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Title Page

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Abstract. Independent Ethics Committees play an important role in clinical trials as well as in all health-related research. Internationally, the national laws of the individual countries have guided their local development and organisation over the decades. Directive 2001/20/EC of the European Parliament and of the Council explicitly recognised the Ethics Committees' duty to protect the rights, safety and wellbeing of human subjects involved in trials and to provide public assurance of that protection. Regulation (EU) 536/2014, which repealed the aforesaid Directive, provides that a clinical trial must be subject to scientific and ethical review, without specifically defining what they consist in. The divide between the evaluation of the ethical value and the scientific value of a study is very faint and for some it may even appear a meaningless distinction. While Regulation (EU) 536/2014 requires Member States to ensure that Ethics Committees are involved in the assessment process within their national territory, it does not require such ethical assessment to be binding. This paper proposes a possible system for interaction between Ethics Committees and local regulatory authorities in which the meaning and purpose of the ethical assessment are conceptually clearly defined and not narrow.

Strengths and limitations of this study.

- the paper delves into a topic on which there is not full understanding and procedural consistency at the European level;
- the paper suggests a model to be discussed and shared;
- the paper does not delve into the internal discussion and legislation specific to each European country, especially when this is not available in English.

Introduction. Today, the commonly accepted basis for conducting clinical trials on humans is firmly founded on the protection of human rights and the dignity of the human being. The reference principles are clearly set out in the leading international guidance documents, such as the 2013 version of the World Medical Association's Declaration of Helsinki and Good Clinical Practice (GCP) **[1]**. Historically, the need to establish mandatory principles of behaviour is usually associated with the Nuremberg trials of 1946 **[2]** as a means of avoiding abusive situations in particular in favour of those in conditions of vulnerability **[3]**. Since then, there have been many regulatory efforts around the world to protect individuals in medical research and practice **[4]**. GCP is an internationally recognised set of ethical and scientific quality requirements, which are mandatory for providing public assurance that the results of clinical trials are reliable **[5]**. Certification of compliance with GCP is required for all submissions approved by regulatory agencies in the European Union, the USA, Japan, and Canada.

It is also worth mentioning the International Ethical Guidelines for Health-related Research Involving Humans drawn up by the Council for International Organizations of Medical Sciences (CIOMS) in concert with the World Health Organization (WHO). These guidelines state that the ethical justification for undertaking health-

related research involving humans is its scientific and social value. However, scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice **[6]**. The highest standards of care and protection should not be waived under any circumstances, even during a pandemic situation, such as that of the COVID-19 emergency, which forced ethics committees to adopt new work methods, and the pressure exerted on medical research must not result in trials that do not comply with all applicable ethical standards **[7-8]**.

Full compliance with these requirements does not seem to be something that can be taken for granted even today **[9]**. It is not possible, in fact, to state that the ethical principles recognised as fundamental are applied in a satisfactory and equitable way around the world and that no improvements to the supervision and review processes are necessary **[10 - 11]**. The very way in which independent review is conducted is far from procedurally incontrovertible **[12]**. There is a long-standing debate regarding the assessment of the quality of the work carried out by the Ethics Committees and the need to empirically verify whether this work actually improves the protection of individuals **[13-14-15-16]**.

It is therefore still necessary to identify the best practices or standards to be adopted in order to ensure adequate protection and to build community trust in research.

Before a clinical trial can start, the sponsor must apply for and be granted clinical trial authorisation (CTA) from the competent regulatory authority. Each EU Member State has its own regulatory authority. In addition to this authorisation, as is stated in the GCP guidelines, before initiating a trial, the investigator must obtain a favourable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

Worldwide, Institutional Review Boards (IRBs) **[17]** or Research Ethics Committees (RECs) **[5]** have the duty to ensure "*the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to independent Ethics Committees may differ among countries, but should allow the independent Ethics Committees to act in agreement with GCP as described in this guideline"* **[5].**

GCP has been incorporated into European legislation; in particular the "Clinical Trials Directive" - Directive 2001/20/EC of the European Parliament and of the Council - refers explicitly to it and defines the Ethics Committee as: "*an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent*" (Art. 2, k)**[18]**.

In 2014, Directive 2001/20/EC was replaced by Regulation (EU) no. 536/2014 on clinical trials on medicinal products for human use, which brought important changes to the organisational structure of clinical trials in Europe **[19-20]**. Although it came into force on 16 June 2014, its implementation was postponed until 31 January 2022, in that it was conditional to the development of a fully functional EU Clinical Trials Information System (CTIS). The Regulation has binding legal force for all EU Member States and stipulates that the study protocol must contain "*a statement that the clinical trial is to be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice*" (Annex 1, D 17(a)).

As mentioned previously, GCP attaches considerable significance to the ethical assessment by the Ethics Committees, making them guarantors of the general protection of the participating subjects, going well beyond the mere aspect of correct information for informed consent purposes. Ethics Committees are not the only subjects that have moral duties and responsibilities towards study participants, as these lie also with all the interested parties including the investigators, sponsors and regulators.

It is conceptually inappropriate to consider that certain aspects of a study design have to do with science and others with ethics, i.e. that statistical method regards science and the informed consent process regards ethics **[21-22]**. A poorly designed study will not be scientifically valid because it will not bring reliable results, nor will it be ethically valid because it will reflect professional negligence, a waste of resources or, in the worst case, the dissemination of unreliable results. A wide range of aspects contributes to determining the value and

acceptability of a study, some of which are complex to evaluate **[23-24]**. It is sufficient to consider, for example, the possible prevalence of commercial interests (for example, in a study in which the benefits to individuals or potential patients are negligible) or the true value of the research for society in relation to the use of public resources **[25-4]**.

