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POINT OF VIEW

Application challenges of the new EU Clinical Trials Regulation

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Abstract
Purpose The purpose of this paper is to discuss the challenges of the upcoming policy change in the field of clinical drug trials due to the shift from the Clinical Trials Directive 2001/20/EC to the new Clinical Trials Regulation 536/2014, adopted in 2014. Although it is expected that the new EU Clinical Trials Regulation will increase Europe's competitiveness in clinical research, the paper argues that some measures to assure protection of research subjects should be taken before the Regulation comes into application in 2018.
Methods The methods used in this paper are comparative analysis of legal documents and related academic papers.
Results The new Regulation serves as an efficient means to harmonize the clinical drug trial evaluation procedures across the EU. However, its application also raises potential challenges regarding interests and safety of research subjects: first, due to the possibility of skipping the assessment and balancing of benefits and risks from the scope of ethical review and limiting such a review to only Part II issues of the assessment report; second, due to direct applicability of the Regulation's rather vague and too general requirements for investigator's qualifications which does not allow the assessors (ethics committees and (or) competent authorities) to introduce higher qualification requirements for the investigators conducting high-risk clinical drug trials in the national legislation.
Conclusions There is an urgent need to raise awareness and facilitate debate on potential application challenges of the new Regulation.

Keywords Research ethics · Ethics committees · Clinical drug trials · Clinical Trials Regulation

Introduction

In less than 2-year time, Europe will face an important policy change in the field of clinical drug trials (the "CDTs") due to the upcoming shift from the Clinical Trials Directive 2001/20/EC [1] (the "Directive") to the new Clinical Trials Regulation 536/2014 [2] (the "Regulation"), adopted in 2014. It was expected that the new Regulation would reduce existing bureaucratic barriers and increase competitiveness of Europe in the field of medicinal product development [3]. However, there has been surprisingly little attention paid in the academic literature to the potential challenges of the new regulatory regime, particularly regarding interests and safety of research subjects. Two such challenges will be discussed in this paper. First, marginalization of ethics committees[1] (the "ECs") by excluding the assessment and balancing of benefits and risks from the scope of ethical review; second, vague requirements for investigator's qualifications which make it possible for a junior medical doctor to be eligible to act as a principal investigator of phase I or II CDT. The urgent need to raise awareness and facilitate discussion on these and other potential

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[1] The term "marginalization of research ethics committees" was used in the Statement of the European Group on Ethics in Science and New Technologies (EGE) 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.

application challenges of the new Regulation is emphasized in the paper.

European clinical drug trial policy change

As claimed in the Explanatory Memorandum to the Regulation, the existing provisions of the Directive appear to have hampered the conduct of CDTs in Europe. For example, it was argued that the number of applications for CDTs decreased by 25% from 2007 to 2011; costs for conducting CDTs were significantly increased, and the average delay for launching a CDT increased by 90% to 152 days [4]. Although it has been admitted that it would be wrong to attribute the fall in CDT activity solely and exclusively to the Directive, the new Regulation is presented as a means to reduce bureaucratic barriers to the application procedure and the conduct of the CDTs as well as the way to restore the EU's competitiveness in this field [5].

However, at the same time, it is of paramount importance to assure that the amendments introduced by the new Regulation will not detrimentally affect the interests and safety of research subjects. Unfortunately, with few exceptions, these concerns have not been reflected in the academic literature. Therefore, it seems important now to raise some of these concerns, assuring some time for the discussion before the Regulation comes into application in 2018. For example, the overall value of the Regulation was recently questioned. It was claimed that the Regulation is just a part of the EU's focus on market optimization rather than a means to seek key public health objectives [6]. However, this paper will concentrate on two more specific threats to the interests of research subjects, which could still be prevented if adequately and timely addressed.

Marginalization of ECs

One particular concern has been raised in relation to the potential of the Regulation to narrow the role of ECs in the prior authorization procedure of CDTs. Despite the fact that some authors have flagged the problem shortly after the Regulation was approved [7], claiming that it "*defeats the role of ethics committees*" and also contradicts the most important international research ethics guidelines [8], so far, rather limited discussion has followed this very important warning.

