation procedure"<br><br>- no objection | Minor<br><br>- "The opinion of a minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity"<br><br>- no objection | - Minors receive information "in a way adapted to their age and mental maturity"<br>- The explicit wish of a minor who is capable of forming an opinion and assessing the information (…) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator<br>- If the minor reaches the age of legal competence during trial he or she has to express informed consent again | | "Any relevant previously expressed objections of the person known to the researcher shall be respected" | |
| No undue influence | "No incentives or financial inducements are given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial" | - Refusal or withdrawal "shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care"<br><br>- "Particular attention must be given to vulnerable or dependent persons" regarding undue influences (including financial) | | No incentives or financial inducements to the minor or legal representatives, "except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial" | **NB : also specified for pregnant women** (R 536/2014, Article 33) | "Particular attention must be given to vulnerable or dependent persons" regarding undue influences (including financial) | NB : **specified for pregnant women and persons deprived of liberty** (Protocol Article 12) |

# 2 The neglected protection of participants who are unable to defend their interests

227. Besides legal or *de facto* incapacity, other contexts put participants into a situation of decisional vulnerability, into a situation where they are not able to defend their interests. However in a lot of those situations, participants are not categorised as vulnerable although they would need protection. In this paragraph, we will see that European law only marginally recognises other decisional vulnerabilities (2.1) and that the elements of protection it offers to them are very insufficient (2.2).

## 2.1 THE MARGINAL RECOGNITION OF THE DECISIONAL VULNERABILITY OF PARTICIPANTS UNABLE TO DEFEND THEIR INTERESTS

228. Other situations of decisional vulnerabilities can stem either from individual factors[432] (2.1.1) or systemic *i.e.* structural factors[433] (2.1.2). Often both are combined. For instance, a psychiatric patient who would be hospitalised against his will already has individual factors of vulnerability, but there could also be a national or local context of a lacking legal framework, of a faulty implementation thereof or even of a history of corruption and abuse as it was in the ECHR court case Bataliny versus Russia[434]. However, the type of protection needed for those two different factors of vulnerability will be different, hence the importance of distinguishing and explaining both separately is great.

### *2.1.1 The cautious recognition of individual factors of decisional vulnerability in European law*

229. There are plenty of individual factors potentially making a person unable to defend her interests, as highlighted in Guideline 15 of the CIOMS, in paragraph 1.61 of the ICH Guideline on Good Clinical Practice or in §27 of the Declaration of Helsinki. Here we will distinguish cognitive factors (2.1.1.1) and relational or social factors (2.1.1.2).

[432] CNCDH, Avis sur le consentement des personnes vulnérables, *op. cit*., al. 11.
[433] The expression "systemic" factors as a reference to the use that is made in the case law of both European Courts.
[434] A psychiatric patient had tried to commit suicide and was thus involuntarily hospitalised. Furthermore, he had been treated against his will, and with a drug that was only experimental. ECtHR, First Section, Case of Bataliny v. Russia, Application n°10060/07, 23 July 2015.

#### *2.1.1.1 Cognitive factors of decisional vulnerability in clinical trials*

230. Suffering from acute pain[435] or from a life-threatening condition can have an impact on the ability to consent[436], even outside obvious cases of incapacity where the patient would be sedated or unconscious. Most of all, acute pain or a life-threatening condition can also trigger a "therapeutic misconception"[437]. Mental and psychiatric disorders, even when not leading to a legal incapacity, can also have an impact on the ability to consent. Along this line, literature has emphasised the case of suicidal patients[438] or patients suffering from depression[439], where it sometimes has an impact on decision making capacity or on the emotional perception of risks[440], although controversial[441]. A key disorder among the older adults that raises similar questions is Alzheimer's disease and dementia which triggers a progressive decline of cognitive capacities. This case leads us to frailty[442] which is a clinical condition that usually comes with ageing, and that also affects cognitive capacities without necessarily being due to dementia[443].

231. In Regulation 536/2014 of the European Union, all these persons with a decisional vulnerability are not part of vulnerable categories. However, as we said before, article 10.4 foresees a generic category called "specific groups and subgroups", which could be meant to

[435] Dick B. D. & Rashiq S., "Disruption of attention and working memory traces in individuals with chronic pain", *Anesthesia & Analgesia*, Vol. 104, n°5, 2007, pp. 1223-1239 ; Tait R. C., "Vulnerability in clinical research with patients in pain: A risk analysis", *Journal of Law, Medicine and Ethics*, Vol. 37, 2009, pp. 59-72 ; Blacksher E., "Hearing from pain : using ethics to reframe, prevent, and resolve the problem of unrelieved pain", *Pain Medicine,* Vol. 2, n°2, 2001, p. 170.

[436] Schaeffer M. H. *et al.*, "The impact of disease severity on the informed consent process in clinical research", *The American Journal of Medicine,* Vol. 100, n° 3, 1996, pp. 261-268; Menikoff J., "The vulnerability of the very sick", *Journal of Law Medicine and Ethics*, Vol. 37, n°1, 2009, p. 53 ; Helmchen H. *et al.*, *From exclusion to inclusion. Improving clinical research in vulnerable people*, Berlin-Brandenburgische Akademie der Wissenschaften (BBAW), Berlin, 2014, p. 41; 2003 CIOMS Guidelines, Guideline 9, Commentary.

[437] Durand-Zaleski I. S. *et al.*, "Informed consent in clinical research in France : assessment and factors associated with therapeutic misconception", *Journal of Medical Ethics,* Vol. 34, 2008, p. e16; Joncas D. & Philips-Nootens S., "Le malentendu thérapeutique: un défi pour le consentement en recherche Clinique", *Revue de Droit de l'Université de Sherbrooke*, Vol. 6, n°36, 2005, pp. 134-163.

[438] Lakeman R. & Fitzgerald M., "The ethics of suicide research. The views of ethics committee members", *Crisis,* Vol. 30, n°1, 2009, p. 16 ; Rudd M. D. *et al.,* "Informed consent with suicidal patients; rethinking risks in (and out of) treatment", *Psychotherapy Theory, Research, Practice, Training,* Vol. 46, n° 4, 2009, pp. 459-468.

[439] Applebaum P. S. *et al.,* "Competence of depressed patients for consent to research", *American Journal of Psychiatry,* n°156, 1999, pp. 1380-1384 ; Elliott C., "Caring about risks: are severely depressed patients competent to consent to research ?", *Archives of General Psychiatry*, Vol. 54, n°2, 1997, p. 113.

[440] Pereira M., Shah N. & Desousa A., "Decisional capacity for research in schizophrenia: a review", *Indian Journal of Applied Research,* Vol. 5, n°12, 2015, p. 376 ; Palmer B. W. & Jeste D. V., "Relationship of individual cognitive abilities to specific components of decisional capacity among middle-aged and older patients with schizophrenia", *Schizophrenia Bulletin,* Vol. 32, n°1, pp. 98-106.

[441] On the controversy: Bielby P., *Competence and vulnerability in biomedical research*, International Library of Ethics, Law and the New Medicine, Springer, 2008, pp. 115-120.

[442] "Frailty was defined as a clinical syndrome in which three or more of the following criteria were present : unintentional weight loss (10lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity". Fried L. P. *et al.*, "Frailty in older adults: Evidence for a phenotype", *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, Vol. 56, n°3, 2001, pp. M146-M157 ; Clegg A. *et al.,* "Frailty in elderly people", *Lancet*, Vol. 381, n°9868, 2013, pp. 752-762 ; Van Kan G. A. *et al*., "The assessment of frailty in older adults", *Clin Geriatr Med,* Vol. n°26, 2010, pp. 275-286.

[443] EMA, Proposal for the development of a points to consider for baseline characterisation of frailty status, EMA/335158/2013, London, 2013 ; Robertson D. A., Savva G. M. et Kenny R. A., "Frailty and cognitive impairment – a review of the evidence and causal mechanisms", *Ageing Research Reviews*, Vol. 12, 2013, pp. 840-851; Hazif-Thomas C., Thomas P. & Walter M., "Motivation sociale, fragilité cognitive et assomption de la vieillesse", *La Lettre du Psychiatre*, Vol. VII, n°5-6, 2011, pp. 148-151.

include all the previously mentioned persons. In fact, the legislators have left a few indications in that direction in recitals 15 and 19 of the regulation. Recital 15 talks about "vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders", and recital 19 about "subjects in emergency situations, minors, incapacitated subjects, pregnant and breastfeeding women and, where appropriate, other identified specific population groups, such as elderly people or people suffering from rare and ultra rare diseases".

232. In the Additional Protocol to the Oviedo Convention, on biomedical research, article 12 warns against undue influences especially regarding vulnerable people. The explanatory report does provide for a lot more details, including cognitive and medical factors of vulnerability[444]. This shows that the Council of Europe actually acknowledges, even if only in the explanatory report, the existence of those other types of decisional vulnerabilities.

#### *2.1.1.2 Social and relational factors of decisional vulnerability in clinical trials*

233. Decisional vulnerability can also stem from relational factors. Inability to protect one's interests can be triggered by social disadvantages, poverty or a lack of access to health care, a perfect example for this would be the famous Tuskegee study[445]. Unfortunately, this type of exploitation has not disappeared even in Europe[446], some authors even call this type of vulnerable participants "the invisible vulnerable"[447].

234. Inability to protect one's interest can also stem from relationships, especially when it triggers a feeling of coercion, manipulation or persuasion[448]. This can happen in cases where the person is institutionalised and dependant on others for decisions: detainees, soldiers in the military, a resident of home for handicapped or elderly persons. Furthermore, this is the case when the person is highly dependent on family, carer, physician, teacher, employer or in any

[444] Explanatory report to the Additional Protocol, §69.

[445] This study was conducted in the United States of America between 1932 and 1972 on an isolated population of black farmers, poorly educated and lacking access to health care. It was examining the naturel evolution of Syphilis until death, which means that many participants were deprived of treatment although researchers knew the cure existed. Chiu C. T. & Katz R. V., "Identifying the 'vulnerables' in biomedical research: The vox populis from the Tuskegee legacy project", *Journal of Public Health Dentistry*, n°71, 2011, pp. 220-228 ; Cuerda-Galindo E., Sierra-Valenti X., González-López E. & López-Muñoz F., "Syphilis and human experimentation from World War II to the present: a historical perspective and reflection on ethics", *Actas Dermosifiliográficas*, Vol. 105, n°9, 2014, p. 850.

[446] Bern Declaration, Clinical drugs trials in Ukraine: myths and realities, Lausanne/Zurich, 2013 ; Bern Declaration, Russia: The mirage of Swiss clinical trials, Lausanne/Zurich, 2013 ; Waligora M., "Failures in clinical trials in the European Union: Lessons from the Polish experience", *Science and Engineering Ethics*, Vol. 19, 2013, pp. 1087-1098.

[447] Stone T. H., "The invisible vulnerable: The economically and educationally disadvantaged subjects of clinical research", *The Journal of Law, Medicine & Ethics*, Vol. 31, n°1, 2003, p. 150 ; Bustillos D., "Limited english proficiency and disparities in clinical research", *Journal of Law, Medicine and Ethics*, Vol. 37, n°1, 2009.

[448] Coercion is "a credible threat of harm or force to a research subject", manipulation consists in "influencing a research subject's decision by altering the available options or information", and persuasion consists in "guiding a research subject to your way of thinking through the disclosure of truthful information, but in a manner that is meant to get the person to think or act in a preferred manner". Schwenzer K. J., "Protecting vulnerable subjects in clinical research: Children, pregnant women, prisoners, and employees", *Respiratory Care*, Vol. 53, n°10, 2008, p. 1343.

case of subordination or deference, which are often underestimated[449]. This influence is not necessarily badly intentioned, but has to be recognised and taken into account to avoid the participant feeling a pressure from outside in one direction or another.

235. European law is alluding to relational and social factors of vulnerability only in a subtle way. In Regulation 536/2014 of the European Union, article 28.1.h cautions against undue influences, including those of financial nature, as part of the general protection regime, and again for certain vulnerable groups but curiously not for all of them: incapacitated adults, minors, pregnant women but not for emergency situations. In addition, recital 31 alludes to "all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial, in particular whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate". Interestingly, this recital can be indirectly linked to vulnerable groups, as article 34 acknowledges the possibility for Member States to add other categories like "persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions".

236. Regarding the Council of Europe, article 12 of the Additional Protocol does warn against "undue influence, including that of a financial nature", with special considerations to vulnerable and dependent persons, which apply exactly to all the examples of decisional vulnerability, which were mentioned above. It does recognise economic and social vulnerability[450], as well as vulnerabilities linked to institutionalisation, deference, and hierarchy. However, it is unfortunate that the protection stops here, as no other provision develops safeguards for those vulnerabilities, then again, only the explanatory report does.

### *2.1.2 The lack of recognition of systemic factors of decisional vulnerability in European law: low resource settings*

237. Systemic or structural factors refer to elements that are extrinsic to the participants and related to national or local system, cultural or political context, quality of the law and effectiveness of its application. Typically, this concerns clinical trials when they are conducted, for instance in poor, emerging or developing countries. However, as stated in the CIOMS guidelines and as one can notice in the literature, these systemic vulnerabilities are not necessarily related to a whole country nor are they necessarily found only in emerging countries[451], although most authors will rather use the expression "developing countries" than "low resource settings". There is an increasing tendency for trial sponsors to conduct trials in low

[449] Bell E. *et al.*, "Beyond consent in research. Revisiting vulnerability in deep brain stimulation for psychiatric disorders", *Cambridge Quarterly of Healthcare Ethics*, Vol. 23, n°3, 2014, pp. 362-365.
[450] Explanatory report to the Additional Protocol, §69.
[451] CIOMS Guidelines, Guideline 2, Commentary, p. 3.

resource settings[452] in order to reduce costs (sometimes by 90%)[453], to find naïve participants (who has never had a treatment)[454], and finally to find a great number of volunteers ready to participate[455]. We will further define systemic vulnerabilities and present their apprehension by European law.

238. Systemic vulnerability can take the form of exacerbated social vulnerability. When poverty and lack of access to health care can be observed at the scale of a whole country or region, the individual vulnerability actually becomes a structural and thus systematic vulnerability. Be it for the money or in the hope of getting health care, participants in low resource settings are easier to recruit, especially when exploitation is systematically organised. For instance, the Wemos Foundation reported that a clinical trial had been conducted in a rural area, offering financial incentives and an experimental treatment for HIV knowing well that the next door over-crowded nurses' office had run out of treatment[456]. As the European Group on Ethics notes, participation in a clinical trial is too often the only opportunity for those persons to get some kind of treatment[457].