A well-devised research protocol that does not protect the subjects involved may be scientifically valid, but it is not ethically acceptable in a society that puts the well-being and dignity of individuals first. The function of Research Ethics Committees constitutes the introduction, into an experimental process that could be imperfect, of a control system. "Ethics" here refers precisely to the scrutiny of a behaviour to appreciate its value in relation to shared principles and reference points. Ethics is not an abstract, philosophical dimension - at least in this particular context - it merely refers to the best possible behaviour expected of someone in a given situation.

In this paper, it is assumed that the behaviour of an investigator can be examined along three necessarily interrelated axes. The first axis is that of scientific action: it concerns the use of a rigorous methodology and the application of scientifically recognised principles. The second axis is that of human protection: it concerns respect for the rights and dignity of the subjects involved. The third axis is the regulatory one: it concerns knowledge and compliance with current regulations. In this perspective, the review by the Independent Committee should take place following these three axes of action; it is the impartial eye on the investigator's planned behaviour. It might be more appropriate to refer to it not as an 'ethics committee', but simply as a 'review committee'. **[26]**.

Regulation (EU) No. 536/2014: critical issues. According to Regulation (EU) No. 536/2014, a clinical trial must undergo scientific and ethical review. In the text, an 'Ethics Committee' is defined as "*an independent body established in a Member State in accordance with the local law and empowered to give opinions for the purposes of the Regulation, taking into account the views of laypersons, in particular patients or patients' organisations*". Regulation 536/2014 allows Member States full discretion regarding the pronouncement of the Ethics Committees, and prescribes: "*The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation 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*" (Art.4). The individual States must "*determine which body or bodies are appropriate for the purpose of evaluating an application for authorization to conduct a clinical trial and to organise the participation of ethics committees*" (recital no. 18) **[20]**. In summary, Part I includes general aspects such as those related to therapeutic benefits, risks to participants, and safety and quality of the therapeutic agent. Part II contains national aspects such as local methods of subject recruitment and the informed consent process.

This provision leaves the authorisation process undefined, particularly regarding the relations between the competent authorities and the Ethics Committees **[27-28-29]**. The Regulation gives Member States full discretion; it does not define the meaning of the assessment required of the Ethics Committees, nor whether it is binding or non-binding; nor whether Ethics Committees should liaise with the sponsor directly or through the competent authority. Some authors have emphasised that the uncertainty regarding these points could lead to diversities between the various countries as well as to situations of marginalisation and ineffectiveness of the action of Ethics Committees **[30-31],** whereas it would be desirable to work on quality standards and accreditation systems for these bodies **[32-33-34]**.

The possible decision to implement a narrow model, only involving Ethics Committees in Part II, could certainly lead to a situation in which participating subjects are not adequately protected, in breach of the Declaration of Helsinki and other international research ethics guidelines **[3]**.

Such a possible decision would also appear difficult to justify, given that the scientific and methodological elements contained in Part I are closely associated with the protection of the subjects involved and therefore with the ethicality of the research. The Part II assessment activity is closely intertwined with the Part I assessment activity, such as formulating the risk-benefit profile and disclosing it during the informed consent process.

The structure and legal basis of Research Ethics Committees in the various EU Member States vary significantly. As far back as 2013, the European Network of Research Ethics Committees (EUREC)

emphasised the importance of having these bodies review both parts I and II of the trial authorisation dossier and of making the authorisation to conduct a biomedical research project conditional to their issuance of a favourable opinion. It is essential to clarify the exact impact of a Research Ethics Committee assessment for the granting of a favourable opinion for the whole assessment process **[35]**.

The new framework requires the committee to issue a single opinion that applies to the entire territory of the Member State participating in a multicentre trial, regardless of whether the trial then takes place at different sites within that State. All Member States are therefore in the position of needing to adapt their national legislation on Ethics Committees in order to achieve a system capable of providing the enactment of the aforementioned single opinion.

Before Regulation (EU) No 536/2014 came into force, in order to start a clinical trial in Italy, it was necessary to obtain authorisation from the competent authority, the Italian Medicines Agency (AIFA), and from an Ethics Committee **[36]**. The opinion of the Ethics Committee was binding and covered all aspects of the submitted study, i.e. all those now provided for in Parts I and II of the Regulation.

At the current time, it has still not been established what form the ethical assessment should take.

It would be appropriate, at European level, to maintain a clear distinction between the work of the competent authority and that of the Ethics Committee, and for the latter's assessment to be traceable at all times, rather than be incorporated into the final assessment. A possible interaction model is proposed below.

A possible model for the role of Ethics Committees.

As required by the Regulation, a sponsor who intends to initiate a clinical trial must submit an application dossier to the Member States involved via the EU portal. Article 5 of the Regulation provides that a rapporteur Member State is to be appointed. The rapporteur Member State will be responsible for validating and evaluating applications, with the involvement of the other States involved in the clinical trial. Validation must take place within 10 days from the submission of the application dossier; the Member States involved may forward to the rapporteur Member State any comments relating to the validation of the application within seven days of submission of the application dossier. In the model proposed here, the rapporteur Member States must identify the relevant local Ethics Committee without delay and involve it as early as the validation phase **(Fig.1)**.

For clinical trials involving more than one State, the assessment process shall include three phases (Art. 6): **(a)** an initial assessment phase carried out by the rapporteur Member State within 26 days from the validation date; **(b)** a coordinated review phase conducted within 12 days from the end of the initial assessment phase and involving all Member States involved; and **(c)** a consolidation phase carried out by the rapporteur Member State within 7 days from the end of coordinated review phase.

