What is the role of ethics committees after Regulation (EU) 536/2014?

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ABSTRACT

EU Regulation 536/2014 stipulates that when assessing applications for authorisation to conduct clinical trials, Member States should formulate a 'single decision'. This raises the problem of identifying: (1) the facility designated to express this 'single decision' and (2) the role of ethics committees in the decision-making process. The article addresses the consequences of the requirement that for each Member State the assessment of an application for approval to conduct a trial must take the form of a 'single decision' by the Member State concerned. Three possible approaches to the procedures for expressing that 'single decision' and to the role of ethics committees in the decision-making process are described, one of which is indicated as the preferred option.

INTRODUCTION

The need for a review of the regulations concerning clinical trials in Europe was widely recognised. Directive 2001/20/EC[1] had revealed numerous weaknesses, particularly in regard to: the excessive bureaucratic burden involved in complying with the administrative provisions it introduced, many of which were effectively unnecessary; the need for multiple applications for trials involving more than one Member State; the issues raised by divergent decisions, especially when these involved differences in the opinions expressed by ethics committees; the delays and uncertainties surrounding the granting of authorisations; discrepancies in the application of the Directive, due largely to inconsistencies in its interpretation across different Member States.[2,3] These circumstances made it increasingly difficult to undertake multinational clinical trials in the European Union. The debate as to how to move beyond this Directive involved numerous stakeholders[4] and lasted several years,[5] culminating in the adoption of Regulation (EU) 536/2014[6] (hereafter the 'Regulation').

The Regulation came into force on 16 June 2014 and shall apply after 28 May 2016, but in any event not until the portal and database provided for in the Regulation have been fully functional for 6 months. Among the Regulation's special objectives are the efficiency and rapidity of the procedures for approving trials, the simplification of sponsors' obligations and guaranteed public access to the data relating to trials.

Many of the procedures envisaged in the Regulation differ from those previously in force.[7] Notably, the new Regulation introduces a single application for approval and a single authorisation valid throughout the European Union. Applications for authorisation are to be submitted through a single, freely accessible European portal and database. The portal will be the single entry point for the submission of all data and information relating to clinical trials and the database will become the single repository of all information submitted through the portal. Information stored in the database will be accessible to the public, except where the protection of personal or commercially confidential data would be compromised. The Regulation also requires that a summary of the results of each trial, written in a manner understandable to lay persons, be published within 1 year of its conclusion.

The Regulation contains a significant novelty in the form of a new category of 'low-intervention clinical trials', for which a simplified procedure will apply. Directive 2001/20/EC was applicable to all interventional trials without distinction and regardless of the amount of risk involved (in other words, regardless of whether the trial was conducted for regulatory approval of new drugs, for the optimisation of treatment or treatment procedures or to compare the effectiveness of existing therapies).

Other significant changes concern: 'co-sponsorship', trials in emergency situations, informed consent in cluster trials and trials involving incapacitated persons or minors. There are nonetheless numerous observers who consider that, for a variety of motives, 'the approved document may still impair, rather than improve, the quality of the ethical review of trial protocols'.[8]

PARTS I AND II OF THE APPLICATION FOR AUTHORISATION TO CONDUCT A CLINICAL TRIAL

The Regulation divides the application for authorisation to conduct a new trial into two parts. Part I concerns the technical–scientific aspects (current knowledge, clinical question, clinical relevance, the hypothesis to be tested, objectives, endpoint, risk/benefit ratio, safety measures, etc), while part II concerns the ethical aspects at the level of each Member State (information given to patients, consent, selection of subjects, recruitment arrangements, suitability of researchers and of clinical trial sites, insurance, damage compensation, etc).

Part I is to be assessed by a 'Reporting Member State' (in agreement with the other 'Member States concerned'). The assessment report covering part I will be valid throughout the European Union, while in the case of part II each 'Member State concerned' will make an assessment for its own territory, involving one or more ethics committees in accordance with local feasibility conditions. Notification is to be given 'by way of one single decision' (Article 8). The 'single decision' of each

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Member State must take local feasibility conditions into account. Member States are free to decide how each 'single decision' is reached and which local ethics committees should be involved. The Regulation contains 85 introductory statements or 'whereas clauses'. 'Whereas clauses', meaning 'considering that', are the introductory statements forming the recital at the beginning of formal documents or contracts to explain the reasons and/or purpose of the document. The 'whereas clause' may properly be used in interpreting the text, but is not an essential component for its operative provisions. 'Whereas' n.18 states that:

> 'It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial and to organise the involvement of ethics committees within the timelines for the authorisation of that clinical trial as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State'.

