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New EU regulation on clinical trials: the impact on ethics and safeguards for participants

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Abstract

The European Commission has proposed a new regulation to replace the current clinical trials directive. The proposed regulation aims at accelerating the application procedure and simplifying and harmonising the administrative requirements for multi-centre trials across the European Union.

One striking feature of the proposed regulation is a two-tiered assessment, one at the central level, to be carried out by a reference member state, binding on all concerned member states; and one at the national level, where the ethics aspects will be assessed. Second, the proposal no longer requires the approval of the clinical trial application by a separate ethics committee. Third, it introduces the concept of "low intervention" trials that will undergo a "light" approval procedure.

The proposed regulation may stimulate clinical trials that yield substantial public health benefits. However, it is a step back in terms of protection of the rights and safety of trial participants. It undermines current frameworks for ethical review by not requiring the involvement of an ethics committee, and by insufficiently integrating the Declaration of Helsinki into assessment procedures at the national and European levels. The introduction of the risk-based approach needs more preparation as there is no consensus yet on key issues, such as how to define risk, and who is going to define it.

Introduction

Background of the new regulation

On July 17, 2012, the European Commission published a proposal for a regulation (1) on clinical trials repealing the existing directive on clinical trials- 2001/20/EC- (hereafter referred to as the directive). This directive has been severely criticised for contributing to a significant drop in the number of clinical trials conducted in Europe due to the administrative burden and corresponding delays and costs. The proposed regulation aims at accelerating the application procedure and simplifying and harmonising administrative requirements, especially for multi-centre trials across the European Union (EU).

The proposed regulation explained in short

The current directive requires the submission of separate application dossiers for each of the countries involved in a multicentre trial. The Commission now proposes the submission of one harmonised application dossier to a single portal managed by the European Commission. The assessment of the application will be split into two parts while making "a clear distinction between aspects where member states cooperate in the assessment and aspects of an intrinsic ethical or national/local nature where the assessment is made by each member state individually" (1:4). One reporting member state, selected by the sponsor, will lead the central assessment (part I) and each involved member state will assess the national/ethical aspects individually (part II). For both parts, very short timelines have been set. The assessment by the reporting member state will be binding on all concerned member states, and only in certain pre-defined cases has a state the right to "opt out" (1:33), and not allow the trial in its country. No option has been created for the concerned member states to influence the decision of the central assessment. Failure to meet the deadlines will be understood as tacit approval.

The proposed regulation chooses "not to interfere" with the member state's internal organization of the bodies involved

in the national/ethical authorisation (1:5). It also introduces a new subcategory of clinical trials, 'low intervention trials' (1:26) which are considered to have a lower risk profile and for which certain obligations are reduced.

Proposed changes

1. Major changes in ethical review

The first change related to ethical review is that the proposed regulation no longer requires the approval of the clinical trial application by an *ethics* committee. This is a major shift from the current directive which requires the establishment of ethics committees in all member states in order to ensure protection of trial subjects. The proposed regulation explicitly states that: "it does not regulate or harmonize the precise functioning of Ethics Committees, nor impose a systematic cooperation at an operational level between ethics committees in the EU [...].Rather the proposed Regulation leaves it up to member states to organize, internally, the attribution of tasks to different bodies" (1:5). The only requirement is that the application must be assessed by a "reasonable number of persons who are independent, who have collectively the necessary qualifications and experience in all relevant fields, including the view of lay persons" (1:5).

Second, the proposed regulation explicitly states that ethical issues should be assessed only at the national level and not during the centralised assessment (1:17). However, aspects which are covered in the central assessment include the anticipated therapeutic and public health benefits and the risks and inconveniences for the subject. These are of an intrinsically ethical nature and hence require an integrated *ethical*, medical and scientific assessment. If this is not done, subjects run the risk of participating in potentially harmful or unnecessary trials. One could contend that there are sufficient opportunities to safeguard the rights of trial subjects as the protocol will be checked for ethical aspects at the national level. However the proposed regulation seriously undermines this safeguard on three counts. First, it does not require *ethics* committees to carry out the ethics assessment, as was already explained above. Second, even though it says ethics should be dealt with at the national level, the proposed regulation severely limits the ethical criteria upon which the ethical assessment should be done (1:32). Important ethical issues such as the acceptance of placebo-controlled trials and post-trial treatment access, for example, are not mentioned. Third, the timeline allotted for the assessment to take place has been shortened from 60 days in the current directive, to 10 days in the proposed regulation.