At the end of the assessment process, the rapporteur Member State shall draw up an assessment report. It must contain one of the following conclusions concerning the aspects addressed in Part I (Art. 6): a) the conduct of the clinical trial is acceptable pursuant to the requirements set out in the Regulation; (b) the conduct of the clinical trial is acceptable pursuant to the requirements set out in the Regulation, but subject to compliance with specific conditions that must be specifically listed in the conclusion; or (c) the conduct of the clinical trial is not acceptable pursuant to the requirements set out in the Regulation.

As mentioned previously, since the Regulation makes no specific provision in this sense, each Member State is at liberty to define its own procedures for involving the Ethics Committees, as well as the specific procedure through which the Ethics Committees must carry out their evaluation; with regard to Part I in particular, the Regulation does not explicitly provide for the opinion of the Ethics Committee to be binding. This could result in a huge change in a country like Italy, where the legislation in force before the Regulation established that the favourable opinion of an Ethics Committee was binding for the start of clinical trial.

To our mind, it is very difficult to conceive the contrary, i.e. to deem it possible to carry out an experimental study that has been received an unfavourable Ethics Committee opinion. We believe that, despite the local organisational and structural differences, action must be taken at European level to harmonise the operation of Ethics Committees, particularly with regard to clinical trials.

In the model postulated and described here, the rapporteur Member State must immediately involve a local Ethics Committee, which must assess the protection afforded to the subjects of the clinical trial **(Fig.1)**. This assessment should form a separate part in the drafting of Part I assessment that the Member State shares with all the other Member States in the coordinated review phase and should contain a reasoned conclusion on the feasibility of the study. In this way, the Ethics Committee's assessment would not be incorporated into that carried out by the competent authority; rather it would maintain an autonomous character and, above all, its own conclusion. The other Member States involved could then consult it and use it to make their own further considerations.

The Regulation provides that, during the consolidation phase, the rapporteur Member State shall take into account the considerations of the other Member States concerned when finalising Part I of the assessment report and should record how all these considerations were dealt with. The opinion of the coordinating Ethics Committee should also be recorded.

It would be of fundamental importance to establish, consistently between the Member States, whether or not the assessment report – particularly the aspects covered by Part I - of the Ethics Committee is binding as this would be equivalent to establishing whether the Ethics Committee acts as a regulatory authority. We believe that in the context of clinical trial regulations, Ethics Committees are regulatory rather than advisory bodies. A negative opinion issued by these bodies cannot in actual fact be a negligible opinion, but rather a reason why it is right, as a precautionary measure, not to initiate the trial **[37]**.

Each Member State involved shall assess, in relation to its own territory, the application for authorisation with regard to the aspects included in Part II (Art.7) and must complete its assessment within forty-five days from the validation date by submitting it through the EU portal. Similarly to what happens for the phase I report, in the model proposed here, the local Ethics Committee carries out an assessment that remains visible and traceable **(Fig.2)**. An example of the format for the Ethics Committee assessment of parts I and II is provided in Boxes 1 and 2.

Box 1. Evaluation scheme for Ethics Committees, Part I, Reg. 536/2014.

ASSESSMENT REPORT PART I.
SECTION FOR ETHICS COMMITTEE:

Compliance with Good Clinical Practice ensures the reliability of the trial. Research Ethics Committees (RECs) have the duty to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance by, among other things, reviewing and providing a favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The Ethics Committee (reference),
with reference to compliance with the principles of WMA Declaration of Helsinky, the Good Clinical Practice and the requirements set out in the Regulation 536/2014, art. 6, expresses the following assessment of the study (reference):

Ethics Committee ASSESSMENT:
a) the conduct of the clinical trial is acceptable;
b) the conduct of the clinical trial is acceptable but subject to compliance with specific conditions which shall be specifically listed;
c) the conduct of the clinical trial is not acceptable;

Reasons for the assessment and any requests:

……
……
……

Box 2. Evaluation scheme for Ethics Committees, Part II, Reg. 536/2014.

ASSESSMENT REPORT PART II (LOCAL ASSESSMENT).
SECTION FOR ETHICS COMMITTEE:
EVALUATION BY THE ETHICS COMMITTEE
OF THE ASPECTS INCLUDED IN ART. 7, REG 536/2014.

Compliance with Good Clinical Practice ensures the reliability of the trial. Research Ethics Committees (RECs) have the duty to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance by, among other things, reviewing and providing a favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The Ethics Committee (reference),
with reference to (a) compliance with the requirements for informed consent as set out in Chapter V of Reg. 536/2014; (b) compliance of the arrangements for rewarding or compensating subjects with the requirements set out in Chapter V and investigators; 27.5.2014 EN Official Journal of the European Union L 158/17; (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V; (d) compliance with Directive 95/46/EC; (e) compliance with Article 49; (f) compliance with Article 50; (g) compliance with Article 76; (h) compliance with the applicable rules for the collection, storage and future use of biological samples of the subject, expresses the following assessment of the study (reference):

Ethics Committee ASSESSMENT:
a) the conduct of the clinical trial is acceptable;
b) the conduct of the clinical trial is acceptable but subject to compliance with specific conditions which shall be specifically listed;
c) the conduct of the clinical trial is not acceptable;

Reasons for the assessment and any requests:
.....
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Conclusion. Regulation (EU) No 536/2014 brought important changes to the organisational structure of clinical trials in the European Union. This reform has also affected the way ethics committees work, imposing a reflection on the meaning of their assessment. The Regulation requires that a clinical trial be subject to scientific and ethical review, but does not specify in detail how they should be conducted, leaving to the Member States to establish how the competent authorities and independent ethics committees should interact. It is important to point out that Reg. 536/2014 does not require that the ethical evaluation be binding by

effectively removing formal regulatory status from the ECs. Some authors have expressed concern that the discretion left to the Member States could lead, in some of them, to a weakening of the Ethics Committees' ethical function and assessment. GCPs attribute a broad meaning to the assessment by the Independent Committees, a supervisory role to ensure the general protection of the participating subjects, which can potentially affect all aspects of the study and therefore go beyond the aspect of correct information for informed consent purposes. It is conceptually inappropriate to hold that certain aspects of a clinical study regard science and others regard ethics, i.e. that statistical method regards science and the informed consent process regards ethics.