239. Additionally, systemic vulnerability can stem from cultural or structural factors. To begin with, informed consent is always an issue, especially in some cultures where the group, rather than the individual, is paramount, making authorisation from a spouse, priest, or any other authoritative figure an indispensable stage[458]. The CIOMS particularly insists on the social vulnerability of women towards masculine figures[459]. These problems in general are compounded with the behaviour of some investigators. Many NGO's report that lying, pressures and intimidations used in these contexts to obtain (many time incomplete) informed consent

[452] Altavilla A., "Ethical standards for clinical trials conducted in third countries: The new strategy of the European Medicines Agency", *European Journal of Health Law*, Vol. 18, 2011, p. 66; Bern Declaration Website, https://www.ladb.ch/themes-et-contexte/sante/essais-cliniques/ [22 May 2016].

[453] Wemos Foundation Interview, https://www.youtube.com/watch?v=aoMnvUyCPuE [20 May 2016] ; Hervey T. K. & McHale J. V., *Health law and the European Union*, Law in Context, Cambridge University Press, Cambridge, 2004, p. 238 ; Wemos Foundation, Clinical trials realities in Zimbabwe. Dealing with possible unethical research, 2015, p. 7.

[454] European Group on Ethics in Science and Technologies (EGE), Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 5.

[455] In South Africa, an NGO reported that 3000 participants had been recruited within 9 days. Couderc M., Enjeux et pratiques de la recherche médicale transnationale en Afrique. Analyse anthropologique d'un centre de recherche clinique sur le VIH à Dakar (Sénégal), Université d'Aix-Marseille, Anthropologie sociale et ethnologie, 2011, p. 163

[456] Wemos Foundation, The clinical trials industry in South Africa: Ethics, rules and realities, 2013, p. 7.

[457] EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, *op. cit*., p. 13.

[458] Vray M., Simon F., Bompart F. *et al*., "Recommandations pour la recherche clinique dans les pays en développement", *Thérapie*, Vol. 62, n°3, 2007, p. 219 ; Caballero B., "Ethical issues for collaborative research in developing countries", *The American Journal of Clinical Nutrition,* Vol. 76, 2002, p. 718 ; EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 12.

[459] « In many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering.(…) Some women become vulnerable in research because of heightened psychological, social, physical, or legal risks. Examples include surveys and interviews regarding intimate partner violence and rape; social and behavioural research involving sex workers or women who inject drugs; and studies that solicit information about sexual behaviour ». CIOMS Guidelines, Guideline 18, Commentary, p. 69.

sheet signed[460]. In Argentina for instance, a study on neonates had become famous for numerous abuses[461]. Some infants were included although the parents had explicitly refused participation; other parents didn't even receive the information sheet and consent-form before the vaccination of their baby with the experimental drug ; others received intimidations and threats of refusing further care.

240. Those problems are also linked to the failure of local ethics committees to guarantee protection[462]. They often do not have enough human or financial resources to function correctly, to make time for evaluations and to have the expertise to conduct ethics review[463]. Even well intentioned ethics committees do not necessarily have the power to stop the violations they observed, for instance like in Zimbabwe when they are reportedly refused the access to the trial site for inspection, when rejected applicants conduct their trial anyway, or when investigators do not even apply for authorisation[464]. This leads us to another serious issue reported too often in literature: the frequency of conflict of interests and corruption in low resource settings: from politics, sponsors, and even the investigators[465], who are paid proportionately to the number of participants they manage to recruit[466].

241. European law does not explicitly acknowledge the general vulnerability of participants in low resource settings, outside from occasional mentions in work-documents or debates. This does not mean legislators won't try to offer some protection through more general means as « exporting research to the south is in itself a context of vulnerability and exploitation that requires more than protecting specifically vulnerable groups »[467]. Unfortunately it may not be sufficient.

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[460] Bern Declaration, Exploratory study on clinical trials conducted by Swiss pharmaceutical companies in India: issues, concerns and challenges, Lausanne/Zurich/New Delhi, 2013, p. 32.

[461] Bern Declaration, Clinical drug trials in Argentina: Pharmaceutical companies exploit flaws in the regulatory system, Lausanne/Zurich, 2013, pp. 16-18.

[462] Emanuel E. J., Wendler D., Killen J. & Grady C., "What makes clinical research in developing countries ethical? The benchmarks of ethical research", *Journal of Infectious Diseases*, Vol. 189, n°5, 2004, p. 934.

[463] Famenka A., "Ethical review of biomedical research in Belarus: current status, problems and perspectives", *Romanian Journal of Bioethics,* Vol. 9, n°2, 2011, pp. 75-79 ; Public Eye, Industry-sponsored clinical drug trials in Egypt: ethical questions in a challenging context, Étude conjointe de Public Eye, la Fondation Somo (Centre for Research on Multinational Corporations), la Fondation Wemos, & Egyptian Initiative for Personal Rights and Shamseya for Innovative Community Healthcare Solutions, 2016, p. 51 ; Bern Declaration, Exploratory study on clinical trials conducted by Swiss pharmaceutical companies in India, *op. cit*., p. 30 et p. 37; Bern Declaration, Clinical drugs trials in Ukraine: myths and realities, *op. cit*., p. 5.

[464] Emanuel E. J., Wendler D., Killen J. & Grady C., "What makes clinical research in developing countries ethical? The benchmarks of ethical research", *op. cit*., p. 930.

[465] European Commission, Directorate General for research, Conference proceedings, Brussels, 14-15 May 2007 : Ethics, research and globalisation. Europe and its partners building capacity in research ethics, Publications Office, 2007, p. 48; Benatar S. & Fleischer T., "Ethical issues in research in low-income countries", *The International Journal of Tuberculosis and Lung Disease*, Vol. 11, n°6, 2007, p. 617;

[466] Bern Declaration, Exploratory study on clinical trials conducted by Swiss pharmaceutical companies in India, *op. cit*., p. 28; Bern Declaration, Clinical drug trials in Argentina: Pharmaceutical companies exploit flaws in the regulatory system, *op. cit*., p. 17 ; Bern Declaration, Russia: The mirage of Swiss clinical trials*, op. cit*., pp. 6-7.

[467] Botbol-Baum M., "Care beyond autonomy : the recognition of our vulnerable capabilities", *International Journal of Bioethics,* Vol. 27, n°3, 2016, p. 39.

## 2.2 THE INSUFFICIENT PROTECTION OF THE DECISIONAL VULNERABILITY OF PARTICIPANTS UNABLE TO DEFEND THEIR INTERESTS

242. CIOMS Guidelines are suggesting a number of ways to avoid facing these systemic problems, for instance by collaborating with the local community to negotiate and elaborate the trial processes including the conditions of obtention of the informed consent, the functionnig of local ethics committees or the prevention of conflicts of interests[468].

243. Instruments of protection are enacted in every European country to comply with the European law. However, the content of protections and their implementation are sometimes insufficient to protect participants who do not constitute a classical vulnerable "group" but who are vulnerable nonetheless because of their inability to protect their interests. There are two explanations for this shortcoming: (2.2.1) it is limited in its possibilities to delve deeper into the ethical issues that are normally legally restricted to national competencies, which makes it particularly difficult to provide protection from individual factors of decisional vulnerability; (2.2.2) the European law is also limited in its territorial application, which makes it very challenging to protect participants from systemic deficits in the local legal framework when the setting is situated outside Europe.

### *2.2.1 Protection of individual decisional vulnerability and limited competence of European law*

244. There is definitely a pressure from scientific and ethical literature to better promote autonomy and means to enhance it whatever the level of capacity. This literature inspires different theories and suggestions around ethics of care, which would imply to better evaluate decision making capacity and its variations in time or according to context. Doing so will put in place appropriate measures of protection and still make sure the person participates as much as possible in the decision-making process.

245. Persons who are vulnerable yet not vulnerable "enough" to benefit from a protective status in European law related to clinical trials need safeguards to prevent harmful decisions and/or informally forced decisions. First it is important to make a clear distinction between the (even if unrealistic) will of the person, the possible and realistic options and the objectively least harmful option[469]. Paternalistic approaches would tend to make vulnerable people choose the least harmful option; the more vulnerable, the more this option will be

[468] For more details : CIOMS Guidelines, Guideline 7 on community engagement, guideline 8 on collaborative partnership and capacity-building for research and research review, guideline 23 on requirements for establishing research ethics committees and for their review of protocols and guideline 25 on conflicts of interests.

[469] Frison-Roche M.-A., "Distinction entre volonté et consentement en droit des contrats", *RTD Civ.*, 1995, p. 573 ; Roman D., "Leçon 4 : Droit de la santé : la décision revient-elle au patient ou au médecin ? ", *Vulnérabilité et droit*, 5 lessons from 13 February to 8 May 2017, http://www.unamur.be/droit/chaire-francqui-diane-roman [29 Avril 2017].

commanded to them even against their will[470]. However, in order to respect autonomy, a compromise has to be found between the three options[471]. Several authors criticise the tendency to suspend capacity when a capable person is partially or temporarily vulnerable, without making the effort to evaluate decision-making capacity: "le paternalisme de la décision compatissante « pour autrui » transformant la bienveillance en violence par l'occultation de l'évaluation fine des capacités du patient"[472]. Ethics of care offers a compromise between oblivious autonomy and oppressive paternalism. It promotes interdependence, the support of the carer in favour of the autonomy of the vulnerable person with three ideas: information, support and participation[473].

246. A strong case is made for continuous evaluation of decision-making capacity and most of all of a specific evaluation according to the area in the corpus of literature on the topic of research[474], as well as in the CIOMS guidelines[475]. There are a lot of different sets of criteria for analysing decision-making capacity in the literature, and methods are quite varied even only in the medical context according to local practices[476], to the medical specialisation or to the patient's medical condition[477]. Evaluation of decision-making capacity goes hand-in-hand with the perspective of assisting the vulnerable person in the informed-consent process, which has especially been developed around the topic of older adults[478].

247. The legal framework of the European Union is silent about such an issue, but the Council of Europe does offer a rich variety of provisions or even guiding instruments. The explanatory report to the Oviedo Convention specifies the precise motives that national law can use to determine if someone is legally competent or not: mental disorder, disease or similar

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[470] Elger B. S. & Anderes C., *Le paternalisme médical : mythe ou réalité ?: aspects philosophiques et empiriques d'un phénomène persistant*, Chêne-Bourg Coll. Médecine & Hygiène, 2010, 359 p ; Mislawski R., « Dignité, autonomie, vulnérabilité : Approche juridique », *in* Hirsch E. (dir.), *Traité de bioéthique I, Fondements, principes, repères*, Érès, Espace éthique, Toulouse, 2010, p. 274.

[471] Hauser J., "Une théorie générale de la protection du sujet vulnérable ? ", *Revue Lamy Droit Civil*, Vol. 38, 2011, p. 6 ; Bernheim-Desvaux S., "La difficile conciliation de la protection et de l'autonomie de la personne vulnérable", *Revue Juridique Personnes et Famille,* n°4, 2010, p. 2.

[472] Botbol-Baum M., "Pour sortir de la réification de la vulnérabilité, penser la vulnérabilité du sujet comme capacité", *International Journal of Bioethics,* Vol. 27, n°3, 2016, p. 18.

[473] Maillard N., *La vulnérabilité. Une nouvelle catégorie morale?*, Le champ éthique n°56, Labor et Fides, Geneva, 2011, p. 176.

[474] Bielby P., *Competence and vulnerability in biomedical research, op. cit*., p. 142.

[475] CIOMS Guidelines, Guideline 9 and guideline 16.

[476] Dunn L. B., Nowrangi M. A., Palmer B. W., Jeste D. V. & Saks E. R., "Assessing decisional capacity for clinical research or treatment: a review of instruments", *American Journal of Psychology*, n°163, 2006, pp. 1323-1334; Dunn L. B. & Misra S., "Research ethics issues in geriatric psychiatry", *op. cit*., p. 2; Meulenbroek O. *et al.*, "Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent", *European Geriatric Medicine*, n°1, 2010, p. 58.

[477] Barron J. S. *et al.*, "Informed consent for research participation in frail older persons", *Aging Clin Exp Res*, Vol. 16, n°1, 2004, p. 82.

[478] AGE Platform Europe & EDE (European Association for Directors of Residential Homes for the Elderly), European Charter of rights and responsibilities of older people in need of long-term care and assistance, June 2010, Article 2-1 ; Favier Y., "Vulnérabilité et fragilité : réflexion autour du consentement des personnes âgées", *RDSS,* 2015, p. 702 ; Bayer A. & Fish M., "The doctor's duty to the elderly patient in clinical trials", *Drugs Aging*, Vol. 20, n°15, 2003, p. 1087 et p. 1093 ; Berdeu D. *et al.*, "Clinical trials in the elderly: Ethical and methodologic considerations", *La Revue de Médecine Interne*, Vol. 21, n°7, 2000, Tableau I, p. 619.

motives[479]. Article 14 of the Additional Protocol on biomedical research requires investigators to actively verify that the participant is competent, especially when there is a doubt. But it is rather with two separate instruments that the Council of Europe has expressed the importance of the evaluation of decision-making capacity and harmonisation of this evaluation, first with a 1999 Recommendation on the legal protection of incapacitated adults[480], and second with the 2014 Guide on the decision-making process regarding medical treatment in end-of-life situations which goes into very much detail regarding the evaluation of capacity[481].

248. Regarding assistance in decision making in the European Union, the new Regulation 536/2014 did improve participation and respect of the opinion of minors and incapacitated adults. However, there were several failed attempts to introduce potentially useful provisions in this regulation, for instance the creation of a vulnerable category for persons with specific needs, including needs regarding information and consent process[482]. In the law of the Council of Europe, there is lack of mention on assisted decision-making as such in the Oviedo Convention or its Additional Protocol on biomedical research, except for the obligation to respect any objection even when formulated in a different way[483]. However, it appears to be a significant and established principle in the instruments of the Council of Europe for instance with recommendations or strategies on dependence, older adults, mental disorders or disabilities[484].

249. Finally, research advance directives can be used to indicate someone's wishes regarding potential participation in a clinical trial and according to the CIOMS, should be respected in the research setting as well[485]. It is not very clear to determine how the legal framework of the European Union would apprehend those should they exist, but it is safe to say that negative research advance directives would definitely be respected. The situation is similar regarding research advance directives in the legal framework of the Council of Europe, although there is a tendency and expertise that is a lot more developed and in favour of the general use of advance directives for research as studied earlier.