The Regulation may weaken the quality of ethical review and consequently the protection of research subjects because it allows the individual EU member states (MSs) to skip one of the most fundamental components—the assessment and balancing of benefits and risks—from the scope of ethical review. The current Directive does not allow this to happen because it clearly defines the scope of ethics review explicitly including evaluation of the anticipated benefits and risks into its scope. On the other hand, the Regulation makes such a reduction of the ECs role possible because it divides the assessment procedure into two different parts. Part I of the assessment report includes some technical issues like manufacturing and labeling of medicinal products as well as scientific and methodological aspects of the CDT. However, its main overall objective is *the assessment of therapeutic and public health benefits as well as risks and inconveniences to research subjects* (Article 6, b i, ii of the Regulation). Part II of the assessment report includes locally relevant issues such as informed consent and recruitment of research subjects, rewarding or compensating research subjects, data protection, suitability of investigators and trial sites, and damage compensation. It should be noted that the Regulation does not explicitly assign what issues are to be assessed by ECs. Its Article 4 only states that "*The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorization of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned*." However, the Part II items are usually referred to as dealing with "locally relevant ethical aspects," while Part I is often presented as a "technical" and "scientific" one [9, 10]. This division of the assessment report is in itself a useful tool to better structure the complex procedure of the review. However, its simplistic interpretation may lead some MSs to limit the scope of ECs review to only the Part II issues.

The problem is that excluding such basic Part I issues as trial design and risk benefit ratio from the scope of ethical review, makes ECs work inherently incomplete and fragmented. To mention but few examples, such a restricted mode of ethical review would not enable ECs to deal with the choice of control, including the use of placebo; more specifically, ECs would not be involved in deliberations which might lead to the member state's refusal to accept Part I and authorize the CDT on the grounds of Article 8.2.a where "*participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned*," which can be seen as one of the most basic safeguards to protect interest of research subjects. Last but not least, excluding Part I from the ethical review also seems to exclude ECs from assuring the protection safeguards to some of the most vulnerable research populations. Included here are persons unable to consent, such as children, as a restricted scope of ethical review leaves to only the competent authority the decision if a particular trial imposes no more than minimal risk (again one of the most complex issues to be dealt with by ECs) in case of "non-therapeutic" CDTs [7, 11]. All the mentioned issues have been regarded as the most fundamental points of ethical review by all the international research ethics guidelines [12–14].

The most evident detrimental consequences of the mentioned scenarios may occur in the case when the sponsor decides to carry out CDT in only those MSs that limit the scope of ECs review to the Part II issues. Some sponsors can opt for these MSs, hoping to escape a thorough and critical evaluation of risks and benefits of ethically problematic trials [7]. It might be

counter argued, however, that it is very unlikely that only the MSs with a "narrow" scope of ethical review would be picked up by the sponsor to conduct a particular CDT. However, similar concerns regarding the protection of interests and safety of research subjects may be raised even in cases where some of the MSs involved in the assessment of CDT had adopted a comprehensive mode of ethical review encompassing both Part I and Part II issues; however, the Part I assessment is led by the so-called reporting Member State (RMS) with the "narrow" scope of ethical review freely suggested by the sponsor. The problem is that the Regulation provides a rather short-time periods for different parts of the assessment report. For example, although the Regulation leaves the final selection of the RMS for all MSs in each CDT, it is unlikely that other MSs will be able to express their willingness to be RMS within a very short legal timeframe, i.e., 3 days after submission of the application to the EU portal (Article 5.1). Furthermore, in case the RMS would have already been selected following the sponsor's proposal, the other MSs would only had a 12-day period after the initial assessment of the CDT application by the RMS (Article 6.5.b of the Regulation) to share any considerations, including those related to the assessment and balancing of benefits and risks. In addition, the MSs will only have 5 days to refuse the authorization of CDT on the grounds of Article 8.2. mentioned above (i.e., *to check if the subjects participating in the CDT do not receive an inferior treatment as compared to normal clinical practice in the Member State concerned*), after the final Part I of the assessment report is submitted by the RMS (Articles 6.6, 8.1).