As an adjective, ethical refers to the goodness of all dimensions of a trial. The ethics of a study refers to every aspect of the behaviour that is expected of an investigator. In this paper, we assume that such behaviour can be examined along three necessarily interconnected axes: the axis of scientific action, that of the protection of subjects and that of compliance with legal provisions. If we focus on the part concerning the methods for acquiring informed consent, particularly for incapacitated subjects, we will be analysing above all the axis of protection. However, any consideration of the quality of existing behaviour will be an ethical consideration. Considerations regarding, for example, the publication of negative results are also important ethical considerations.

The independent Ethics Committees, understood as third parties, should be called on to express an opinion on clinical trials regarding the aspects included in both part I and part II of the Regulation (EU) No 536/2014. In the model proposed here, they should be involved from the validation phase and the assessment expressed should constitute a recognisable document in its own right, rather than being incorporated into the assessment by the rapporteur Member State.

This approach would help to ensure a clear conceptual definition of the role and function of these bodies, as is recognised internationally. The application of a uniform model in all EU Member States would encourage the development of standardised procedures aimed at achieving similar standards of protection in the different States. However, future research would be useful in order to investigate how multidisciplinary committees should actually act to ensure a high-quality review and how to develop consistency among them.

Competing Interests

The authors declare the absence of conflicts of interest.

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Contributorship statement

LR and CP contributed to the conceptualization of the work and the structuring of the concluding proposals. LR drafted the manuscript.

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[37] McGuinness S. Research ethics committees: the role of ethics in a regulatory authority. J Med Ethics 2008;34:695-700.

Fig. 1 Validation process, Reg EU 536/2014.