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[479] Explanatory report to the Oviedo Convention, § 43.

[480] Recommendation N°R(99)4 on principles concerning the legal protection of incapable adults, Adopted by the Committee of Ministers on 23 February 1999, at the 660th meeting of the Ministers' Deputies, Principle 3.1.

[481] Council of Europe, Bioethics Unit, The Guide on the decision-making process regarding medical treatment in end-of-life situations, May 2014, pp. 16-17.

[482] Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.,* Amendments 125 & 189.

[483] Explanatory report to the Additional Protocol, § 86.

[484] Recommendation (98)9 of the Committee of Ministers to member States on dependence, Adopted by the Committee of Ministers on 18 September 1998 at the 641st meeting of the Minister's Deputies, Recital 5, Principles 2 & 3 ; Recommendation (2004)10 of the Committee of Ministers to member States concerning the protection of the human rights and dignity of persons with mental disorder, Adopted by the Committee of Ministers on 22 September 2004 at the 896th meeting of the Minister's Deputies, Article 6 ; Recommendation CM/Rec(2014)2 of the Committee of Ministers to member States on the promotion of human rights of older persons, Adopted by the Committee of Ministers on 19 February 2014 at the 1192nd meeting of the Ministers' Deputies, §9.

[485] CIOMS Guidelines, Guideline 16.

### *2.2.2 Protection of systemic vulnerabilities and limited applicability of European law*

250. The possibilities of protection from the Council of Europe with the Additional Protocol on biomedical research are quite limited regarding third countries. Article 29 does require research projects conducted in third countries to be in conformity with the provisions of the Additional Protocol. However, the explanatory report has quite a pessimistic (and rather realistic) stance: "while it may be impracticable to implement all the detailed provisions contained in this Protocol when a research project is carried out in a State that is not party to the Protocol, it is nevertheless mandatory to observe the principles that those provisions develop"[486]. Surprisingly, this report even states that "the article is not intended to discourage otherwise ethical research in less developed countries that might utilise less expensive treatment than that routinely utilised in wealthier countries". However, it does require a double evaluation from the origin country in settings where ethical evaluation might be unreliable.

251. The legal framework of the European Union offers more concrete ways to protect against systemic vulnerabilities, but is also quite limited. According to article 25 of the new Regulation, clinical trials conducted outside the European Union "shall have been conducted in accordance with principles equivalent to those of this Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial". However, no further detail is given on how to actually prove equivalent principles have been respected. Several organs within the European Union are putting pressure on the European Commission in favour of stricter ethical rules for trials conducted in low resource settings, notably the European Group on Ethics[487], the European Medicines Agency[488] as well as some parliamentary members and even directorates[489]. These pressures mainly concern the conditions around informed-consent procedures and the responsibility of European sponsors to guarantee ethical principles, for instance through a commercial sanction (some parliamentary members unsuccessfully suggested to not apply data protection related to results of trials when those were conducted unethically[490], to not grant a marketing authorisation in those cases[491], or

[486] Explanatory report to the Additional Protocol, § 138.
[487] EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, pp. 14-15.
[488] EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit.*, p. 16.
[489] Schipper I., Directorate-General for external policies of the Union (DG-EXPO), European Parliament, Clinical trials in developing countries: How to protect people against unethical practices?, EXPO/B/DEVE/2008/45 PE 406.974, Brussels, 2009, p. 5.; See also repeated written questions of parliamentary members to the European Commission: Recours à des cobayes humains pour tester des médicaments européens dans des pays à bas ou moyens revenus, E-005984-15, Parliamentary written question, J. Sargentini J. (Verts/ALE) & M. Rivasi (Verts/ALE), 15 April 2015 ; Contrôle du caractère éthique de nouveaux médicaments : négligence des autorités d'enregistrement européenne, E-0777/2007, Parliamentary written question, M. Van den Berg (PSE), 19 February 2007 ; Lignes directrices contraignantes pour les tests pharmaceutiques réalisés à l'étranger, E-1805/2006, Commission response, M. Verheugen, 20 June 2006.
[490] Contrôle du caractère éthique de nouveaux médicaments : négligence des autorités d'enregistrement européenne, E-0777/2007, Parliamentary written question, M. Van den Berg (PSE), 19 February 2007.

to systematically make public the proven violations of ethical principles[492]). The consequences of such violations, according to article 94 of the new Regulation, have to be decided and organized nationally by Member States.

252. Nevertheless, Regulation 536/2014 does offer more ways to protect systemic vulnerabilities than Directive 2001/20/EC did, notably through improved provisions on transparency and inspections even outside European Union. In fact, after numerous pressures in that direction from parliamentary members[493], a big progress with the new Regulation is the obligation for European sponsors to register all clinical trials, even when conducted in third countries[494]. But most of all, on-site inspections of clinical trials conducted outside of the European Union could be developed in the future. There has been a continuous pressure in this direction from the European Parliament but also from the European Medicines Agency[495], which is particularly promising as the Agency is in charge of coordinating inspections by European Union Member States. In 2013 the Agency thus published criteria to be applied to choose the sites or clinical trials that should be inspected[496], including participation of vulnerable categories and research conduct in low resource settings. Finally, Regulations 536/2014 and 2017/556 are facilitating those inspections outside European Union[497], but most of all, the Commission has now the possibility to evaluate the legal framework of a third country to determine if it can safeguard research ethics principles from Regulation 536/2014[498].

253. Finally, another useful though indirect way for the European Union to avoid systemic vulnerabilities in clinical trials goes with framework programs which often promote capacity building in developing countries: scientific capacities but also institutional capacities and even ethics capacities and education. This was indeed the case with the first[499] and especially with the second European & Developing Countries Clinical Trials Partnership (EDCTP) which emphasized even more the importance of and means for compliance to ethics principles, to European law as

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491 EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit.*, p. 18 ; Essais cliniques dans les pays en développement, E-1167/2008, Parliamentary written question, D. Corbey (PSE) *et al.*, 5 March 2008.

492 Schipper I., DG EXPO, Clinical trials in developing countries: How to protect people against unethical practices?, *op. cit.*, p. 57.

493 Schipper I., DG EXPO, Clinical trials in developing countries: How to protect people against unethical practices?, *op. cit.*, p. 49 ; Essais cliniques dans les pays en développement, E-1167/2008, Commission response, M. Verheugen, 21 May 2008 ; Contrôle du caractère éthique de nouveaux médicaments : négligence des autorités d'enregistrement européenne, E-0777/2007, Parliamentary written question, M. Van den Berg (PSE), 19 February 2007.

494 Regulation 536/2014, Article 80, Article 81.4, Recitals 25 & 67.

495 EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit.*, p. 10.

496 EMA, Good Clinical Practice Inspectors Working Group (GCP IWG), Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections, EMA/INS/GCP/167386/2012, London, 2013.

497 Regulation 536/2014, Article 78.2 ; Regulation 2017/556, Article 1 & 7, Recital 3.

498 Regulation 536/2014, Recitals 65 et Article 79

499 Decision n° 1209/2003/EC of the European Parliament and of the Council of 16 June 2003 on Community participation in a research and development programme aimed at developing new clinical interventions to combat HIV/AIDS, malaria and tuberculosis through a long-term partnership between Europe and developing countries, undertaken by several Member States (Hereafter "Decision 1209/2003/EC").

well as national laws[500]. Regular calls for projects are thus published in order to finance, not directly clinical trials but projects that will improve ethics scrutiny in countries that need it most[501].

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254. The above analysis in Section 1 leads to the conclusion that the European legal frameworks for clinical trials do protect vulnerable people when they participate in clinical trials. Vulnerable categories are quite restricted in comparison to other areas of European law and though vulnerable participants receive protection for their health and safety, it is clear that the main criterion in clinical trials to designate vulnerable categories is the need for protection of autonomy. Protection is relatively harmonised between the instruments of the European Union and of the Council of Europe. However, decisional vulnerability affects a lot more people than those included within the few vulnerable categories, and it is these who are excluded from these categories who only receive limited protection from European law.

[500] Decision n° 556/2014/EU of the European Parliament and of the Council of 15 May 2014 on the participation of the Union in a second European and Developing Countries Clinical Trials Partnership Programme (EDCTP2) jointly undertaken by several Member States (Hereafter "Decision 556/2014/UE"), Annex I, §1, p. 48.
[501] Website of the EDCTP, http://www.edctp.org/call/ethics-regulatory-capacities-3/ [16 March 2018].

# Section II: Vulnerable people and representation in clinical trials

255. Clinical trials constitute a necessary tool to elaborate new and better drugs with increasing safety and efficacy. The perspective of vulnerability will change here from an inability to protect one's own interests to a special medical need, a particular physical or psychological condition that changes the safety and efficacy of a medicine. Too many people are excluded from clinical trials because of their inability to defend their interests, because of their poor medical condition or because of commercial considerations. However, this exclusion, even if sometimes well intentioned, is harmful on the long term as it marginalises whole groups of people by excluding them from trials and thereby its potential health benefits. In this section we are not intending to raise the issue of individual access to a trial in the hope of direct benefits, nor the issue of compassionate use of unlicensed drugs. We will be dealing with representation of vulnerable groups in clinical trials in a public health perspective.

256. In a first paragraph we will see that European law does protect some vulnerable patients against exclusion from clinical trials, but in a disordered manner (1). In a second paragraph we will adopt a prospective approach to examine ethical and legal principles that would legitimate a more general approach on health-vulnerability in clinical trials and adequate representation, or even rather equitable representation (2).

## 1 The disordered health promotion of vulnerable patients against exclusion from clinical trials

257. Vulnerable patients who are not represented in clinical trials are even more vulnerable when being administered a drug which, although in the market, has never been tested on persons representing their health vulnerability. European law provides for entire protection regimes against exclusion of (only) two groups of vulnerable patients from clinical trials (1.1), and provides for emerging processes which, although not comparable to the former palliative regimes, are also promoting representation of a few vulnerable groups in clinical trials (1.2).

### 1.1 Protection regimes against exclusion of vulnerable patients from clinical trials

258. Because some vulnerable patients urgently need better medicines, because they are particularly excluded from trials or because this group as a market is particularly unattractive to pharmaceutical industry, the European Union provided two palliative regimes, first in 2000 for

clinical trials on orphan medicines (1.1.1) and in 2006 for clinical trials on paediatric medicines (1.1.2).

### *1.1.1 Orphan medicines*

259. Orphan diseases marginalize patients due to their rarity (5 cases out of 10 000 people[502]). For most rare diseases no treatments are available and diagnostic is yet to be mastered. Due to the difficulties in gathering sufficient participants who are even rarer than the patients themselves, and most of all due to the lack of commercial attractiveness of marketing orphan diseases, there is a significant lack of research and of clinical trials related to orphan medicines[503]. Considering the scattering of patients suffering from orphan diseases, of researchers with an expertise on orphan medicines and the colossal costs of fundamental research and clinical trials, the implication of European law was especially justified in order to coordinate and rationalise expertise, costs and patient participation in these trials.

260. Hence the legislator of the European Union elaborated Regulation 141/2000[504] in order to promote clinical trials for orphan medicines. Article 4 created an expert committee within the European Medicines Agency in order to evaluate the orphan medicine designation and to produce scientific expertise. 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 provided for a centralised authorisation procedure for orphan medicines, which at the time did not exist yet, with fees exemption to the European Medicines Agency[505]. 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[506].

261. The initial success of this regulation has fallen short on the longer term. After a few years of implementation, applications for orphan medicines had significantly increased and some new treatments were developed[507]. However, these positive results were not sufficient to have a

[502] Regulation (EC) N° 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (Hereafter "Regulation 141/2000"), Recital 4.
[503] 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 (Hereafter "Communication from the Commission"); EURORDIS, EURORDIS' position on rare disease research, 2012 ; Regulation 141/2000, Recital 1.
[504] Regulation 141/2000.
[505] It was estimated in 2016 that the loss of the European Medicines Agency according to this fee exemption was around 78,4 millions euros. European Commission, Inventory of Union and Member State incentives to support research into, and the development and availability of orphan medicinal products, State of play 2015, SWD(2015) 13 final, p. 4.
[506] 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.
[507] European Commission, Inventory of Union and Member State incentives to support research into, and the development and availability of orphan medicinal products , *op. cit*., p. 13.

noticeable impact on the general quality of health protection for orphan diseases[508]. 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 attributed 620 million Euros for it[509]. Two committees were launched about rare diseases research: the EUCERD which later became CEG-RD and the IRDiRC. There has been an ongoing project of a European register for rare diseases notably in order to coordinate the 62 already existing ones in Europe[510], which may be easier to put in place once the Union portal will be functioning. The 8th framework program Horizon 2020 is supporting research on rare diseases, notably through the funding of the E-RARE project trying to coordinate activities between research centres in Europe[511].

262. To date, 150 marketing authorisations have been granted for orphan medicines, 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[512]. 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[513]. The same year, the European Commission published a report entitled "Rare diseases. A major unmet medical need", confirming that the incentives of Regulation 141/2000 are not enough to compensate the difficulties and costs related to the development of orphan medicines.

263. A few years later, a similar regime for paediatric medicines has been elaborated, which added two more years of marketing exclusivity to the 10 already granted, when a marketing authorisation is for a both orphan and paediatric medicine[514].

### *1.1.2 Paediatric medicines*

264. The clear lack of research on paediatric medicines has lead the European Union legislators to elaborate Regulation 1901/2006[515] (1.1.2.1). Results of the implementation of this regulation on paediatric trials and medicines have recently been evaluated after 10 years (2).

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[508] European Commission, Rare Diseases: Europe's challenges, *op. cit*., p. 3 ; Directorate General for Research, Ethics, research and globalisation. Europe and its partners building capacity in research ethics, *op. cit*., p. 34 ; European Commission, Inventory of Union and Member State incentives to support research into, and the development and availability of orphan medicinal products, *op. cit*., p. 13.

[509] European Commission, Inventory of Union and Member State incentives to support research into, and the development and availability of orphan medicinal products, SWD(2015) 13 final, State of play, p. 6.

[510] Execution report on the Communication from the Commission, European Commission, Rare Diseases: Europe's challenges, *op. cit*., p. 10.

[511] E-Rare Project Website, http://www.erare.eu/ [15 March 2018].

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

[513] European Parliament Resolution of 2 March 2017, Recital 50.