In the proposed regulation, the European Commission offers no justification of why ethical review should be left completely to the national level. It seems to contradict point 66 of the Introduction which says: "Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while *ensuring the safety and rights of subjects,* cannot sufficiently be achieved by Member States and can by reason of the scale of the measure be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity, which determines when the EU is competent to legislate, as set out in Article 5 of the Treaty of the European Union." (1:25) Furthermore, the 'Charter of Fundamental Rights for the European Union' (binding law for most Member State s) includes a high level of human health protection in all its policies (2). In our opinion, the protection of trial subjects against unethical clinical trials is covered by this Charter and therefore provides the legal basis to also assess ethical aspects at the central level.

By including international ethical standards in the central assessment, protection of trial participants will be harmonised and better safeguarded in each country. For example, it often happens that a sponsor declares that the regulator demanded a placebo-controlled trial for scientific reasons. While western European ethics committees may reject it on ethical grounds, eastern European committees may accept it, subjecting eastern European participants to unethical clinical trials (3). If compliance with international ethical guidelines were to be assessed at the central level, such a double standard for western and eastern European participants would be avoided. This does not negate the right that member states have to assess the trial for compliance with national ethical guidelines and laws.

2. Effects on trial participants

The proposed regulation seriously undermines the ethical framework which the current directive had started to build. Currently the procedures, composition and quality of ethics committees across the EU vary greatly (4,5) and, as a result, clinical trial participants across Europe do not have the same levels of protection. The proposed regulation does not set out to harmonise the quality of European ethics committees to a high common standard, either by demanding clearly defined standards for individual ethics committees, or by demanding collaboration among ethics committees at the EU level. As a result, the quality of ethics committees across Europe runs the risk of becoming diluted in time. This lack of emphasis on ethics is in stark contrast to the emphasis the Commission has given to speeding up the approval process.

The proposed regulation introduces the subcategory of so-called 'low-intervention trials' which are considered to have a lower risk profile. This measure seems to correspond especially with the need for less red tape for non-commercial sponsors, academicians, or groups like cancer research associations testing different treatments. Many of these trials are driven by pressing public health needs (6) and the introduction of this subcategory would allow them to start faster and operate with less regulation. Such trials are considered less risky by the Commission than commercial trials because they experiment with drugs already on the market (7), for which reason the proposed regulation allows for less stringent rules (1:17) and shorter timelines for authorisation (1:35).

However, the fact that a drug is already on the market does not necessarily lower the risk for patients. Examples of studies that would have fallen into the category of low intervention

trials are the REGULATE study with benfluorex (Mediator) and the VIGOR study with rofecoxib (Vioxx) (8) which resulted in countless deaths.

According to the proposed regulation, low-intervention trials need not provide for damage compensation (be it insurance or indemnification) for the trial (1:9) (1:60). It is irresponsible to not demand insurance for trials aiming to improve treatments, or comparing drugs on the market. Nor is it responsible to introduce a risk-based approach without a consensus agreement on how to define the risk and without developing tools and guidelines on risk assessment.

The proposed regulation states that modifications only need to be subject to an authorisation procedure similar to the initial assessment "when those modifications have substantial impact on the safety or rights of the subjects"(1:18). However, there is no definition of what is "substantial", and the procedures are unclear (for example it is unclear who decides it is substantial) which also leads to a negative impact on the safeguards.

The official acceptance of co-sponsorship in the proposed regulation acknowledges the fact that "clinical trials are increasingly initiated by loose networks of scientists and scientific institutions with one Member State or across several Member States" and that these networks have "legal difficulties in forming, jointly, one legal entity to act as a 'single sponsor'" (1:9) which is currently required by the directive. Although the proposed regulation does specify the sponsor's responsibilities within co-sponsorships (1:59), it categorically rejects the need for the sponsor to cover "liability for harm of a patient"; the rules on "liability depend on the applicable national liability laws and are independent from the responsibility of a sponsor". Covering of liability therefore falls outside the scope of this regulation. However, when participants experience damage in a multicentre trial which includes third countries, how will they solve the question of liability when the legal entity is not identified? The obstacles for victims to start litigation are already insurmountable (9). The regulation only worsens the situation and leads to even fewer victims having access to compensation.

The proposed Regulation places the obligation on member states to set up a national indemnification mechanism which shall be free of charge for trials not intended for marketing authorisations, and subject to fee for all other trials. This will help, in particular, non-commercial sponsors who face high costs and great difficulty obtaining coverage (1:60). But it will also apply to commercial sponsors for whom it can be extremely beneficial (as they will profit from public money). Further, it is doubtful if all member states can afford and maintain such a scheme, and this can lead to double standards in compensating damage.