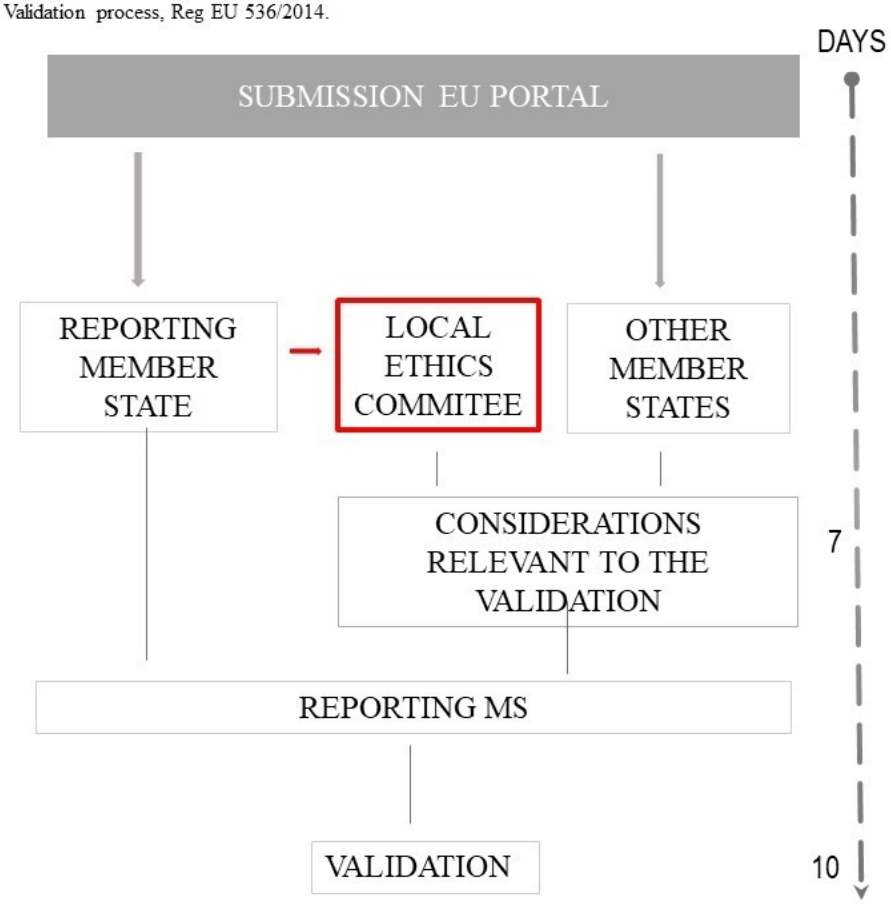

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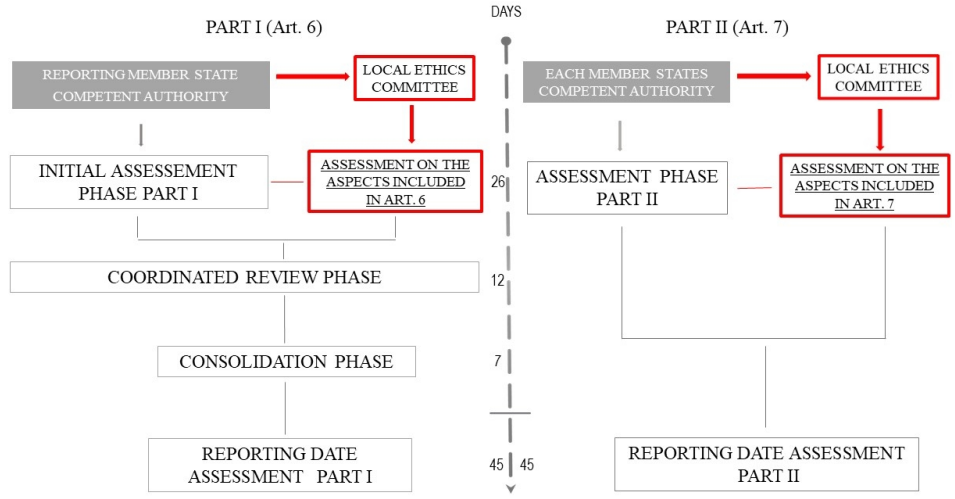
Fig. 2 Assessment process, Reg EU 536/2014.



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REGULATION (EU) 536/2014 AND THE ROLE OF ETHICS COMMITTEES: A PROPOSAL FOR A REVIEW SYSTEM MODEL

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Title Page

Title: REGULATION (EU) 536/2014 AND THE ROLE OF ETHICS COMMITTEES: A PROPOSAL FOR A REVIEW SYSTEM MODEL

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Abstract. Independent Ethics Committees play an important role in clinical trials as well as in all health-related research. Internationally, the national laws of the individual countries have guided their local development and organisation over the decades. Directive 2001/20/EC of the European Parliament and of the Council explicitly recognised the Ethics Committees' duty to protect the rights, safety and wellbeing of human subjects involved in trials and to provide public assurance of that protection. Regulation (EU) 536/2014, which repealed the aforesaid Directive, provides that a clinical trial must be subject to scientific and ethical review, without specifically defining what they consist in. The divide between the evaluation of the ethical value and the scientific value of a study is very faint and for some it may even appear a meaningless distinction. While Regulation (EU) 536/2014 requires Member States to ensure that Ethics Committees are involved in the assessment process within their national territory, it does not require such ethical assessment to be binding. This paper proposes a possible system for interaction between Ethics Committees and local regulatory authorities in which the meaning and purpose of the ethical assessment are conceptually clearly defined and not narrow.

Strengths and limitations of this study.

- the paper delves into a topic on which there is not full understanding and procedural consistency at the European level;
- the paper suggests a model to be discussed and shared;
- the paper does not delve into the internal discussion and legislation specific to each European country, especially when this is not available in English.

Introduction. Today, the commonly accepted basis for conducting clinical trials on humans is firmly founded on the protection of human rights and the dignity of the human being. The reference principles are clearly set out in the leading international guidance documents, such as the 2013 version of the World Medical Association's Declaration of Helsinki and Good Clinical Practice (GCP) **[1]**. Historically, the need to establish mandatory principles of behaviour is usually associated with the Nuremberg trials of 1946 **[2]** as a means of avoiding abusive situations in particular in favour of those in conditions of vulnerability **[3]**. Since then, there have been many regulatory efforts around the world to protect individuals in medical research and practice **[4]**. GCP is an internationally recognised set of ethical and scientific quality requirements, which are mandatory for providing public assurance that the results of clinical trials are reliable **[5]**. Certification of compliance with GCP is required for all submissions approved by regulatory agencies in the European Union, the USA, Japan, and Canada.

It is also worth mentioning the International Ethical Guidelines for Health-related Research Involving Humans drawn up by the Council for International Organizations of Medical Sciences (CIOMS) in concert with the World Health Organization (WHO). These guidelines state that the ethical justification for undertaking health-

related research involving humans is its scientific and social value. However, scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice **[6]**. The highest standards of care and protection should not be waived under any circumstances, even during a pandemic situation, such as that of the COVID-19 emergency, which forced ethics committees to adopt new work methods, and the pressure exerted on medical research must not result in trials that do not comply with all applicable ethical standards **[7-8]**.

Full compliance with these requirements does not seem to be something that can be taken for granted even today **[9]**. It is not possible, in fact, to state that the ethical principles recognised as fundamental are applied in a satisfactory and equitable way around the world and that no improvements to the supervision and review processes are necessary **[10 - 11]**. The very way in which independent review is conducted is far from procedurally incontrovertible **[12]**. There is a long-standing debate regarding the assessment of the quality of the work carried out by the Ethics Committees and the need to empirically verify whether this work actually improves the protection of individuals **[13-14-15-16]**.

It is therefore still necessary to identify the best practices or standards to be adopted in order to ensure adequate protection and to build community trust in research.

Before a clinical trial can start, the sponsor must apply for and be granted clinical trial authorisation (CTA) from the competent regulatory authority. Each EU Member State has its own regulatory authority. In addition to this authorisation, as is stated in the GCP guidelines, before initiating a trial, the investigator must obtain a favourable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

Worldwide, Institutional Review Boards (IRBs) **[17]** or Research Ethics Committees (RECs) **[5]** have the duty to ensure "*the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to independent Ethics Committees may differ among countries, but should allow the independent Ethics Committees to act in agreement with GCP as described in this guideline"* **[5].**

GCP has been incorporated into European legislation; in particular the "Clinical Trials Directive" - Directive 2001/20/EC of the European Parliament and of the Council - refers explicitly to it and defines the Ethics Committee as: "*an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent*" (Art. 2, k)**[18]**.