[514] Regulation (EC) N° 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Hereafter "Regulation 1901/2006"), Recital 29 & article 37.

#### *1.1.2.1 Incentives and obligations from Regulation 1901/2006*

265. Paediatric trials are more difficult due to legal incapacity of children but also due to their physical and physiological specificities compared to adults as well as in between different age subgroups from neonates to adolescents[516]. The lack of research has led to lack of treatments, and consequent frequent use of off label medications[517]. As the Regulation states in recital 3 : "Problems resulting from the absence of suitably adapted medicinal products for the paediatric population include inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality".

266. The Regulation 1901/2006 sets up obligations, rewards and incentives for development of paediatric medicines. According to articles 7, 8 and 17, at a very early stage of development of any medicine, sponsors have to elaborate, with the help and approval of the European Medicines Agency, a Paediatric Investigation Plan (PIP) which guarantees the paediatric application of any medicine under study. This applies to new medicine as well as already marketed medicines, unless a waiver has been agreed by the Agency for not testing a medication that will not benefit children. If sponsors comply with this obligation, they get a reward of six supplementary months of marketing exclusivity (article 36). If sponsors fail to comply, the Agency can block the corresponding marketing authorisation, financial sanctions can even be applied according to articles 49.4 and 50.1. Article 30 even created a new type of marketing authorisation, the paediatric use marketing authorisation (PUMA), meant to increase the development of paediatric indications for off-patent products with the perspective of getting a 10 year data exclusivity.

267. Other measures also indirectly help raising attractiveness of paediatric trials: the creation of the Paediatric Committee within the European Medicines Agency in charge of evaluating the PIPs, of providing free scientific advice to sponsors, or of updating a Union inventory of paediatric needs (articles 6, 23 and 43). Finally, new transparency rules were created, for instance with obligations to declare through a public database the start, end and interruption of paediatric trials as well as the results or reasons for interruptions. Sponsors also

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[515] Regulation 1901/2006.

[516] European Commission, Report from the Commission to the European Parliament and the Council. Better medicines for children - from concept to reality. General report on experience acquired as a result of the application of regulation (EC) no 1901/2006 on medicinal products for paediatric use, COM(2013) 443 final, Brussels, 2013, p. 3 ; Expert group on clinical trials, Ethical considerations for clinical trials on medicinal products conducted with minors, Recommendations for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 18 September 2017, revision 1, p. 4 ; 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 (Hereafter "Directive 2001/20/EC"), Recital 3.

[517] European Commission, Better medicines for children - from concept to reality, *op. cit*., p. 3.

have to communicate to national regulatory authorities any data related to clinical practice or phase IV trials on children (articles 45 and 46). Finally, a European network has been created within the Agency in order to coordinate all existing networks related to paediatric research, the European network for paediatric research.

268. In conclusion, the system elaborated in the paediatric regulation goes far beyond the orphan regulation as the latter only provides for incentives, which has shown in the results related to ten years of implementation of the paediatric regulation.

#### *1.1.2.2 10 years-assessment of the paediatric regulation*

269. Early on, the implementation of the paediatric Regulation was already deemed as a success[518]. For instance in 2012, 18 000 existing studies about 2200 marketed medicines had been communicated, showing how much information can be gathered just by sharing and centralising data, all the more than those information lead to the marketing of 16 new paediatric indications. Both the European Medicines Agency[519] and the European Commission[520] have published 10 years reports which summarize the main achievements, deficiencies and the way forward. For instance, the number of orphan diseases related PIPs are growing every year: 2 in 2008, 13 in 2012, 29 in 2013 and 49 in 2015. Another progress concerns neonates for which there has always been a particular reluctance to conduct clinical trials: from 470 in 2009, 13 000 neonates had been included in trials in 2015[521]. The Regulation has had some very successful results (see Table III). In a more general perspective, there are definitely more paediatric trials and more medicines that have been authorised for children thanks to the paediatric Regulation, and these numbers will grow further as a lot of PIPs have been agreed but not yet implemented.

270. The reports further show some pitfalls and new goals to be achieved as the European Parliament observed in its 2017 Resolution on the access to medicines in the European Union[522]. The PUMA for instance have constituted the greatest disappointments for the European legislators: only three PUMAs have been granted to date[523]. Moreover, the European Medicines Agency has highlighted the fact that there are still some areas where there are almost no PIPs, for instance in paediatric oncology for which, when there are treatments, some of them date from the 90's[524]. In general, the Agency has also expressed worries regarding the small percentage of PIPs that are actually fully conducted: a lot of trials are interrupted because PIPs

[518] EMA, Successes of the Paediatric Regulation after 5 years. August 2007-December 2012, EMA/250577/2013, London, 2013.
[519] EMA, 10-year report to the European Commission. General report on the experience acquired as a result of the application of the paediatric regulation, EMA/231225/2015, London, 2016.
[520] European Commission, Better medicines for children - from concept to reality, *op. cit*., p. 40
[521] EMA, 10-year report to the European Commission. General report on the experience acquired as a result of the application of the paediatric regulation, *op. cit*., p. 6.
[522] European Parliament Resolution of 2 March 2017, §65.
[523] European Commission, State of Paediatric Medicines in the EU. 10 years of the EU Paediatric Regulation, Report from the Commission to the European Parliament and the Council, COM (2017) 626, p. 13.
[524] EMA, 10-year report to the European Commission. General report on the experience acquired as a result of the application of the paediatric regulation, *op. cit*., p. 8.

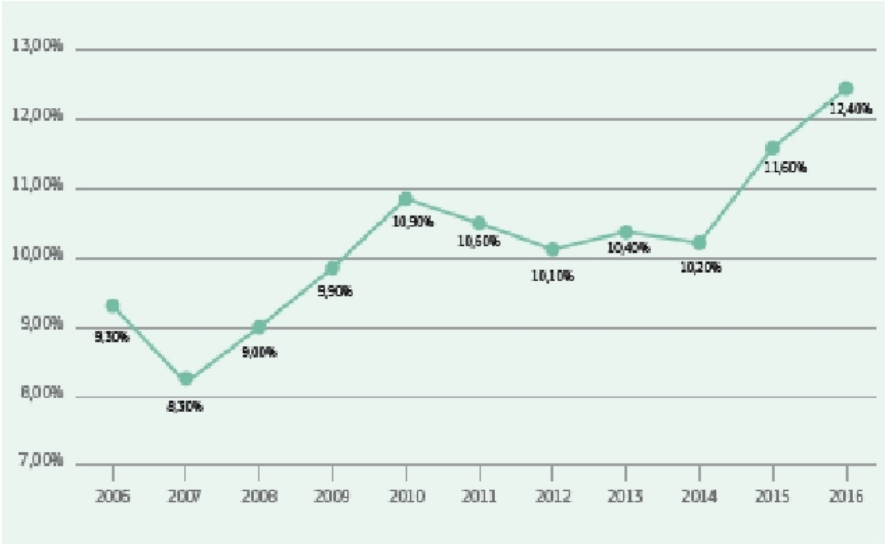
are elaborated very early in the process, and most of the time too early for sponsors and investigators to predict the paediatric relevance[525].

[525] European Commission, Better medicines for children - from concept to reality, *op. cit*., p. 88.

## Table III : Results of Regulation 1901/2006 after 10 years

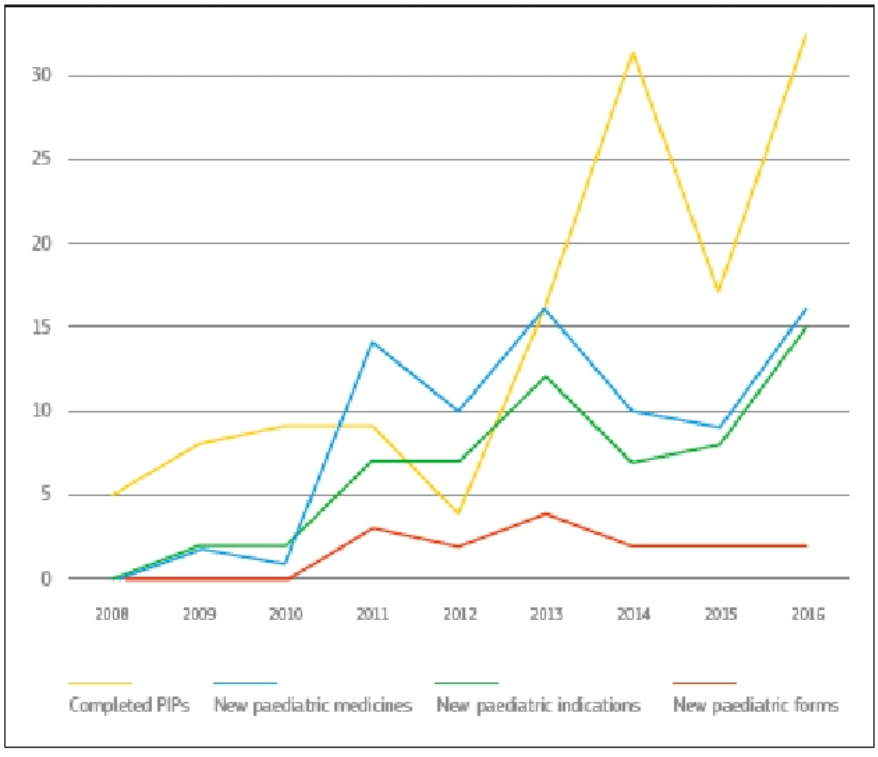
Source : European Commission, State of Paediatric Medicines in the EU. 10 years of the EU Paediatric Regulation, Report from the Commission to the European Parliament and the Council, COM (2017) 626 (pp. 26-27).

### More paediatric trials




*Source: EudraCT database*

### More authorised medicines




*Source: EMA databases (only centrally authorised medicinal products).*

## 1.2 EMERGING PROCESSES AGAINST EXCLUSION OF VULNERABLE PATIENTS FROM CLINICAL TRIALS

271. Apart from the previously mentioned palliative regimes against exclusion from clinical trials, there are other emerging processes that have the same goal but they lack a proper regime of incentives and obligations. The two types of vulnerable populations who could benefit from diverse provisions preventing their exclusion from clinical trials are the older adults (1.2.1) and those in developing countries (1.2.2).

### *1.2.1 Older adults*

272. In 2050, people older than 65 will constitute 28% of the population (18% in 2013), and among those, people aged over 80 will double in number[526]. Older adults are the largest consumers of medicines, 90% of adults aged over 80 consume over 10 medicines per day[527]. Needless to say it would be very important for those medicines to be tested on frail older people, which is better acknowledged now in European law but unfortunately has not resulted much progress yet, as extensively demonstrated before.

273. Older adults have a declining condition often accompanied with physical[528] as well as cognitive frailty[529]. The specific characteristics, when not studied, mean that physicians have no indications, which impedes informed prescription[530]. However, frailty makes clinical trials much more complicated, expensive, time consuming and above all, much more uncertain regarding ethical and scientific acceptability[531]. The PREDICT study at the scale of the European Union[532],

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526 Eurostat Website, http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing#Trends_of_population_ageing_in_the_EU [8 May 2015].

527 Fréour P., "Les personnes âgées prennent trop de médicaments", 17 September 2013, http://sante.lefigaro.fr/, [3 December 2013].

528 Fried L. P. *et al.*, "Frailty in older adults: Evidence for a phenotype", *op. cit*. ; EMA, Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials, EMA/CHMP/778709/2015, London, 2018, p. 8.

529 EMA, ICH Topic E7. Studies in support of special populations: Geriatrics. Questions and answers., EMA/CHMP/ICH/604661/2009, London, 2010, p. 2 ; Piette F. & Le Quintrec J.-L., "L'emploi d'un médicament nouveau chez les personnes âgées: Terra incognita", *Gérontologie et société*, Vol. 4, n°103, 2002, p. 80.

530 EMA, Geriatric Medicines Strategy, EMA/CHMP/137793/2011, London, 2011, p. 3 ; Bortz W., "Understanding frailty", *J Gerontol A Biol Sci Med Sci*, Vol. 65, n°3, 2010, pp. 255-257 ; Clegg A. *et al.,* "Frailty in elderly people", *op. cit.* ; Van Kan G. A. *et al*., "The assessment of frailty in older adults", *op. cit*.

531 Cherubini A. *et al*., "Fighting against age discrimination in clinical trials", *Journal of the American Geriatrics Society*, Vol. 58, n°9, 2010, p. 1792; Ridda J. *et al*., "Difficulties in recruiting older people in clinical trials: An examination of barriers and solutions", *Vaccine*, Vol. n°28, 2010, pp. 901-906 ; Marcantonio E. R. *et al.*, "Maximising clinical research participation in vulnerable older persons : Identification of barriers and motivators", *Journal of the American Geriatrics Society*, Vol. 56, n°8, 2008, pp. 1522-1527 ; Townsley C. A. *et al*., "Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials", *Journal of Clinical Oncology*, Vol. 23, n°13, 2005, pp. 3112-3124 ; Aapro M. S. *et al*., "Never too old? Age should not be a barrier to enrollment in cancer clinical trials", *Oncologist*, Vol. 10, n°3, 2005, pp. 198-204 ; Kaźmierska J., "Do we protect or discriminate? Representation of senior adults in clinical trials", *Reports of Practical Oncology & Radiotherapy*, Vol. 18, n°1, 2013, pp. 6-10.

532 Crome P. *et al.*, "Exclusion of older people from clinical trials. Professional views from nine European countries participating in the PREDICT study", *Drugs Aging*, Vol. 28, n°8, 2011, pp. 667-677.

ICH guidelines since 1993[533] which were then updated in 2008[534], and multiple scientific papers have denounced this deficiency and analysed its reasons for a long time. In spite of these repeated denunciations, there continues to be a lack of representation of older adults in clinical trials, which worsens even more the quality of treatment of this already vulnerable population[535].

274. The Council of Europe, although more and more interested in human rights of older adults for instance with the 2014 Recommendation[536], does not take the public health perspective on access to biomedical research. This may change in the future, as it has been one main topic during the 2017 conference for the 20th anniversary of the Oviedo organised by the DH-BIO[537].

275. European law has acknowledged several times the need for better representation of older adults in clinical drug trials, but without comparable decisions as for paediatric or orphan medicines. First of all, the European Commission does provide for regular funding through framework programs. However it is difficult to evaluate how much funding has been dedicated to geriatric clinical research as it is scattered between funding for diverse diseases which are frequent yet not exclusively related to very old age like cardiovascular or neurodegenerative diseases and general funding on the topic of ageing, which might favour clinical research on geriatric medicines but not directly. The European Commission estimates that more than 115 million Euros have been attributed to projects related to ageing[538].

