Health Policy 119 (2015) 925–931

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

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

Éloïse Gennet[a,b,*], Roberto Andorno[c], Bernice Elger[d]

[a] Institute for Biomedical Ethics, University of Basel, Bernoullistrasse 28, 4056 Basel, Switzerland
[b] Centre de Droit de la Santé UMR 7268, University of Aix-Marseille, 5 avenue Robert Schuman, 13 628 Aix-en-Provence, France
[c] Law School, University of Zurich, Rämistrasse 74/65, 8001 Zurich, Switzerland
[d] Institute for Biomedical Ethics, University of Basel, Bernoullistrasse 28, 4056 Basel, Switzerland

ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form 23 March 2015
Accepted 15 April 2015

Keywords:
Biomedical research
Vulnerable populations
Health policy
Research ethics
Europe
Health legislation

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 [1,2] and European [3,4] 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." [5] 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 [6]. 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

* Corresponding author at: Institute for Biomedical Ethics Basel, Medical Faculty, Bernoullistrasse 28, 4056 Basel, Basel-Stadt, Switzerland. Tel.: +41 782003579.
E-mail addresses: eloise.gennet@unibas.ch, eloisegennet@gmail.com (É. Gennet), roberto.andorno@rwi.uzh.ch (R. Andorno), b.elger@unibas.ch (B. Elger).

http://dx.doi.org/10.1016/j.healthpol.2015.04.007
0168-8510/

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 N° 536/2014 [7], which will replace in May 2016 the currently applicable 2001 Clinical Trials Directive (CTD) [8]. 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 [9]. These problems were particularly exacerbated for multinational clinical trials – which concern almost any trial 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 [10]. 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 [11].

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 [12], or that it is too difficult to conceptualize the notion of vulnerability [13]. 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 [14]. Yet, as we will see below, this approach leads to both an overprotection of persons belonging to a vulnerable group, and an underprotection 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 [15]. 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 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, or 'therapeutic misconception'. The risk of health harm is the risk of greater negative health effects from the trial because of, for instance, disease, age, poly-medication, comorbidity, or pregnancy.

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 – risks of exploitation and risks of health harm – as a whole, which complicates the organisation of an appropriate protection for vulnerable research participants.

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;