Taking into account, these very short-time periods as well as high relevance of Part I assessment report issues for ethics review, it is very important to involve ECs into the CDT assessment process in all the countries chosen by the sponsor. Publicly available information shows that some EU countries, such as Denmark [15], Germany, Belgium [16], and Spain [17] have already committed themselves to the comprehensive model of ethics review. However, some other MSs, such as France, in the "pilot phase" of the CDT assessment expressed the intent to opt for a narrow model of ethics review covering only Part II issues of the assessment report [18]. Taking into account challenges raised by the new regulatory regime for the CDTs ethics review as well as some evidence that not all 28 EU MSs have established efficient systems of ECs [19], it is likely that some MSs might be tempted to choose logistically easier way (that is a narrow scope of ethics review), which unfortunately can marginalize ECs and weaken the protection of research subjects.

Vague requirements for investigator qualifications

The second concern regarding the protection of safety of research subjects is related to Article 49 of the Regulation, which provides for a definition of the investigator as "*a medical doctor as defined in national law, or a person following a profession which is recognized in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care*."

If taken literally, this provision could lead to the situation where in some countries a junior medical doctor (e.g., someone in his or her first years of residency) will be eligible to act as a principal investigator of phase I or II CDTs. The problem is that very often these trials include unproven interventions, in some cases leading to serious adverse reactions requiring highly qualified medical professionals capable to cope with them in a timely and efficient manner. At present, this scenario is prevented because the Directive still allows individual MSs to introduce additional qualification requirements for the investigators conducting higher risk CDTs in their national legislation. For example, it seems that a principal investigator conducting a particular CDT should be obliged to have a medical license in the medical field relevant to this CDT. Requirements to have a defined number of training hours in the principles of good clinical practice as well as a sufficient experience in patient care acquired after completion of the residency training seem to be also relevant [20].

However, it seems that the new Regulation will not allow the individual MSs to follow this route. Here, the Regulation must be directly applicable and does not allow MSs introducing additional qualification requirements for the medical doctors conducting CDTs and the Article 49 requirement of "*necessary scientific knowledge and experience in patient care*" seems to be applicable to only professionals other than the medical doctors. It might, of course, be argued that Article 49 should be interpreted in the light of the Preamble (para 45) of the Regulation, which says that "*The individuals involved in conducting a clinical trial, in particular investigators and other healthcare professionals, should be sufficiently qualified to perform their tasks….*" It might also be referred to paragraph 65 of the Annex I which reads "*Description of the qualification of the investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of good clinical practice or experience obtained from work with clinical trials and patient care shall be described*." However, neither the Preamble nor the Annex provide for more detailed criteria. This can raise uncertainty both for the ethics committees and (or) competent authorities (they will not have criteria established in advance to evaluate qualifications of investigators) as well as for investigators (they will not know what criteria they would have to follow to be eligible as an investigator in a particular CDT). In sum, it seems that the provisions of the new Regulation are too general and do not provide for a sufficient level of specificity and content that an instrument of this kind is supposed to do to harmonize the practices across the EU.

Concluding remarks

Although preparatory work has already been started in many MSs to meet the challenges of the assessment procedure of

CDTs when the Regulation comes into application in 2018, the concerns raised in this paper have not been adequately addressed. In the authors' view, the application guidelines for the new Regulation should explicitly address the research subject safety and interest concerns and be preferably developed on the EU[2] level. If this is not possible, the MSs should consider drafting such guidelines on the national level. These guidelines would facilitate the work of institutions assessing the CDTs applications, including assessment of investigator's qualifications. With regard to the ethical review by ECs—the MSs should be urged to implement a comprehensive model of ethical review and not to follow the simplistic version limiting the EC assessment to just Part II issues of the report.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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[2] For example, through an already existing expert groups established by the European Commission, like Ad hoc group for the development of implementing guidelines for Regulation (EU) no. 536/2014 on clinical trials on medicinal products for human use.