276. Second of all, the European Medicines Agency has shown great interest in older adults representation in clinical trials since 2006[539]. Its activities have led to the elaboration, instead of a regulation like for paediatrics, to a strategy, the Geriatric Medicines strategy[540]. The goal of the Strategy was to enhance geriatric medicines and increase representation of old, very old and frail adults in clinical trials, for instance through the creation of the Geriatric Expert Group within the Agency giving free scientific advice and through the perspective of a stricter evaluation of research protocols in favour of geriatric patients. Although the means are quite similar to orphan or paediatric medicines, the fact that none of it is mandatory was its greatest

[533] ICH, Studies in support of special populations: Geriatrics E7, 1993.
[534] ICH, Final concept paper E7(R1) : Studies in support of special populations: Geriatrics, p. 1-3.
[535] Davidoff A. J. *et al*., "Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria", *J Am Geriatr Soc*, Vol. 63, n°3, 2015, pp. 486-500 ; Cherubini A. *et al*., "The persistent exclusion of older patients from ongoing clinical trials regarding heart failure", *Arch Intern Med*, Vol. 171, n°6, 2011, pp. 550-556; Lloyd-Williams F. *et al*., "Why are patients in clinical trials of heart failure not like those we see in everyday practice? ", *Journal of Clinical Epidemiology*, Vol. n°56, 2003, pp. 1157-1162.
[536] Recommendation CM/Rec(2014)2.
[537] Council of Europe, Conference proceedings, International Conference organized by the DH-BIO, 24-25 October 2017, Room 1 Palais de l'Europe, Strasbourg, https://rm.coe.int/english-proceedings-20-anni/168089e570 [16 May 2018], p. 38
[538] European Commission Website, https://ec.europa.eu/research/health/index.cfm?pg=area&areaname=ageing [23 March 2018].
[539] EMA, Adequacy of guidance on the elderly regarding medicinal products for human use, Doc. Ref. EMEA/498920/2006, London, 2006.
[540] EMA, Geriatric Medicines Strategy, EMA/CHMP/137793/2011, London, 2011.

shortcoming. The Geriatric medicines Strategy was never applied, except for the scientific activity of the Geriatric Expert Group for instance with guidelines on frailty[541] or various reviews and revisions of existing guidelines in Europe (93% would not comply) or of the geriatric data in marketed products (75% would be incomplete)[542]. The Agency has recently published a public consultation on a reflection paper about the development of medicines for geriatric use[543].

277. It seems thus that the activity of the European Union will remain focused on unbinding scientific guidelines for now. The new Regulation on clinical trials does not include elements in favour of older adults' representation. It does require the research protocol to justify age and sex distribution of participants compared to the future or probable patient population[544]. Recitals 15 and 19 of the Regulation do explicitly designate "frail or older people" as a "vulnerable group" requiring specific expertise and specific study of medicines' effects. However, these provisions will certainly not constitute a trigger for better representation of older adults in clinical trials, given that extensive regimes of incentives and obligations are barely working for orphan and paediatric medicines.

### *1.2.2 Developing countries*

278. Instead of "low resource settings" we will now only talk about "developing countries" because the goal here is to emphasize the ethnic, environmental and cultural differences of participants that have an impact on clinical trials. In fact, testing medicines with participants from developing countries can cause problems of extrapolation of the results for European patients. Still our focus will not be on a potential vulnerability of European patients due to the ethnic differences with trials participants. On the contrary, we will focus on the vulnerability of local participants of the developing countries (1.2.2.1), who most of the time lack health care and deem clinical trial participation as their only opportunity to access medical treatment, whereas the trials do not target medical conditions that are relevant for the local population. Organised exploitation is made possible by an, although improving, insufficient European legal framework (1.2.2.2).

#### *1.2.2.1 Vulnerability to health exploitation*

279. Participants from developing countries are not only vulnerable regarding their inability to protect their interests (social, economic and systemic factors as was mentioned before), they are also vulnerable because of their health and the impossibility for them to

[541] EMA, Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials, *op. cit*.
[542] EMA, Report analysis of scientific guidelines. EMA Geriatrics Medicines Strategy, EMA/352591/2013, 2013, p. 2.
[543] EMA, Reflection paper on the pharmaceutical development of medicines for use in the older population, Draft for public consultation, EMA/CHMP/QWP/292439/2017, London, 2017.
[544] Regulation 536/2014, Annex I, D.17.y combined with Article 6.1.b.i and Recital 14.

receive treatment[545]. The global health disparities are increasingly growing[546], and the proportion of trials conducted on poorer participants for richer patients is exploding[547]. Around 90% of the global research costs are allocated to only 10% of the health needs[548].

280. Sponsors tend to have more freedom to use placebos in developing countries than in most European countries. Any experimental treatment has to be compared either to a placebo or to the currently available treatment in order to prove efficacy. Comparing a treatment to a placebo can be dangerous if it means depriving the patient/participant of an effective treatment, especially in developing countries where the trial might be the only chance for a patient to get a medication. In order to legitimate their use of placebo, some sponsors use the argument that patients in developing countries would anyway not get any treatment at all, either because it would be too expensive, or because the country is not able to store and/or to commercialise the medication[549].

281. Another example would be the question of (free) access to the experimental medication that turned out to be safe and effective. There seem to be quite an ethical consensus on the (moral) obligation for sponsors to provide for the medicine after the end of the trial[550]. However recent and diverse reports have shown that in practice this ethical principle is rarely applied[551].

#### *1.2.2.2 Improving but insufficient European legal framework*

282. The European legal framework is increasingly getting involved on these issues, but it still seems insufficient. The explanatory report of the Additional Protocol to the Oviedo Convention on biomedical research specifies that "importance of the aim of research" required at article 7 implies relevance to the health needs of the local community[552]. The legal framework of the European Union is more extensive on the topic.

283. To begin with, several organs from the European Union are explicitly pleading for ethical principles to be respected when conducting clinical trials in developing countries. For

[545] EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit*., p. 24.
[546] EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 11 ; Benatar S. & Fleischer T., "Ethical issues in research in low-income countries", *op. cit*., p. 617.
[547] CCNE, Inégalités d'accès aux soins et dans la participation à la recherche à l'échelle mondiale – problèmes éthiques, Avis n°78, 18 September 2003, p. 3 ; EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 6.
[548] Nuffield Council on Bioethics, *The ethics of research related to healthcare in developing countries,* Nuffield Council on Bioethics, 24 April 2002, p. 21.
[549] "Economic (or logistical) reason for the unavailability of an established effective intervention cannot justify a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention outside the study". EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit*., p. 27.
[550] EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit*., p. 28 ; Declaration of Helsinki, § 34 ; CIOMS Guidelines, Guideline 2.
[551] Schipper I., DG EXPO, Clinical trials in developing countries: How to protect people against unethical practices?, *op. cit*., p. 56 ; Wemos Foundation, The clinical trials industry in South Africa: Ethics, rules and realities, 2013, p. 7 ; Public Eye, Industry-sponsored clinical drug trials in Egypt: ethical questions in a challenging context, *op. cit*., p. 50.
[552] Explanatory report to the Additional Protocol, § 30.

example, the sponsor has to guarantee other benefits than those from the trial itself, like basic health care for participants even when unrelated to the trial, ethical or scientific capacity building, and donation of equipment[553], to name a few. But the most important principle here is the principle that requires the clinical trial conducted in a developing country to target the specific needs of the local population[554]. As the European Group of Ethics emphasised, the condition can be specific to the local community, it can be particularly spread in this community, or the trial aims at elaborating a more general treatment but in the sole interest of the community (for instance in order to find a less expensive version of a medication) [555]. In order for European sponsors to grasp the medical priorities of a developing country, they must develop a partnership to collaborate with local physicians and experts[556].

284. The latter principle has been materialised thanks to the creation of the first partnership between European and developing countries EDCTP in 2003[557] that was mentioned previously. The ethical principle requiring sponsors to respond to local health needs is not only written down in the decision but it is concretely applied. In fact, EDCTP was first focussing on HIV/AIDS, malaria and tuberculosis which were deemed to be the three main poverty related diseases, for which the European Union doled about 200 million Euros (article 1.2). Among others, 100 clinical trials were conducted, 8 of them leading to improvement of treatments[558]. Although the EDCTP enabled professional education and specialisation of hundreds of African investigators as part of these collaborative clinical trials, the problem remains persistent and research is still insufficient and scattered[559]. Contributing for up to 22% of all global investments related to poverty and neglected infectious diseases[560], the European Union renewed the

[553] EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 18 ; Essais cliniques dans les pays en développement, E-1167/2008, Parliamentary written question, D. Corbey (PSE) et al., 5 March 2008.
[554] CIOMS Guidelines, Guideline 2.
[555] EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 16 ; Vray M., Simon F., Bompart F. *et al*., "Recommandations pour la recherche clinique dans les pays en développement", *op. cit*., p. 217 ; Caballero B., "Ethical issues for collaborative research in developing countries", *op. cit*., p. 717.
[556] EGE, Opinion n°17 on ethical aspects of clinical research in developing countries, 2003, p. 15 ; CCNE, Inégalités d'accès aux soins et dans la participation à la recherche à l'échelle mondiale – problèmes éthiques, *op. cit*., p. 12 ; "A disturbing issue for [private and public] sectors is the fact that most trials are designed and finalised before they are brought to us, with little if any room for changing the design or inclusion/exclusion criteria… Really they are using us for our numbers, they are not interested in any intellectual input we make in the developing world ; it is only about the number of patients we can recruit… Let's be honest, the drug companies are just trying to sell their products and believe the experts are all in the Northern Hemisphere ; we are non-entities". Wemos Foundation, The clinical trials industry in South Africa: Ethics, rules and realities, 2013, p. 31.
[557] Decision 1209/2003/EC.
[558] Decision 556/2014/UE, Recitals 5 & 8 ; European Commission, Executive summary of the impact assessment accompanying the document "Proposal for a Decision of the European Parliament and of the Council on the participation by the European Union in a second European and Developing Countries Clinical Trials Partnership programme (EDCTP2) undertaken by several Member States, SWD(2013) 254 final, Brussels, 10 July 2013.
[559] Decision 556/2014/UE, Recital 9.
[560] Decision 556/2014/UE, Recital 7.

partnership with EDCTP 2[561]. This time more neglected diseases were included like dengue, yellow fever, Ebola and many more[562]. The funding was tripled to 683 million Euros[563].

285. The European Parliament insisted again in its 2017 Resolution on access to quality medicines that local health needs in developing countries still require attention through capacity building and public-private partnerships. It invites the Union to further intensify the efforts, especially for vulnerable communities[564]. Recent calls for projects within EDCTP 2 launched in 2018 for instance concerned a phase I-III trial in Sub-Saharan Africa (30 millions for 3 to 5 projects)[565], or any clinical trial aimed at reducing health inequities of pregnant women, neonates or children (38 millions for 5 to 10 projects) [566].

286. In sum, European law does take into account health related vulnerabilities, but offers protection in a scattered manner: the form of protection may vary from an organized and complete palliative regime to various indirect and parallel instruments. The reasons for this choice of certain vulnerable groups over others are rather unclear. Nevertheless the very existence of such measures is promising for the awareness on health vulnerability that it brings. In the next paragraph, we will examine how to legally and ethically justify and generalize a mandatory promotion of the health needs of vulnerable and marginalized patients through an equitable representation in clinical trials.

## 2 Towards a mandatory health promotion of vulnerable patients through equitable representation in clinical trials

287. In this paragraph, an argument will be built for an equitable access to medicines through equitable representation in clinical trials. The notion of equity can act as a bridge between moral, legal and ethical norms, all of which refer to justice[567]. We begin by justifying the legitimacy of an ethical principle of health promotion of vulnerable patients through equitable representation in clinical trials (2.1) before examining the different elements from European law that could base and support such a claim (2.2).

[561] Decision 556/2014/UE.
[562] EDCTP2 Work plan 2017, 5 July 2017, p. 6.
[563] Decision 556/2014/UE, Article 2.
[564] European Parliament Resolution of 2 March 2017, §109.
[565] EDCTP Website, http://www.edctp.org/call/treatment-innovations-poverty-related-diseases/ [26 March 2018].
[566] EDCTP Website, http://www.edctp.org/call/clinical-trials-reduce-health-inequities-pregnant-women-newborns-children/ [26 March 2018].
[567] Jarrosson C & Testu F.-X., "Équité", *in Dictionnaire de la culture juridique*, Alland D. & Rials S. (eds.), PUF Coll. Quadrige, Paris, 2003, p. 638.

## 2.1 FOUNDATION OF AN ETHICAL PRINCIPLE OF EQUITABLE REPRESENTATION IN CLINICAL TRIALS

288. Observing the causes and consequences of health vulnerability (2.1.1), we will explain how it can be considered as a normative principle (2.1.2).

### *2.1.1 Vulnerability as an observation*

289. Exclusion of vulnerable patients from clinical trials can happen for two reasons. The first one is related to health issues of the participant. If the patient/participant is vulnerable, it is going to be more time consuming, more complex and more expensive to conduct a trial. Patients can have a decisional vulnerability as we have seen in Section 1 (legal incapacity, de facto incapacity as well as a simple inability to defend one's own interests), and investigators could be reluctant to include them because of all the supplementary protections (and thus complications) that it implies. Patients can also have a rather medical or health related vulnerability increasing the risks of adverse events during a clinical trial: comorbidities, chronic disease, palliative care[568], but also as we have seen before physical frailty, pregnancy or ethnic differences.

290. The second reason for exclusion of vulnerable patients is related to economic factors[569]. As we have seen with orphan or paediatric medicines, market needs do not always match health needs of vulnerable patients. To begin with, a clinical trial is limited in time and scale to reduce costs to the minimum that is already colossal. Recruiting a homogeneous and uncomplicated set of participants (male adult in good health versus frail elderly woman) will increase the chances of obtaining positive and homogeneous results[570]. Moreover, the exclusion of vulnerable patients from representation in clinical trials is also due to other economic factors, notably the choice of experimental treatment or disease, to develop a drug according to the disease prevalence or to the probable reimbursement. The reasonable chances of financial profitability do play a big role in pharmaceutical industries choosing their focus of research.