The last issue that potentially affects clinical trial safeguards concerns safety reporting. The proposed regulation requires only the reporting of *unexpected* adverse events that affect the benefit-risk balance through the EU portal. Some argue that all serious events should be reported as all of them could affect the benefit-risk balance (10).

Several of the changes mentioned above, such as the introduction of low intervention trials, the introduction of the principle of co-sponsorship and the less stringent rules on safety reporting are welcomed by non-commercial sponsors and seem to be designed to respond to their needs. However, the proposed regulation, as it is now, may undermine some existing safeguards for participants. The proposed regulation covers all clinical trials, of which the majority is commercially sponsored. It does not take sufficient account of the effect on commercially sponsored trials.

3. Effects on third countries

Although the proposed regulation is intended to govern clinical trials on European soil, it does include references to clinical trials in third countries with the aim of building in better safeguards.

First of all, it refers to clinical trials in third countries that have already been finalised and that are part of the application dossier. It states that they should be carried out according to principles equivalent to those set out in the regulation. However, it seems unlikely that compliance with ethical principles will be considered a priority by those bodies in Europe which will assess the application dossier.

Second, the proposed regulation gives the European Commission an opportunity to carry out inspections in third countries to establish whether the regulatory system in third countries is compliant with Good Clinical Practice and ethical standards (1:61). However, this measure will most likely not be taken seriously if the EU places so little emphasis on ethics in its own territory. Our main concern is that lowering of ethical requirements in Europe will ultimately have a negative spin- off on the protection of clinical trial participants outside Europe. The proposed regulation will most likely have a negative impact on ethics assessment during the market authorisation procedure for pharmaceuticals entering the EU market. Currently, the marketing authorisation in the EU requires ethics committee approval for clinical trials carried out in third countries. How can the European Medicines Agency (EMA) maintain this requirement, if the EU does not maintain it for its own territory? Will the EMA drop the requirement once the regulation is implemented? This would be another setback for the protection of trial participants; as it was when the US Food and Drugs Administration (FDA) decided that compliance with the Declaration of Helsinki (DOH) was no longer needed for trials carried out outside the US.

4. What should be done?

The regulation needs to be modified. In order to protect the rights and safety of clinical trial subjects it is necessary to assess ethical aspects of a clinical trial application not only at the *national* level but also at the *central* level. The aspects covered at the centralised level, part 1, assessment, are already of an intrinsically ethical nature; hence the proposed regulation should insist on the involvement of experts in medical ethics at this level. Although the proposed regulation refers to the DOH,

it does not firmly integrate crucial elements of the DOH in the assessment procedure. Essential requirements to protect the rights of trial participants such as post trial treatment access and justification of the use of a placebo should be mentioned in the proposed regulation. Assessment of compliance with international ethical guidelines at the central level will avoid double standards for participants in different countries.

As mentioned above, the diversity in the functioning of ethics committees leads to diverging levels of protection of citizens across Europe. Therefore the standards of ethics committees should be harmonised through clear requirements regarding composition and procedures. The development of a European body monitoring the quality of ethics committees across Europe could heighten the overall standard.

Further, the introduction of the binding single decision by only one reference state should be removed, the short timelines should be modified, and the 'tacit' authorisation removed.

The introduction of certain measures, such as the risk-based approach, co-sponsorship and the national indemnification mechanism, might have a negative impact on the rights and safety of the trial participants and definitely need more work in order to provide the maximum protection for trial subjects. Although there seems to be a broad consensus on adopting a risk-based approach to clinical trial regulation, there is no consensus on key issues, such as how to define the risk, and who is to define it. Tools and guidelines on risk assessment need to be developed.

Conclusion

The proposed regulation is very emphatic in terms of harmonisation and acceleration of the authorisation procedure. As such, the regulation could prove a stimulus to clinical trials that might yield substantial public health benefits. However, it is a step back in terms of protection of the rights and safety of trial participants. The proposed regulation undermines the current frameworks for ethical review by not requiring the involvement of an ethics committee, and by insufficiently integrating the Declaration of Helsinki into the assessment procedures at the national and the European level. Furthermore, the proposed regulation introduces concepts such as low risk trials and co-sponsorship which in the current formulation could jeopardise the position of clinical trial participants. This proposed regulation clearly gives more importance to the promotion of science and future public health benefits than to the rights and safety of the individual clinical trial participant. As such, the regulation contradicts the fundamental principle of medical research involving human beings as set out in the Declaration of Helsinki, in the Nuremberg Code, and in the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, namely that the well-being of the individual research subject must take precedence over all other interests.

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