In other words, each Member State has to decide how the competent authorities should cooperate effectively with one or more ethics committees to reach a national single decision within the brief timelines established in the Regulation. The definition of these procedures is, for each Member State, one of the key challenges involved in applying the Regulation and calls for a review of the functioning of ethics committees.

THE 'SINGLE DECISION' OF A MEMBER STATE

As just mentioned, the Regulation omits to establish the procedures to be followed when formulating the 'single decision' of each Member State or for the involvement of ethics committees to assess part II of applications. Whatever solution is adopted, it is appropriate that each committee involved in the assessment procedure comprise a limited number of members and be efficient in order to ensure full compliance with the timelines laid down in the Regulation. To this end, the committee members should be engaged on a full-time basis, their mandates should be brief (in order, among other things, to reduce as far as possible any conflicts of interest), they should be able to call upon selected external experts (also with brief mandates) and they should be independent of the regulatory authority.

The following paragraphs describe three possible alternative solutions that I consider practicable.

Solution n.1: a single national committee

The 'single decision' could be assigned to a single ad hoc ethics committee that would assess all the trials conducted throughout the national territory in accordance with the provisions of the Regulation. The promoters of a single committee envisage the total abolition of local ethics committees, although their existence, for the provision of advice on issues of clinical and research ethics within the facilities to which they are attached, is nonetheless not incompatible with the establishment of a single ethics committee with overall responsibility for decision-making.

Positive aspects:

- A single committee composed of a restricted number of members would contribute to efficiency and promptness in decision-making.

Negative aspects:

- A single committee might not be able to combine all the specialised skills necessary to assess all types of trial.
- The fact that such a committee would have to handle all requests for authorisation to conduct trials throughout the state would cause a serious work overload.
- Such a committee would have no territorial roots; its members would possibly have insufficient knowledge of the various Italian research centres and would therefore be unable to properly evaluate their suitability for proposed trials.
- Pressure from sponsors and possible conflicts of interest would be concentrated on a single body and few individuals.
- The total elimination of local committees would deprive the facilities with which they are affiliated of the valuable opinions they provide on both clinical and research issues.

Solution n.2: no more than 10 specialised national committees, plus local committees with territorial roots

Responsibility for reaching a 'single decision' could be assigned to a limited number of committees (not more than 10), each being established at national level and each representing a specific therapeutic field. As an example, one could be specialised in oncology, another in neurosciences and another in metabolic diseases. A coordinating mechanism would need to be put in place for the centralised handling of applications and assessments.

Alongside specialised committees, local ethics committees with territorial roots should be maintained (as suggested for solution n.1). These should liaise with the specialised committees and with the coordinating body. Each local committee would decide, in each case, on the participation of the research centre it represents, and the same committees would also provide advice on issues of clinical and research ethics.

Positive aspects:

- The specialised committees would together provide a range of multidisciplinary qualifications that it would be difficult to combine in a single committee. This solution would have the additional advantage that the decision-making powers and the pressures inevitably exerted by sponsors—as well as possible conflicts of interest—would be dispersed, rather than concentrated in a single body.
- This solution is particularly favourable as it would comply with the provisions of the Regulation while simultaneously not undermining the important function of local ethics committees in regional facilities.

Negative aspects:

- There could be an overlapping of specialisations among the committees.

Solution n.3: maintenance of the status quo, plus a coordinating committee (to be decided for each occasion) that would deliver the 'single decision'

The ethics committee of one of the national research centres participating in a multicentre international trial could act as coordinator and propose an opinion to the ethics committees of the other national participating institutions. On approval of this opinion, with possible modifications, by the majority of ethics committees involved, it would be adopted as the national 'single decision'. The role of coordinator for each trial could be assigned to the ethics committee attached to one or the other of the centres taking part in that particular trial based on the type of its involvement in the research.

The same solution could also be adopted in States in which ethics committees are territory based (ie, regional) rather than directly linked to a particular research centre. Because in some Member States ethics committees are affiliated to research centres or healthcare facilities while in others they operate on a territorial basis, the numbers of such committees vary widely among Member States (eg, Belgium 215, France 40, Germany

53, Poland 52, Spain 136, Sweden 6, UK, 104).[9] Whatever the situation, however, the role of coordinator would be assigned to a local committee on a case-by-case basis.

Positive aspects:

- The maintenance of territory-based ethics committees would prevent the loss of both the potential deriving from their vicinity to patients and a direct contact with the facilities conducting the trials.

Negative aspects:

- The involvement of large numbers of committees makes it difficult to adhere to the timelines set out in the Regulation.
- A large number of committees imply a risk that some of them may not meet the standards of efficiency and expertise in the different disciplines that need to be represented on the committee.
- The ethics committees linked to the more dynamic research centres in each nation would become dominant at national level, whereas the others would assume a subsidiary role.

Competing interests None declared.

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