291. This exclusion leads to frequent off-label use of drugs, *i.e.* administration of a drug outside of the available information from the marketing authorisation[571]. As we have said before regarding orphan and paediatric medicines, the absence of information on medicines can lead to risks of overdosing and possible serious adverse effects, as well as risks of under-dosing and thus non-treatment. Risks that are not taken by vulnerable participants will inevitably be taken later

[568] Badano L. P. *et al.*, "Patients with chronic heart failure encountered in daily clinical practice are different from the 'typical' patient enrolled in therapeutic trials", *Ital Heart J*, Vol. 4, n°2, 2003, pp. 84-91 ; Keeley P. W., "Improving the evidence base in palliative medicine: a moral imperative", *Journal of Medical Ethics*, Vol. 34, 2008, pp. 757-760.

[569] Méchin H., "Intégration des perspectives du marché dans la stratégie de conduite de l'essai clinique", *in* Laude A. & Tabuteau D. (eds.), *Essais cliniques, quels risques ?*, PUF Coll. Droit et santé, Vendôme, 2007, p. 67.

[570] Rogers W. & Ballantyne A., "Justice in health research: What is the role of evidence-based medicine ? ", *Perspectives in Biology and Medicine*, Vol. 52, n°2, 2009, p. 191.

[571] Aronson J. K. & Ferner R. E., "Unlicensed and off-label uses of medicines: definitions and clarification of terminology", *British Journal of Clinical Pharmacology,* Vol. 83, n°12, 2017.

on by vulnerable patients but without the safety-net provided by the obligatory close surveillance and medical care during a clinical trial.

292. One particularly revealing example is that of pregnant women. There is very little information on the effects of drugs on pregnant women and on their foetus/embryo because of their almost systematic exclusion from clinical trials[572]. A British study showed that, among all prescriptions to pregnant women in one hospital during three months, only 25% were administered according to a pregnancy related marketing authorisation, 19% were based on literature studies, 55% were contraindicated, and 10% were deemed very dangerous[573]. The lack of information prevents prescribing physicians to know about the teratogenicity when administering a medication, *i.e.* the potential dangers for the embryo or foetus[574]. This led to the famous Thalidomide scandal when over 10 000 neonates suffered from congenital dysmorphia because of a simple medicine against nausea administered during pregnancy[575]. Moreover, the fear from potential unknown teratogenic effects prevents pregnant women from receiving the correct care, which can be very dangerous for instance if she is suffering from a chronic disease, diabetes or a psychiatric disease. Their exclusion from clinical trials also prevents physicians from getting the specific information that would be needed to adapt to the particularities of the pregnant body: « A pregnant woman is not just a woman with a bigger belly. The maternal-fetal-placental system brings its own pharmacokinetics and dynamics »[576].

293. Health vulnerability and consequent undocumented and dangerous off-label use does not only concern pregnant women, it is very frequent in vulnerable populations[577]. Another study reported that more than a third of prescriptions in palliative care were off-label[578], the same in psychiatric hospitals with about 40% of off-label prescriptions[579] as well as in oncology[580].

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[572] Lyerly A. D., Little M. O. & Faden R., "The second wave: Toward responsible inclusion of pregnant women in research", *International Journal of Feminist Approaches to Bioethics,* Vol. 1, n°2, 2008, p. 11.

[573] Herrin C., McManus A., & Weeks A., "Off-label prescribing during pregnancy in the UK: an analysis of 18,000 prescriptions in Liverpool Women's Hospital", *Int J Pharm Pract*, Vol. 18, n°4, 2010, pp. 226-229.

[574] Friedman J. M., "The obscenity of postmarketing surveillance for teratogenic effects", *Birth Defects Research, Part 1 : Clinical and Molecular Teratology,* Vol. 94, n°8, 2012, pp. 670-676; Schonfeld T., "The perils of protection: Vulnerability and women in clinical research", *Theoretical Medicine and Bioethics*, Vol. 34, n°3, 2013, pp. 197-198.

[575] Feldschreiber P. & Breckenridge A., "After Thalidomide – do we have the right balance between public health and intellectual property", *Reviews on Recent Clinical Trials,* Vol 10, 2015, p. 15.

[576] Lyerly A. D., Little M. O. & Faden R., "The second wave: Toward responsible inclusion of pregnant women in research", *op. cit*., p. 7; Schonfeld T., "The perils of protection: Vulnerability and women in clinical research", *op. cit.,* p. 197.

[577] Lenk C. & Duttge G., "Ethical and legal framework and regulation for off-label use : European perspective", *Therapeutics and Clinical Risk Management,* n°10, 2014, p. 538.

[578] Kwon J.H., Kim M.J., Bruera S., Park M., Bruera E., Hui D., "Off-Label Medication Use in the Inpatient Palliative Care Unit", *J Pain Symptom Manage*, Vol. 54, n°1, 2017, pp. 46-54 ; Culshaw J., Kendall D., Wilcock A., "Off-label prescribing in palliative care: a survey of independent prescribers", *Palliat Med*, Vol. 27, n°4, 2013, pp. 314-319.

[579] Martin-Latry K., Ricard C., Verdoux H., "A one-day survey of characteristics of off-label hospital prescription of psychotropic drugs", *Pharmacopsychiatry*, Vol. 40, n°3, 2007, pp. 116-120.

[580] Saiyed M. M., Ong P. S. & Chew L., "Off-label drug use in oncology: a systematic review of literature", *J Clin Pharm Ther*, Vol. 42, n°3, 2017, pp. 251-258.

### *2.1.2 Vulnerability as a normative principle*

294. Drawing from the idea of social justice, the notion of vulnerability triggers a renewed debate on the repartition and distribution of social goods[581]. We will first explain why we consider the principle of social justice as a basis for an ethical obligation to promote the health of vulnerable people (2.1.2.1) and then develop the idea of a social responsibility to represent them in clinical trials (2.1.2.2).

#### *2.1.2.1 Social justice as a basis for an ethical obligation to promote the health of vulnerable people*

295. John Rawls' theory of justice tends to be more prone to protect vulnerable people than other social justice theorists[582]. According to Rawls, distributive justice should permit to compensate inequities by providing for a set of primary goods[583]. Still a repeated critique against his theory is that it mainly evaluates inequities with the criteria of income or material goods[584], because he considers that some inequities cannot be compensated or would be too expensive to systematically compensate[585]. As a consequence, Rawls' theory of justice does not take into account very ill or seriously handicapped people[586]. Not only vulnerable people are not taken into account, but their "non-existence" prevents society from adapting to them as they would do for other members of society, which further marginalizes vulnerable people.

296. Amartya Sen and Martha Nussbaum's capability theory will bring a new perspective on social justice and on inclusion of vulnerable people[587]. They suggest focusing rather than on income, on the actual possibilities of a person to choose and achieve personal goals. « Capability concentrates on the opportunity to be able to have combinations of functionings (…), and the person is free to make use of this opportunity or not. A capability reflects the alternative combinations of functionings from which the person can choose one combination »[588]. This resonates with the lack of effectivity of vulnerable people's rights[589]: they have rights but are prevented or not given the opportunity to enjoy their rights. Capabilities emphasize, rather than

[581] Roman D., "Leçon 5 : Accès au droit et à la justice", *Vulnérabilité et droit*, 5 leçons du 13 février au 8 mai 2017, http://www.unamur.be/droit/chaire-francqui-diane-roman [21 December 2017].
[582] Maillard N., *La vulnérabilité. Une nouvelle catégorie morale?*, *op. cit*., p. 128 ; Rawls J., *A theory of Justice*, Belknap Press of Harvard University Press, Cambridge, 1971, 607 p.
[583] Rawls J., La justice comme équité. Une reformulation de Théorie de la justice, La Découverte, Paris, 2008, pp. 89-90.
[584] Nussbaum M. C., "Capabilities and human rights", *Fordham Law Review*, Vol. 66, n°2, 1997, p. 284.
[585] Daniels N., "L'extension de la justice comme équité à la santé et aux soins de santé", *Presses de Science Po (PFNSP)*, Vol. 2, n°34, 2009, p. 17.
[586] Rawls J., "Kantian constructivism in moral theory", *Journal of Philosophy,* Vol. 77, n°9, 1980, p. 546.
[587] Sen A., *L'idée de justice*, Flammarion Coll. Champs Essais, Paris, 2010, pp. 286-287 ; Nussbaum M. C., *Creating capabilities. The human development approach*, The Belknap Press of Harvard University Press, Cambridge, Massachusett, London, 2011, p. 37.
[588] Sen A., "Human rights and capabilities", *Journal of Human Development*, Vol. 6, n°2, 2005, pp. 154-155.
[589] Paillet É. & Richard P. (eds.), Effectivité des droits et vulnérabilité de la personne, op. cit.

on the passive perspective of not violating someone's liberty, on the active perspective of actively promoting adequate means for the person to exercise his or her liberty[590].

297. This is particularly true concerning the capability of health. Indeed, two philosophers – Norman Daniels and Sridhar Venkatapuram – have extended Rawls' theory of justice to suggest health related goods[591] or a "entitlement to the capability to be healthy"[592]. They are both basing their suggestion on the fact that health is both a means for other capabilities, a "meta-capability" [593], a primary good that has to be prior to everything else to guarantee normal functioning of a person[594] ; and an end in itself given how much impact social, cultural, environmental and political factors have on the quality of health protection[595]. When those factors can be controlled, for instance through political choices, it becomes a moral obligation for society to react and offer protection, especially concerning vulnerable people[596].

#### *2.1.2.1 Social responsibility to represent vulnerable people in clinical trials*

298. The level of health protection in a given society varies according to the context. The higher the general level of health, the lower is the tolerance for health problems[597]. "It makes profound sense that, because individuals living in rich countries continually push at the upper boundaries of longevity, individuals in such societies should be able to make claims for the social basis of the most commonly achieved life plans, or even states of well-being"[598]. As a consequence, in our modern societies where medicine is constantly improving and where personalised medicine is developing, it is less and less acceptable for vulnerable people to not have adequate treatments and be administered off-label drugs.

299. Claiming for an obligation to adequately and equitably include vulnerable patients in clinical trials can even be supported by ethics principles. The aspect of justice is now obvious here [599] as exclusion from clinical trials maintains and even worsens health disparities. Beneficence and non-maleficence[600] could also very much justify such an obligation in order to prevent then dangers of not treating a disease or off-label use: "Though proper protection of

[590] Hurst S., "Éthique et santé publique", *Les ateliers de l'éthique,* Vol. 7, n°3, 2012, p. 62 ; Nussbaum M. C., "Capabilities as fundamental entitlements: Sen and social justice", *Feminist Economics*, Vol. 9, n°2-3, 2003, p. 38.
[591] Daniels N., "L'extension de la justice comme équité à la santé et aux soins de santé", *op. cit*., p. 13.
[592] Venkatapuram S., *Health and justice: The capability to be healthy*, University of Cambridge, 2007, p. 53.
[593] *Ibid*., p. 9.
[594] Daniels N., "L'extension de la justice comme équité à la santé et aux soins de santé", *op. cit*., p. 13.
[595] *Ibid*., p. 21.
[596] Ruger, J. P., "Toward a theory of a right to health: capability and incompletely theorized agreements", *Yale Journal of Law and Humanities,* n°18, 2006, p. 318 ; Venkatapuram S., *Health and justice: The capability to be healthy*, *op. cit.,* pp. 193-194.
[597] Whitehead M. & Dahlgren G., Concepts and principles for tackling social inequities in health. Levelling up Part 1, WHO Regional Office for Europe, Copenhagen, 2007, p. 19 ; Hurst S., "Éthique et santé publique", *op. cit*., p. 61.
[598] Venkatapuram S., Health and justice: The capability to be healthy, op. cit., p. 205.
[599] Rogers W. & Ballantyne A., "Justice in health research: What is the role of evidence-based medicine ? ", *op. cit*., p. 199 ; EURORDIS, Position on rare disease research, 2012, p. 4.
[600] Beauchamp T. L. et Childress J. F., *Principles of biomedical ethics*, Oxford University Press, New York, 2013, 459 p.

vulnerable populations is without question mandatory, it appears that the strong focus on preventing harm has been realised mainly by setting high standards for the enrolment of such populations in clinical research projects. But the result has been a considerably less than satisfactory therapeutic situations for vulnerable populations in comparison with that for the non-vulnerable majority"[601].

300. The obligation to equitably include vulnerable people in clinical trials would also be supported by ethics of care, emphasising on interdependence and protection[602]. In fact, ethics of care also focuses on resilience and on giving the means to as much autonomy as possible and preventing situations from getting worse (rather than only treating the symptoms) [603]. As Joan Tronto criticises, ethics of care is, because of its emphasis on inter-dependence between individuals, too often limited to private relations whereas it should have and it definitely has a political aspect[604].

301. Finally, the idea of considering an equitable representation of vulnerable people in clinical trials as an ethical obligation is also supported by main research ethics stakeholders. This is for instance the case of the World Medical Association who, in the Declaration of Helsinki, considers 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).

302. This also the case of the CIOMS guidelines, especially in the 2016 revised version where several guidelines and provisions are dedicated to a claim of adequate representation of vulnerable participants in the perspective of a fair distribution of research benefits. 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, it is mainly Guideline 3 which is helpful for our claim as it urges "Sponsors, researchers, governmental authorities, research ethics committees and other stakeholders" to "ensure that the benefits and burdens of research are equitably distributed", and it even explicitly states: "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 unlikely to benefit from any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation. Groups that are under-represented in medical research should be provided appropriate access to participate".

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[601] Helmchen H. et al., From exclusion to inclusion. Improving clinical research in vulnerable people, op. cit., p. 45.

[602] Roman D., "Leçon inaugurale : la vulnérabilité régénère le droit!", *Vulnérabilité et droit*, 5 leçons du 13 février au 8 mai 2017, http://www.unamur.be/droit/chaire-francqui-diane-roman [29 April 2017].

[603] Jonas H., *Le principe de responsabilité,* Paris, Flammarion, 1995, p. 182 ; Blondel M., *La personne vulnérable en droit international*, Université de Bordeaux, 2015, p. 440.

[604] Tronto J., Un monde vulnérable. Pour une politique du care, Éditions La Découverte, Paris, 2009, p. 168. ; Maillard N., La vulnérabilité. Une nouvelle catégorie morale?, op. cit., p. 193.