In 2014, Directive 2001/20/EC was replaced by Regulation (EU) no. 536/2014 on clinical trials on medicinal products for human use, which brought important changes to the organisational structure of clinical trials in Europe **[19-20]**. Although it came into force on 16 June 2014, its implementation was postponed until 31 January 2022, in that it was conditional to the development of a fully functional EU Clinical Trials Information System (CTIS). The Regulation has binding legal force for all EU Member States and stipulates that the study protocol must contain "*a statement that the clinical trial is to be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice*" (Annex 1, D 17(a)).

As mentioned previously, GCP attaches considerable significance to the ethical assessment by the Ethics Committees, making them guarantors of the general protection of the participating subjects, going well beyond the mere aspect of correct information for informed consent purposes. Ethics Committees are not the only subjects that have moral duties and responsibilities towards study participants, as these lie also with all the interested parties including the investigators, sponsors and regulators.

It is conceptually inappropriate to consider that certain aspects of a study design have to do with science and others with ethics, i.e. that statistical method regards science and the informed consent process regards ethics **[21-22]**. A poorly designed study will not be scientifically valid because it will not bring reliable results, nor will it be ethically valid because it will reflect professional negligence, a waste of resources or, in the worst case, the dissemination of unreliable results. A wide range of aspects contributes to determining the value and

acceptability of a study and some of which are complex to evaluate **[23-24]** such as, for example, the possible prevalence of commercial interests (for example, in a study in which the benefits to individuals or potential patients are negligible) or the true value of the research for society in relation to the use of public resources **[25-4]**.

A well-devised research protocol that does not protect the subjects involved may be scientifically valid, but it is not ethically acceptable in a society that puts the well-being and dignity of individuals first. The function of Research Ethics Committees constitutes the introduction, into an experimental process that could be imperfect, of a control system. "Ethics" here refers precisely to the scrutiny of a behaviour to appreciate its value in relation to shared principles and reference points. Ethics is not an abstract, philosophical dimension - at least in this particular context - it merely refers to the best possible behaviour expected of someone in a given situation.

In this paper, it is assumed that the behaviour of an investigator can be examined along three necessarily interrelated axes. The first axis is that of scientific action: it concerns the use of a rigorous methodology and the application of scientifically recognised principles. The second axis is that of human protection: it concerns respect for the rights and dignity of the subjects involved. The third axis is the regulatory one: it concerns knowledge and compliance with current regulations. In this perspective, the review by the Independent Committee should take place following these three axes of action; it is the impartial eye on the investigator's planned behaviour. It might be more appropriate to refer to it not as an 'ethics committee', but simply as a 'review committee'. **[26]**.

Regulation (EU) No. 536/2014: critical issues. According to Regulation (EU) No. 536/2014, a clinical trial must undergo scientific and ethical review. It prescribes a precise and detailed procedure for the submission and assessment of authorisation requests. A sponsor who intends to initiate a clinical trial must submit an application dossier to the member states involved via the EU portal. The reporting Member State appointed (Regulation, Art.5) will be responsible for validating and evaluating applications, with the involvement of the other states involved in the clinical trial. Validation must take place within 10 days from the submission of the application dossier and the member states involved may forward to the rapporteur member state any comments relating to the validation of the application within seven days of submission of the application dossier.

This is followed by the assessment phase. The issues to be considered in the assessment phase are detailed in Part I (Regulation, Art. 6) and Part II (Regulation, Art. 7). Part I represents a general analysis of the study protocol: it includes general aspects such as those related to therapeutic benefits, risks to participants, and safety and quality of the therapeutic agent. This part is assessed by the "reporting member state" and is valid for the entire EU. Part II covers local feasibility, such as local subject recruitment methods, the informed consent process, and subject compensation, which is assessed separately by each state.

For clinical trials involving more than one State, the Part I assessment process shall include three phases (Art. 6):(a) an initial assessment phase carried out by the rapporteur Member State within 26 days from the validation date; (b) a coordinated review phase conducted within 12 days from the end of the initial assessment phase and involving all Member States involved; and (c) a consolidation phase carried out by the rapporteur Member State within 7 days from the end of coordinated review phase.

Each Member State concerned shall assess, in relation to its own territory, the application for authorisation with regard to the aspects included in Part II (Art.7) and must complete its assessment within forty-five days from the validation date by submitting it through the EU portal.

At the end of the assessment process, the rapporteur Member State shall draw up an assessment report. It must contain one of the following conclusions concerning the aspects addressed in Part I (Art. 6): a) the conduct of the clinical trial is acceptable pursuant to the requirements set out in the Regulation; (b) the conduct of the clinical trial is acceptable pursuant to the requirements set out in the Regulation, but subject to compliance with specific conditions that must be specifically listed in the conclusion; or (c) the conduct of the clinical trial is not acceptable pursuant to the requirements set out in the Regulation.

Regulation (EU) 536/2014 refers to the 'Ethics Committee' as "*an independent body established in a Member State in accordance with the local law and empowered to give opinions for the purposes of the Regulation, taking into account the views of laypersons, in particular patients or patients' organisations*".

