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

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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.

## 1 Introduction

All major international<sup>1</sup> and European<sup>2</sup> standards relating to biomedical research expressly stipulate that vulnerable research participants deserve special protection because they “may have

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<sup>1</sup> 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.

<sup>2</sup> 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.

an increased likelihood of being wronged or of incurring additional harm"<sup>3</sup>. 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<sup>4</sup>. 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.

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<sup>5</sup>, which will replace in 2016 the currently applicable 2001 Clinical Trials Directive (CTD)<sup>6</sup>. 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<sup>7</sup>. These 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.

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<sup>8</sup>. 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<sup>9</sup>.

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<sup>3</sup> 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.

<sup>4</sup> WMA, Declaration of Helsinki, §20.

<sup>5</sup> 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").

<sup>6</sup> 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").

<sup>7</sup> 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.

<sup>8</sup> 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.

<sup>9</sup> 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](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

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

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<sup>10</sup>, or that it is too difficult to conceptualize the notion of vulnerability<sup>11</sup>. This is why ethicists and lawmakers tend to adopt a so-called *labelling approach*: instead of giving an abstract definition of vulnerability, they give a list of populations who are considered vulnerable<sup>12</sup>. 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.

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<sup>13</sup>. 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.

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.

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

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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").

<sup>10</sup> Hurst S., "Vulnerability in research and health care; describing the elephant in the room?", *Bioethics*, Vol. 22, n°4, 2008, pp. 191-202.

<sup>11</sup> Schroeder D. et Genefas E., "Vulnerability : Too vague and too broad?", *Cambridge Quarterly of Healthcare Ethics*, n°18, 2009, pp. 113-121.

<sup>12</sup> 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.

<sup>13</sup> 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.

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.

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 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.

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

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)<sup>14</sup>.

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.

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"<sup>15</sup> vulnerable persons: those under hierarchical pressure, or socially or economically or educationally disadvantaged<sup>16</sup>. In this sense, some scholars distinguish between "intrinsic vulnerability" and "relational vulnerability".<sup>17</sup> The inability to give a truly free informed consent does not only result from the intrinsic frailty of potential participants (e.g. their

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<sup>14</sup> 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").

<sup>15</sup> 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.

<sup>16</sup> Denny C. C. & Grady C., "Clinical research with economically disadvantaged populations", *Journal of Medical Ethics*, Vol. 33, 2007, pp. 382-385.

<sup>17</sup> 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.

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<sup>18</sup>, sometimes abusing from the lack of money, from the lack of education, the lack of health care, or the lack of ethics committees.

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**

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"<sup>19</sup>, which has been denounced, consists in an under-representation in clinical trials, for instance of pregnant women<sup>20</sup>, very elderly<sup>21</sup> or palliative care populations<sup>22</sup>. 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<sup>23</sup>.

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"<sup>24</sup>. This principle obliges researchers to promote research benefitting persons who are particularly in need of suitable therapies because of their

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<sup>18</sup> 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.

<sup>19</sup> 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.

<sup>20</sup> 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.

<sup>21</sup> 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.

<sup>22</sup> Keeley P. W., "Improving the evidence base in palliative medicine: a moral imperative", *Journal of Medical Ethics*, Vol. 34, 2008, pp. 757-760.

<sup>23</sup> Regulation 1901/2006

<sup>24</sup> Eckenwiler L. A. et al., "Hopes for Helsinki: Reconsidering 'vulnerability'", *Journal of Medical Ethics*, Vol. 34, n°10, 2008, pp. 765-766.

physical or psychological vulnerability<sup>25</sup>. 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**

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.

##### **4.1 An improved but still unclear consideration of vulnerable populations**

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.

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.

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

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<sup>25</sup> 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.

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.

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<sup>26</sup>.

## **4.2 A legal protection of vulnerable participants lacking thoroughness**

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**

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.

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".

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.

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*.

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<sup>26</sup> 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.



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**

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.

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.

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).

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**

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***

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).

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***

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***

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).

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)

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 the 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***

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.

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**

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.

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.