303. Even if Guideline 3 does not use the explicit term “vulnerable”, and even if Guideline 15 on vulnerable groups does not mention the principle of equitable distribution of benefits of research because it is focused on decisional vulnerability, one can deduce the link between Guideline 3 and health related vulnerability. In fact, the principle is further developed in the comments of Guideline 3 for most vulnerable categories as well as in each respective guideline: low resource settings (Guideline 2), incapacitated adults (Guideline 16), children (Guideline 17), women (Guideline 18)[605] and pregnant women (Guideline 19).

## 2.2 ELEMENTS OF EUROPEAN LAW SUPPORTING EQUITABLE REPRESENTATION IN CLINICAL TRIALS

304. In the search for provisions in European law supporting a principle of equitable representation of vulnerable people in clinical trials, two main legal areas appear as a potential basis: fundamental rights and a potential principle of equitable access to benefits of clinical trials (2.2.1), and pharmaceuticals market law and notably the requirement to promote a high level of human health protection (2.2.2).

### *2.2.1 Fundamental rights and equitable access to benefits of clinical trials*

305. In favour of equitable access to benefits of clinical trials, we can find both rights of vulnerable patients (2.2.1.1) as well as obligations for pharmaceutical companies (2.2.1.2).

#### *2.2.1.1 Rights of vulnerable patients*

306. First of all, vulnerable patients should be guaranteed an equal health protection. This is the case for the Council of Europe with vulnerability being more and more used in the case law of the European Court of Human Rights as a tool to better protect equality[606] including sometimes in health protection[607]. Council of Europe’s Committee on Social Rights is also increasingly giving importance to health protection, particularly when it comes to vulnerable categories and when the health system is well-developed in the given Member State[608]. This is also the case in the law of the European Union, observing two growing issues: vulnerability

[605] Women of childbearing potential are also often excluded from trials, even if it would be far-stretched to consider them as having a health vulnerability. Schonfeld T., "The perils of protection: Vulnerability and women in clinical research", *op. cit.*

[606] For comprehensive case law overview and analysis : Peroni L. et Timmer A., "Vulnerable groups : The promise of an emerging concept in European human rights convention law", *International Journal of Constitutional Law*, Vol. 11, n°4, 2013, p. 1057

[607] ECtHR, Fourth Section, case of M.S. v. United-Kingdom, Application n°24527/08, 3 August 2012, §§ 41-44.

[608] For more details : Gründler T., "Le droit à la protection de la santé", *in* Roman D. (ed.), *"Droits des pauvres, pauvres droits ?" Recherches sur la justiciabilité des droits sociaux,* www.droits-sociaux.u-paris10.fr, 2010, p. 276 ; For instance : Council of Europe, Digest of the case law of the European Committee of Social Rights, 1 September 2008, p. 81.

through the lens of equality and non-discrimination and solidarity rights[609] as well as equity of health protection regarding vulnerable people[610]

307. Second of all, this equal health protection should lead to equal representation in clinical trials. The Council of Europe's Oviedo Convention protects equitable access to health care in its article 3, which has to be evaluated depending on the Member State's resources[611]. Article 5 on informed consent can actually also be used to claim an equal representation in clinical trials as "informed" consent is not possible for most vulnerable patients for which no data is available on specific safety and efficacy. The law of the European Union also protects informed consent to (future) treatments (for instance through article 3 of the Charter of fundamental rights), however, other provisions that relate more directly to equal representation of vulnerable people in clinical trials are not binding. The textbook published by the European Commission on research ethics does explicitly denounce discriminations and injustices in access for vulnerable people to benefits of research and safe treatments[612]. Moreover, the previously mentioned 2017 resolution of the European Parliament insists on access to quality medicines to be part of the fundamental right to health protection and health care access[613]. It also denounces the dangers of off-label use of medicines and the fact that 5% of hospital admissions are due to drugs' adverse effects and that adverse drug effects is the 5th major cause of death in the European Union[614]. Particular emphasis is put on vulnerable categories like children and older adults[615]. Even if this Resolution cannot have a direct impact on national legislations, it may have an impact on future European Union law or jurisprudence as it brings increasing awareness.

#### *2.2.1.2 Obligations of pharmaceutical companies*

308. Those patients' rights might however go against rights and freedoms of pharmaceutical companies. European law protects freedom of research in article 13 of the Charter of fundamental rights of the European Union, in article 15 of the Oviedo Convention and article 4 of its Additional Protocol on biomedical research. However, those rights are rather formulated in favour of researchers and their potential findings for public health, against

[609] O'Cinneide C., "The principle of equality and non-discrimination within the framework of the EU Charter and its potential application to social and solidarity rights", *in* Palmisano G. (ed.), *Making the Charter of fundamental rights a living instrument*, Brill Nijhoff, 2015, p. 213.

[610] Regulation (EU) N° 282/2014 of the European Parliament and of the Council of 11 March 2014 on the establishment of a third Programme for the Union's action in the field of health (2014-2020) and repealing Decision No 1350/2007/EC, Recitals 10 and 11 ; For more details on health protection in EU law : Bailleux A., "L'apport de la Charte des droits fondamentaux de l'Union européenne au 'droit' à la santé", *in* Brosset E., *Droit européen et protection de la santé. Bilans et perspectives*, Larcier – Bruylant, Bruxelles, 2015, p. 117; Lukas K., "The fundamental rights Charter of the European Union and the European social Charter of the Council of Europe: partners or rivals?", *in* Palmisano G. (ed.), *Making the Charter of fundamental rights a living instrument*, *op. cit*.

[611] Explanatory report to the Oviedo Convention, §§ 23, 26 & 27.

[612] European Commission, European textbook on ethics in research, EUR 24452 EN, Brussels, 2010, p. 120.

[613] European Parliament Resolution of 2 March 2017, Recitals A & C. and Observation 3.

[614] *Ibid*., Observation 16.

[615] European Parliament Resolution of 2 March 2017, Observation 23.

limitations from public authorities[616]. The reverse situation of public authorities wanting investigators to prioritize one type of research over another to favour vulnerable patients is not mentioned. In fact it seems far stretched from the current jurisprudence to impose research obligations to private companies, even on an important issue like health. The only possibility would be for judges to use limitations to freedom of expression (often related to freedom of research like in the case of Hadjanastassiou against Greece[617]) in order to prevent sponsors from hiding the lack of research and the consequent lack of data reliability regarding their marketed medications[618] and oblige them to write all cases in which it has not been tested and might have unpredictable adverse effects. However, the Parliamentary Assembly of the Council of Europe adopted a resolution and a following recommendation suggesting ways to guarantee the primacy of public health interests over the interests of the pharmaceutical industry[619]. Even if this document does not have a mandatory effect, it is still interesting to note that the Council of Europe is recommending measures to Members States for which it does not usually have a role, notably on the conditions for market authorisations or on how to guarantee the absence of conflic of interests bewteen public health authorities and private stakeholders from the pharmaceutical industry.

309. Because of its links with market considerations, pharmaceuticals related instruments are also related to freedoms to work, to conduct a business, as for instance protected in articles 15 and 16 of the Charter of fundamental rights of the European Union and in article 1 of the Social Charter. However, health interest is deemed to have priority over economic interests, especially regarding pharmaceuticals[620]. Moreover, health protection constitutes an exception, Member States are allowed to go against European Union market considerations when it aims to favour national protection of health (articles 36, 52 et 62 TFEU). European judges have been keen on accepting these exceptions even against former case law[621]. Unfortunately, isolated national measures are probably not the key for equitable representation of vulnerable people in clinical trials because they would be easy to circumvent by conducting a trial in another Member State or outside European Union.

310. In this same 2017 resolution, the European Parliament introduced in the field of access to medicines the notion of “social responsibility”[622] of pharmaceutical companies. This has been developed in international law especially concerning developing countries and

[616] Explanatory report to the Oviedo Convention, § 95 ; Explanatory report to the Additional Protocol, § 22.
[617] ECtHR, Chamber, Case of Hadjianastassiou v. Greece, Application n°12945/87, 16 December 1992, A 252, §39.
[618] Ovcearenco A., "La liberté de recherche des scientifiques au regard de l'article 10 de la Convention européenne des droits de l'homme", *Journal International de Bioéthique*, Vol. 15, n°1, 2004, p. 73.
[619] PACE, Resolution 2071 (2015), Public health and the interests of the Pharmaceutical industry : how to guarantee the primacy of public health interests ?, adopted on 29 September 2015.
[620] Brosset E., "La justification aux libertés pour des raisons de protection de la santé", *in* Brosset E., *Droit européen et protection de la santé. Bilans et perspectives*, *op. cit*., p. 102. ; Bonnichot J.-C., "La Cour de Justice et la santé publique: prudence imitée ou audace mesurée?", *Gazette du Palais*, n°171, 20 juin 2009.
[621] Brosset E., Brosset E., "La justification aux libertés pour des raisons de protection de la santé", *op. cit.*
[622] European Parliament Resolution of 2 March 2017, Recommendation 52.

emergency situations[623]. But the European Parliament is calling for national and European measures guaranteeing, in cooperation with the pharmaceutical industry, that research and development be oriented towards unmet medical needs[624]. In the Additional Protocol on biomedical research, such a suggestion 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[625]

### *2.2.2 Pharmaceuticals market and high level of human health protection*

311. European Union law is slowly acknowledging the importance of clinical trials for access to medicines for vulnerable populations (2.2.2.1), and promoting a legal framework fostering complementary trials on vulnerable people with authorized medicines (2.2.2.2).

#### *2.2.2.1 Clinical trials as a mean for access to medicines of vulnerable people*

312. Even when it refers to "medical vulnerability"[626], Council of Europe does not actually refer to a lack of access to quality medicines or to representation in clinical trials. Rather it only considers medical vulnerability as a cause for decisional vulnerability, which does not apply to our concern here.

313. On the contrary, the new clinical trials Regulation from the European Union has created a generic sub-category of vulnerable people, which could, although only potentially, serve as provision to introduce a protection regime for health vulnerability, pleading for better representation. In fact, article 10.4 of Regulation 536/2014 introduces a new vulnerable category: "specific groups or subgroups of subjects", which seems to be a more generic version of a parliamentary amendment initially referring to "persons with specific needs including the elderly, frail people and people with dementia"[627]. The latter has been complemented and moved to recital 15 referring to "vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders", and recital 19 referring to "other identified specific population groups, such as elderly people or people suffering from rare and ultra rare diseases".

[623] Lee J.-Y. & Hunt P., "Human rights responsibilities of pharmaceutical companies in relation to access to medicines", *Journal of Law, Medicine and Ethics,* Vol 40, 2012, p. 223.
[624] European Parliament Resolution of 2 March 2017, Recommendation 52 et 62.
[625] Explanatory report to the Additional Protocol, § 37.
[626] *Ibid*., § 69.
[627] Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.*, Amendment 125.

314. Article 10.4 does not go further than requiring a specific expertise for these "specific groups and subgroups" and thus does not acknowledge the need for representation in trials. This need is nonetheless highlighted in recital 14, added according to a parliamentary amendment[628]: "Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial". Moreover, this need is also underlined in recital 15: "In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including as regards requirements related to their specific characteristics and the protection of the health and well-being of subjects belonging to these groups". Finally, recital 13 and article 6 of Regulation 536/2014 do require future patients to be represented in clinical trials, as an evaluation criteria of relevance[629]. Another criteria of relevance given in article 6 is the compliance with national or European regulatory authorities' recommendations. Interestingly, this could be referring to the previously mentioned work of the European Medicines Agency on geriatric medicines or on health needs of developing countries.

315. This generic category is thus promising, especially as the European Parliament Resolution has raised the issue of access to quality medicines for vulnerable people and has put pressure on the European Commission to guarantee trial subject to better represent future patients and to take more into account unmet medical needs[630]. In particular, the Parliament is giving recommendations insisting on paediatric medicines (Recommendations 65-66), orphan medicines (73), poverty related diseases (109), various unmet medical needs regarding cancer (70), Hepatitis C (69) or antimicrobial agents (64), elderly people (63), pregnant women (63) and even female patients as such (68).

#### *2.2.2.2 A legal framework fostering complementary trials on authorized medicines*

316. Failure of clinical trials to provide enough information on vulnerable people being administered medicines can be compensated with a more proactive pharmacovigilance system. Pharmacovigilance is not directly our topic of interest, but it is worthwhile to quickly mention it for its complementary role. In fact, European Union law does allow for a few drug categories to be marketed although there were not enough trials conducted but with the condition of a

[628] Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.*, Amendment 17.
[629] This requirement was also added thanks to a parliamentary amendment. *Ibid*., Amendments 91& 95.
[630] European Parliament Resolution of 2 March 2017, Recommendation 63 & 89

proactive pharmacovigilance phase, which would later complete the needed information[631]. This is the case for certain serious or life-threatening conditions, for emergency public health situations and for orphan diseases. Furthermore, the European Medicines Agency has provided for good clinical practices regarding pharmacovigilance in vulnerable categories like children[632] and pregnant women[633], and is currently developing a similar instrument for older adults[634].

317. Nevertheless, pharmacovigilance might not be enough to palliate the aforementioned lacks of trials on vulnerable people – especially when there is no proactive obligation for sponsors like the one that exists for medical devices[635]. European Union law does offer the possibility to conduct or even to demand the conduct of complementary trials after marketing authorisations are granted. In fact, two separate provisions might foster complementary trials on vulnerable people. First, the Regulation 536/2014 introduced a new category of trials, "low intervention trials", for which conditions for authorizations will be facilitated because they concern already authorised medicinal products and only pose minimal risks and burdens to participants (article 2.2.3). This is particularly interesting for vulnerable people as the simplified and faster procedures are meant to be more attractive for sponsors (for instance regarding deadlines, insurance or consent procedures, see articles 76.3 and 3.3.c.)

318. Second, the new pharmacovigilance framework strengthened the provisions on post-marketing safety studies as a condition for obtaining and keeping a marketing authorisation. This new possibility has been described as one of the major input of the pharmacovigilance framework reform in 2010 and 2012[636]. They can be imposed by the European Commission when granting the marketing authorisation but also anytime during the pharmacovigilance phase, for instance if some adverse events are reported and justify a more proactive data collection through phase IV clinical trials[637]. Those studies can indeed be

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631 Commission Regulation (EC) N° 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, Recital 2 & Article 2.

632 EMA, Guideline on good pharmacovigilance practices (GVP). Product – or population specific considerations IV : Paediatric population, EMA/572054/2016, Draft for public consultation, London, 2017.

633 EMA, Guideline on the exposure to medicinal products during pregnancy : need for post-autorisation data, EMEA/CHMP/313666/2005, London, 2005.