In relation to the role of Ethics Committees, Regulation requires Member States to organize the involvement of these bodies in the evaluation process.
It allows Member States full discretion regarding the pronouncement of the Ethics Committees, and prescribes: "*The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation 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*" (Art.4). The individual States must "*determine which body or bodies are appropriate for the purpose of evaluating an application for authorization to conduct a clinical trial and to organise the participation of ethics committees*" (recital no. 18) **[20]**.
This provision leaves the authorisation process undefined, particularly regarding the relations between the competent authorities and the Ethics Committees **[27-28-29]**. It does not define the meaning of the assessment required of the Ethics Committees, nor whether it is binding or non-binding; nor whether Ethics Committees should liaise with the sponsor directly or through the competent authority. Some authors have emphasised that the uncertainty regarding these points could lead to diversities between the various countries as well as to situations of marginalisation and ineffectiveness of the action of Ethics Committees **[30-31],** whereas it would be desirable to work on quality standards and accreditation systems for these bodies **[32-33-34]**.
The possible decision to implement a narrow model, only involving Ethics Committees in Part II, could certainly lead to a situation in which participating subjects are not adequately protected, in breach of the Declaration of Helsinki and other international research ethics guidelines **[3]**.
Such a possible decision would also appear difficult to justify, given that the scientific and methodological elements contained in Part I are closely associated with the protection of the subjects involved and therefore with the ethicality of the research. The Part II assessment activity is closely intertwined with the Part I assessment activity, such as formulating the risk-benefit profile and disclosing it during the informed consent process.
The structure and legal basis of Research Ethics Committees in the various EU Member States vary significantly. As far back as 2013, the European Network of Research Ethics Committees (EUREC) emphasised the importance of having these bodies review both parts I and II of the trial authorisation dossier and of making the authorisation to conduct a biomedical research project conditional to their issuance of a favourable opinion. It is essential to clarify the exact impact of a Research Ethics Committee assessment for the granting of a favourable opinion for the whole assessment process **[35]**.
The new framework requires the committee to issue a single opinion that applies to the entire territory of the Member State participating in a multicentre trial, regardless of whether the trial then takes place at different sites within that State. All Member States are therefore in the position of needing to adapt their national legislation on Ethics Committees in order to achieve a system capable of providing the enactment of the aforementioned single opinion.
Before Regulation (EU) No 536/2014 came into force, in order to start a clinical trial in Italy, it was necessary to obtain authorisation from the competent authority, the Italian Medicines Agency (AIFA), and from an Ethics Committee **[36]**. The opinion of the Ethics Committee was binding and covered all aspects of the submitted study, i.e. all those now provided for in Parts I and II of the Regulation.
At the current time, it has still not been established what form the ethical assessment should take.
It would be appropriate, at European level, to maintain a clear distinction between the work of the competent authority and that of the Ethics Committee, and for the latter's assessment to be traceable at all times, rather than be incorporated into the final assessment. A possible interaction model is proposed below.

A possible model for the role of Ethics Committees.

As mentioned previously, since the Regulation makes no specific provision in this sense, each Member State is at liberty to define its own procedures for involving the Ethics Committees, as well as the specific procedure

through which the Ethics Committees must carry out their evaluation; with regard to Part I in particular, the Regulation does not explicitly provide for the opinion of the Ethics Committee to be binding.
This has led to significant heterogeneity among European states.
Currently in Italy the Ethics Committees evaluate the aspects included in part II autonomously and independently. They may also comment on Part I, but the competent authority responsible for completing the Part I assessment could hypothetically avoid taking into account comments raised by ethics committees. The significance of their role in this case is therefore rather undefined. We believe that, despite the local organisational and structural differences, action must be taken at European level to harmonise the operation of Ethics Committees, particularly with regard to clinical trials.
In the model postulated and described here, the rapporteur Member State must immediately involve a local Ethics Committee, which must assess the protection afforded to the subjects of the clinical trial **(Fig.1)**. This assessment should form a separate part in the drafting of Part I assessment that the Member State shares with all the other Member States in the coordinated review phase and should contain a reasoned conclusion on the feasibility of the study **(Fig.2).** In this way, the Ethics Committee's assessment would not be incorporated into that carried out by the competent authority; rather it would maintain an autonomous character and, above all, its own conclusion. The other Member States involved could then consult it and use it to make their own further considerations. Boxes 1 shows a possible example of a format for the evaluation of Parts I by the Ethics Committee.
It would be of fundamental importance to establish, consistently between the Member States, whether or not the assessment report – particularly the aspects covered by Part I - of the Ethics Committee is binding as this serves to define the very meaning given to these bodies. We believe that in the context of clinical trial regulations, Ethics Committees are oversight rather than advisory bodies, which also means they take on a guarantor role toward the public. A negative opinion issued by these bodies cannot in actual fact be a negligible opinion, but rather a reason why it is right, as a precautionary measure, not to initiate the trial **[37]**.

Box 1. Evaluation scheme for Ethics Committees, Part I, Reg. 536/2014.

ASSESSMENT REPORT PART I.
SECTION FOR ETHICS COMMITTEE:

Compliance with Good Clinical Practice ensures the reliability of the trial. Research Ethics Committees (RECs) have the duty to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance by, among other things, reviewing and providing a favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The Ethics Committee (reference),
With reference to compliance with the principles of WMA Declaration of Helsinky, the Good Clinical Practice and the requirements set out in the Regulation 536/2014, art. 6, expresses the following assessment of the study (reference):

Ethics Committee ASSESSMENT:
a) the conduct of the clinical trial is acceptable;
b) the conduct of the clinical trial is acceptable but subject to compliance with specific conditions which shall be specifically listed;
c) the conduct of the clinical trial is not acceptable;

Reasons for the assessment and any requests:

……
……
……

Conclusion. Regulation (EU) No 536/2014 brought important changes to the organisational structure of clinical trials in the European Union. This reform has also affected the way ethics committees work, imposing a reflection on the meaning of their assessment. The Regulation requires that a clinical trial be subject to scientific and ethical review, but does not specify in detail how they should be conducted, leaving to the Member States to establish their own organizational model and how the competent authorities and independent ethics committees should interact. It is important to point out that Reg. 536/2014 does not require that a favourable ethics evaluation be binding for the beginning of a trial. Some authors have expressed concern that the discretion left to the Member States could lead, in some of them, to a weakening of the Ethics Committees' ethical function and assessment. GCPs attribute a broad meaning to the assessment by the Independent Committees, a supervisory role to ensure the general protection of the participating subjects, which can potentially affect all aspects of the study and therefore go beyond the aspect of correct information for informed consent purposes. It is conceptually inappropriate to hold that certain aspects of a clinical study regard science and others regard ethics, i.e. that statistical method regards science and the informed consent process regards ethics.