634 EMA Website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation /document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c [20 March 2018]; Cerreta F. et Bowen D., "European Medicines Agencey (EMA): regulatory perspectives on geriatric medicines", *in* Stegemann S. (dir.), *Developing drug products in an aging society. From concept to prescribing,* AAPS Advances in the Pharmaceutical Sciences Series, Vol. 24, Springer, 2016, p. 718.

635 Rage-Andrieu V., "L'apport du règlement 2017/745 à l'évaluation clinique des dispositifs médicaux", *RDSS*, Vol. 1, 2018, p. 47.

636 Dagron S., "Regulating pharmaceuticals in the European Union: a human rights perspective", *in* den Exter A. (ed.), *European health law,* Maklu, 2017, p. 150.

637 Regulation (EC) N° 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, Article 9.4.c & b, Article 10.a.1.a ; Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Article 21.a.b & Article 22.a.1.a. ; Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a

especially useful to gather data on the long term use, on specific populations groups (like older adults or pregnant women for instance) or specific contexts of use (poly-medication for example) [638]. In its 2017 Resolution, the European Parliament emphasised again the importance for the European Commission to make sure this new possibility will be used by the European Medicines Agency and the number of post marketing safety studies will be increased[639].

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319. To conclude, the injustice created towards vulnerable patients is more and more acknowledged and is gaining some traction in the legal framework of the European Union regarding clinical trials. Specific regimes for paediatric and orphan medicines have now been implemented for more than a decade and have generated valuable, although still insufficient, results in terms of access to quality medicines. Although not going as far as implementing a specific regime for clinical trials for older adults similar to what is done for paediatric patients and those with rare disease, the European Union is attempting to promote research on unmet medical needs for older adults as well as for poverty related diseases in developing countries.

320. However, these provisions are quite scattered and, most importantly developed over political decisions lacking coherency as there are a lot more vulnerable groups who would need the same promotion of their health interests, the most illustrative example being for instance pregnant women. As we have demonstrated, this protection should rather stem from a more generic approach grounded in the need for equitable access to health care, and promoted through different instruments like specific phase III clinical trials, specific pharmacovigilance practices, or phase IV clinical trials be it low intervention trials or post marketing safety studies.

321. An optimistic point of view would consist in noting all the different tools available to promote an equitable representation of vulnerable people in clinical trials. However a more pessimistic perspective would be to recall that the implementation of those tools will depend on a political will with which the European Medicines Agency must come to terms with when giving advices and recommendations to the European Commission.

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European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, Recital 16 & Article 1.4.

[638] EMA, Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-autorisation safety studies (Rev 3), EMA/813938/2011 Rev3*, London, 2017, p. 6.

[639] European Parliament Resolution of 2 March 2017, Recommendation 74.

# Conclusion

322. This work analysed what constitutes a vulnerable group within clinical trials and critically examined how they are protected in the current European law. This analysis was carried out through the lens of type of risk or damage that could result when participating in a clinical trial. We found that there are two main types of risks in clinical trials: first of all the risk to autonomy and second, the risk to health.

323. Decisional vulnerability, *i.e.* the inability to protect one's own interests, seems to be the main criteria for designating a vulnerable group, notably vulnerable participants. Thus, the notion of vulnerability is quite reduced and is all the more so that European law is only recognizing and protecting legal or *de facto* incapacity. As demonstrated, a lot of decisional vulnerabilities can have unfortunate consequences on informed consent but are not sufficiently protected, for instance, in the cases of dependence, social disadvantage, lack of healthcare, mental or psychiatric difficulties or even just the fact of being in a low resource setting.

324. Interestingly, vulnerable people can also exclusively have health related vulnerability, such as a physically frail (but mentally competent) older adult. The confusion between health and decisional vulnerability stems from the frequent parallel existence of the two, for example, in children, or in elderly people who are both physically and cognitively frail. However, vulnerability can be solely related to health, as an inherent characteristic and/or as a consequence of exclusion from clinical trials and thereby, their benefits. European Union law offers protection against discrimination in representation in clinical trials, thanks to two palliative regimes for orphan and paediatric medicine, and scattered provisions for geriatric medicine and poverty related diseases. However, here again the recognition of vulnerability is very restricted as there are, given the abundant literature, many more vulnerable people who are under-represented in clinical trials, the best example being pregnant women.

325. The task of finding and highlighting a principle of protection of vulnerability in European law and ethics is tricky. As demonstrated, vulnerability is a complex and polysemous notion that is used in European law with great disparities and incoherences. Basing the reflection

on the type of risks that are specific to clinical trials, this thesis suggested a concept of vulnerability. The latter distinguished between decisional vulnerability and health related vulnerability, with the hope to better understand the rationale for protection offered in European law, and most of all to highlight the elements to improve in order to give more coherency (and better equity) to the European legal framework protecting vulnerable people in clinical trials.

326. The notion of vulnerability has constituted an enlightening lens through which we could analyse European law on clinical trials. Maybe science and technology will soon outrun these specific ethical reflexions on participation and representation of vulnerable people in clinical trials by using the power of statistics and big data and the future Union portal and database. Furthermore, *in silico* trials *i.e.* computer simulated trials[640] are currently emerging and penetrating European law[641]. They might considerably reduce development costs of drugs and make up for deficiencies regarding vulnerable people for instance regarding recruitment difficulties, as it has already started for orphan paediatric diseases[642] and hopefully as it will develop further.

[640] Viceconti M., Henney A. et Morley-Fletcher E., "*In silico* clinical trials : how computer simulation will transform the biomedical industry", *International Journal of Clinical Trials,* Vol. 3, n°2, 2016, pp. 37-46 ;

[641] In Silico trials are already fostered in the United States and will also be in Europe. FDA News Website, "Congress Pushes for In Silico Trials Modeling", 18 July 2017, https://www.fdanews.com/articles/182663-congress-pushes-for-in-silico-trials-modeling [3 June 2018]; A working group has been created in the European Medicines Agency on modeling and simulation. EMA Website, http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/PDCO/people_listing_000123.jsp&mid=WC0b01ac05806f485 [3 June 2018].

[642] Carlier A., Vasilevich A., Marechal M., de Boer J. et Geris L., "*In silico* clinical trials for pediatric orphan diseases", *Scientific reports,* n°8, 2018, pp. 2465-2473.

# Curriculum Vitae


# Éloïse GENNET

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**Foreign languages**:
**German,** proficient
**English,** proficient
**Spanish,** basic knowledge

## PROFESSIONAL EXPERIENCE

### Research positions

| | |
|---|---|
| Since February 2019 | **Post doc position, INSERM, UMR 1027.** Working on two H2020 projects (CINECA and EASI Genomics) within the ELSI work packages, dominantly on health and genomic data related questions |
| August 2012 to February 2018 | **Research assistant** at the **Institute for biomedical ethics**, University of Basel (Switzerland)<br>- Teaching and/or scientific coordination (in German language): contemporary debates in bioethics, Psyche Ethik Recht Tutoriat, Grundlagen in Bioethik…<br>- Administrative tasks: organize university courses, seminars and international conferences, translations in French/German/English, data entry, transcriptions, book indexing |

### Administrative positions

| | |
|---|---|
| October to December 2018 | Administrative assistant of the **Center of International and European studies and research (CERIC)** UMR DICE 7318, Aix-Marseille University: management of two master programms (timetables, external teachers, exams) and secretarial work (reception, activity report, scientific events) |
| September 2017 to August 2019 | Administrative assistant of the **Jean Monnet Excellence Center** du CERIC, Aix-Marseille University: Conferences organisation, digital communication (Website and social networks) |

### Internships

| | |
|---|---|
| September 2016 to February 2017 | **Traineeship at the Council of Europe**, Directorate General Human Rights and Rule of Law, Human Rights Directorate, Human Rights Policy and Co-operation Department, Bioethics.<br>Tasks varied between research reports and administrative missions: reports on topics including older adults' and children's rights in biomedicine or on the case law relative to surrogacy, organization of seminars, conferences, plenary assembly of the DH-BIO, translations and proof reading. |

| | |
|---|---|
| September 2013 | **Study visit at the Council of Europe**, Human Rights Law and Policy Division, Strasbourg (France). Punctual observation periods of the elaboration by the CDDH-AGE group of the Recommendation CM/Rec(2014)2 on the promotion of human rights of older persons. |
| May-August 2011 | **Internship in the *Espace Éthique Méditerranéen,*** Hospital La Timone (Marseille, France). Research in European and comparative law related to bioethics. |

## EDUCATION

| | |
|---|---|
| 2012-2018 | **Joint PhD (Cotutelle de thèse)**: *Vulnerable people and clinical trials. Reflections in European law,* defended on 28 September 2018.<br>- **PhD in law**, Dr. iur. from the legal faculty of the University of Aix-Marseille (France)<br>- **PhD in bioethics**, Dr. sc. med. from the medical faculty of the University of Basel (Switzerland)<br>- **PhD prize in European law** from the legal faculty of Aix-Marseille<br>Complementary education during the PhD (mostly in English or German language)<br>- International Summer School of Mercantour, 2017<br>- Mentoring program between Basel University and Novartis, Antelope@Novartis, 2015<br>- Master Class for PhD Students organized by the Association JC - RDST (Jeunes chercheurs - Réseau Droit Sciences et Techniques) in Nantes (France), Summer 2014<br>- Summer school "Ethical challenges in a European perspective", in Strasbourg (France), Summer 2013<br>- Introduction to philosophy, mixed methods research, statistics, empirical quantitative methods |
| 2012 | **Master's degree in « Private and public health law »,** Aix-Marseille University, top two grades.<br>- Dissertation: « *Fundamental rights and common bioethics law in Europe* ».<br>- 1st year research report: « *Reification of the human body* » |
| 2010 | **Bachelor's degree in law**, Rennes 1 University (France), with distinction, **one year Erasmus** in Saarbrücken (Germany) |
| 2007 | **French scientific *Baccalauréat***, graduated with very good distinction. |
| 2002 | **Six-months linguistic exchange** in Hannover (Germany**)** with the Association *En famille International.* |

## OTHER EXPERIENCES

**SUMMER JOBS**

- 2007 to 2011: **Auxiliary nurse** (Dol-de-Bretagne, France) in a foster home for handicapped, demented and elderly people, team work to care for residents' personal hygiene, meals and entertainment
- 2005-2007: **Secretary in a medical practice** (Dol-de-Bretagne, France)

**DANCING**

- Former dancer of different companies: *Jeune Ballet Malouin* (2006-2008), *Jazzmatics* (2013-2014), *Funky Divas* (2016) and *Les Transe mutants* (2007-2008 and 2017-2018)
- Former member of the communication team: design of the website, social networks, digital communication, fund raising, competitions, and promotion for shows
- Occasional teaching activity in ballet and salsa

# PUBLICATIONS

## Peer-reviewed articles

T. Wangmo, S. Hauri, É. Gennet, E. Anane-Sarpong, V. Provoost & B. S. Elger, « An update on the "empirical turn" in bioethics: analysis of empirical research in nine bioethics journals », *BMC Medical Ethics,* Vol. 19, 2018, pp. 6-15.

É. Gennet & R. W. Kressig, « Les personnes âgées vulnérables dans les recherches biomédicales : quelles réponses du droit européen? », *Journal International de Bioéthique,* Vol. 27, n°3, 2016, pp. 117-143.

É. Gennet & A. Altavilla, « Paediatric research under the new EU regulation on clinical trials : old issues new challenges », *European Journal of Health Law*, Vol. 23, n°4, 2016, pp. 325-349.

R. Andorno, É. Gennet, K. Jongsma & B. S. Elger, « Integrating Advance Research Directives into the European Legal Framework », *European Journal of Health Law*, Vol. 23, n°2, 2016, pp. 158-173.

É. Gennet, R. Andorno & B. S. Elger, « Does the new EU Regulation on clinical trials adequately protect vulnerable research participants? », *Health Policy,* Vol. 119, n°7, 2015, pp. 925-931.

## Book chapters

B. S. Elger Elger & É. Gennet, « Personnes âgées privées de liberté et protection de leurs droits liés à la santé : cadre légal et dilemmes éthiques », *in* A.-S. Dupont & O. Guillod (dir.), *Réflexions romandes en droit de la santé : mélanges offerts à la Société suisse des juristes*, Dicke Verlag, Zurich, 2016, pp. 49-65.

É. Gennet, « Retour sur la réforme du droit de l'Union européenne en matière d'essais cliniques », *in* E. Brosset (dir.), *Droit européen et protection de la santé. Bilan et perspectives.* Bruylant, Brussels, 2015, 464 p., pp. 221-242.

## Contributions to group publications

Training and Resources in Research Ethics Evaluation (TRREE), Review of the draft CIOMS guidelines presented for public consultation, Position statement from TRREE, February 2016, http://elearning.trree.org/mod/forum/discuss.php?d=31 [June 2016].

## Presentations at international conferences

"Health vulnerability and the European framework on access to orphan medicines" (Invited conference). Oral presentation, Workshop on Innovative Medicine And Research: Ethical, Legal And Regulatory Issues, EAHL 7th Conference on Health law, "Innovation & Healthcare New challenges for Europe", organized by the European Association of Health Law under the auspices of the Secretary General of the Council of Europe in Toulouse (France), 25-27 September 2019.

"Vulnerable people and clinical trials. Reflexions in European law". Oral presentation, Young researchers' seminar, EAHL 7th Conference on Health law, "Innovation & Healthcare New challenges for Europe", organized by the European Association of Health Law under the auspices of the Secretary General of the Council of Europe in Toulouse (France), 25-27 September 2019.

"Health data and European research ethics: protecting the vulnerable". Oral presentation, EACME Annual Conference "Rethinking Ethics in 21st Century Europe", organized by the European Association of Centres of Medical Ethics in Oxford (UK), 12-14 September 2019.

"Vulnerable research subjects and the new EU regulation on clinical trials". Oral presentation, EACME Annual Conference "Frailty, vulnerability and social participation. Ethical, social and political challenges for an inclusive society", organized by the European Association of Centres of Medical Ethics in Lille (France), 2-4 October 2014.

"Defining an interdisciplinary research methodology linking legal, normative and empirical ethics". Session co-chair and oral presenter, 9th World Conference of the UNESCO Chair in bioethics in Naples (Italy), 19-21 November 2013.

"European fundamental rights, vulnerability and biomedical research on elderly people". Poster presentation, 9th Congress of the European Union Geriatric Medicine Society in Venice (Italy), 2-4 October 2013.