As an adjective, ethical refers to the goodness of all dimensions of a trial. The ethics of a study refers to every aspect of the behaviour that is expected of an investigator. In this paper, we assume that such behaviour can be examined along three necessarily interconnected axes: the axis of scientific action, that of the protection of subjects and that of compliance with legal provisions. If we focus on the part concerning the methods for acquiring informed consent, particularly for incapacitated subjects, we will be analysing above all the axis of protection. However, any consideration of the quality of existing behaviour will be an ethical consideration. Considerations regarding, for example, the publication of negative results are also important ethical considerations.

The independent Ethics Committees, understood as third parties, should be called on to express an opinion on clinical trials regarding the aspects included in both part I and part II of the Regulation (EU) No 536/2014. In the model proposed here, they should be involved from the validation phase and the assessment expressed should constitute a recognisable document in its own right, rather than being incorporated into the assessment by the rapporteur Member State.

This approach would help to ensure a clear conceptual definition of the role and function of these bodies, as is recognised internationally. The application of a uniform model in all EU Member States would encourage the development of standardised procedures aimed at achieving similar standards of protection in the different States. However, future research would be useful in order to investigate how multidisciplinary committees should actually act to ensure a high-quality review and how to develop consistency among them.

Figure legends

Figure 1 shows the validation process of a trial authorization request submitted by the sponsor. The left part of the figure represents the timing of the Regulation (EU) No 536/2014, the right part a possible model that provides for the immediate involvement of an Ethics Committee.

Figure 2 shows the different phases of the assessment process of the aspects covered by Part I of the Regulation (EU) No 536/2014 (ART. 6). The left part of the figure represents the timing of the Regulation, the right part a possible model of involvement of the Ethics Committee.

Patient and Public Involvement

None

Competing Interests

The authors declare the absence of conflicts of interest

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LR and CP contributed to the conceptualization of the work and the structuring of the concluding proposals.

LR performed the literature search, wrote the article and is the guarantor.

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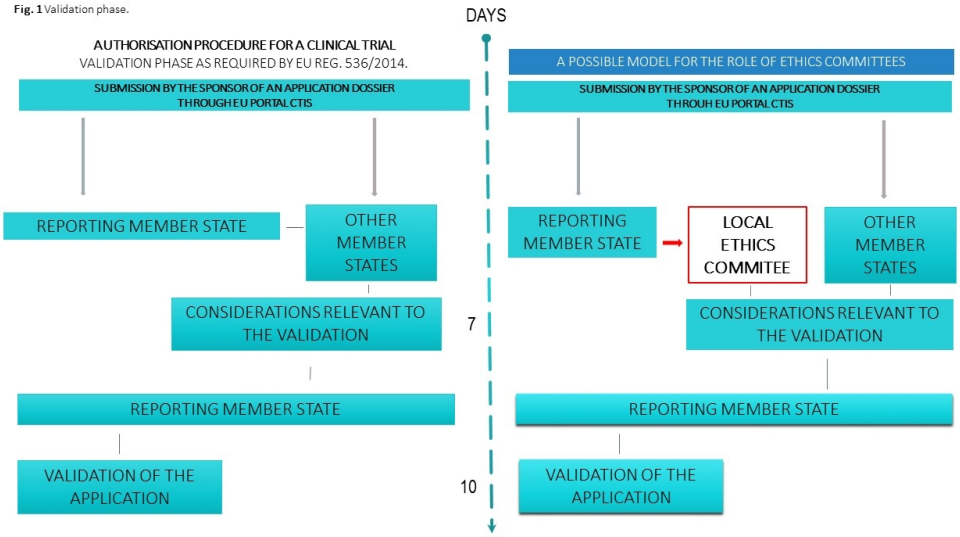
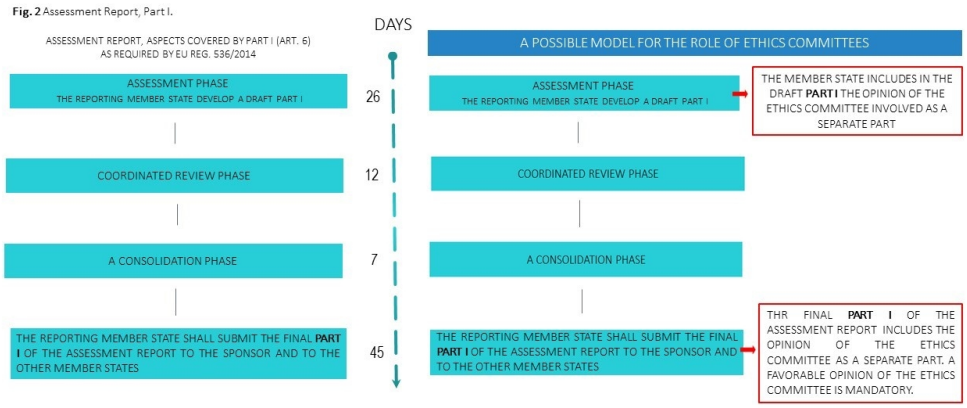


Fig. 1 Validation phase.

338x190mm (96 x 96 DPI)



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