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Clinical trial regulation and ethical committees

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Disclosure

Conflict of interest: nothing to disclose

Self assessment questions

1. Does the new EU **Regulation require a single opinion by each MS**? ***TRUE/FALSE***

2. **Shall ERC assess scientific related issues** (ie., on methodology, adequate design of the project in relation to the implication of human beings, the use of personal data, human biological samples and animals) **in addition to the purely ethical and legal issues**? ***TRUE/FALSE***

3. Should **independence of ERC** be **understood** also as a conflict of interests? ***TRUE/FALSE***

Introduction: The social value of biomedical research (1)

Clinical research makes it possible to

(1) *generate high quality knowledge,*

(2) *to develop therapeutic tools that improve those already available and*

(3) *contribute to the prevention, alleviation and cure of diseases and improve the quality of life of the population.*

Introduction: The social value of biomedical research (2)

The aim of regulating clinical trials with medicaments is:

i. Clinical trial be evaluated by qualified Research Ethics Committees
ii. Medicines are authorised by the medicament agencies
iii. Be marketed by their holders with the guarantees of quality, eficiency, transparency and safety of participants required by law
iv. Finally the usefulness of the results arriving at clinical practice for the benefit of patients and society as a whole.

Introduction: The social value of biomedical research (3)

The principal purpose of a legal framework regulating clinical research is to consolidate society's confidence in research and promote its progress by the way of promote and facilitate clinical research with medicines in the EU space.

An ethical & legal framework for clinical trials

Clinical research must be conducted in an environment that guarantees:

- ✓ The protection of persons participating in a clinical trial.
- ✓ Respect for the basic principles of patient autonomy and the rights and obligations regarding clinical information and documentation.
- ✓ That the results derived from it are of quality and useful.

Clinical research on orphan medicaments *for the treatment of population groups such as children, women and the elderly who have traditionally been under-represented in clinical research* ***needs to be encouraged***.

The general legal framework on clinical trials with medicaments in the EU (1)

European harmonisation on clinical trials has been due to **Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials**.

It stablished the basic principles and requirements that have until now regulated:

** The conduct of clinical trials with medicines and the

** Clinical Research Ethics Committees as guarantors of their ethical and scientific quality.

This regulation has been subject to some public criticism, which has focused on:

- ✓ the complexity of the authorisation procedure for the trial
- ✓ the disproportionate bureaucratic burden on the authorisation that has hindered clinical research in the EU.

The general legal framework on clinical trials with medicaments in the EU (2)

Regulation (EU) No 536/2014 of the European Parliament and of the Council **of 16 April 2014 on clinical trials of medicinal products for human use (CTR)**.

*This is the **current** legal framework for clinical trials at the EU* (Directive 2001/20/EC has been repealed)

It makes far-reaching changes with a view to simplifying procedures without undermining guarantees for participants in clinical trials.

What does mean the way of a regulation?

** A direct application to the MS

** Less variability in the application of the rules

Contents of Regulation 536/2014 (1)

1. The CTR covers:

- Interventional clinical trials with human medicinal products.
- New category of **low intervention clinical trials** with adapted requirements.

2. Not covered:

- Non-interventional trials
- Trials without medicinal products (e.g. devices, surgery, etc).

Contents of Regulation 536/2014 (2)

The CTR leaves out of MS cooperation:

- aspects of an intrinsically national nature which require an assessment by each MS
- the organization by which each State reaches a unique position in the assessment
- evaluation of ethical aspects and informed consent
- compensation mechanisms

Conclusion:

Relevance of the State's way of implementation on matters that are not regulated by the CTR 536/2014

Important:

The CTR sets out requirements which are crucial: timelines that every MS must comply with

Main principles of Regulation 536/2014 (1)

The new Regulation establishes (1):

i. common procedures for the authorisation of clinical trials throughout Europe
ii. urges MS to cooperate in the evaluation through a single common position
iii. fixes highly priced evaluation deadlines
iv. maintains the tacit authorization concept

Main principles of Regulation 536/2014 (2)

The new Regulation establishes (2):

vi. does not set minimum time limits for authorisation

vii. increased efficiency in the communication and evaluation processes

viii. delineation of responsibilities of all actors involved

Practical solutions: *low-intervention clinical trial*

CTR introduces some changes in the definitions that are of great relevance for research promoted by the academic sector:

the ***concept of a "low-intervention clinical trial",*** which calls for the adoption of *less stringent standards* in areas such as

(1) monitoring

(2) master file content

(3) traceability, without compromising the safety of individuals participating in them.

EU Clinical Trial Portal and Database

The establishment of an EU Portal and Database has been previewed (Arts. 80 and 81):

- ✓ **The EU Portal** will be a single entry point for submission of data and information relating to clinical trials required by the Regulation.
- ✓ **The EU Database** will contain all data and information submitted via the EU Portal.

They will facilitate:

- the *application for clinical trials authorisation to the sponsor*, in particular in case of *multinational clinical trials*;
- the *assessment carried out by national authorities*;
- and *access to clinical trials information by the general public*.

Their creation is a task of the EMA

(Due to technical difficulties with the IT systems, the portal's go-live date had to be **postponed** and therefore **the EU CTR will come into application during 2019**).

Transparency

The CTR provides **more transparency on clinical trials data**.

All information in the EU database will be publically accessible **unless** its confidentiality can be justified on the basis of:

- Protection of commercially confidential information
- Protection of personal data
- Protection of confidential communication between EU countries

Safety reporting

The Regulation **simplifies the rules on safety reporting**:

- The protocol may provide that not all adverse events (AE) and serious adverse events are recorded and reported.
- For a clinical trial involving more than one investigational medicinal product a single safety report can be submitted in the Clinical Trial Eudravigilance database.
- Suspected unexpected serious adverse reactions (SUSARs) can be reported via the database.

Clinical trials conducted outside the EU

Clinical trials conducted outside the EU, but submitted for marketing authorisation in the EU:

- similar principles to the provisions of the Clinical Trials Directive of 2001/83/EC (Annex I, point 8).
- in accordance with principles equivalent to those of the CTR as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

Relevant bodies

1) Ethics Research Committees: (ERC)

the regulation intends to ensure a more eficient and dynamic work by ERC

2) European Medicines Agency (EMA):

it strengthens some skills of the EMA

Ethics Research Committees (1)

Definition:

'Ethics committee' means an independent body established in a MS in accordance with the law of that MS and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations

a) Ethics committees will be involved in the assessment of clinical trials application

b) ERC responsibilities and detailed composition will be determined independently by each EU MS

c) The plural traditions in the various MS are observed

Ethics Research Committees (2)

One single decision by MS

CTR 536/2014 stipulates that when assessing applications for authorisation to conduct clinical trials, MS 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

Consequences of the requirement that for each MS the assessment of an application for approval to conduct a trial must take the form of a 'single decision' by the MS concerned.

Ethics Research Committees (3)

Procedure for giving an opinion

a) A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with the Regulation (Art. 4)

b) The ethical review shall be performed by an ethics committee in accordance with the law of the MS concerned (Art. 4)

c) Where an ethics committee has issued a negative opinion which in accordance with the law of the MS concerned is valid for that entire MS.

d) That MS shall provide for an appeal procedure in respect of such refusal (Art. 8)

e) The ERC opinion shall be given within the timelines for the authorisation of that clinical trial as set out in this Regulation (Preamble, 18)

Ethics Research Committees (4)

Membership for ERC:

When determining the appropriate body or bodies, MS should ensure:

- ✓ the involvement of laypersons, in particular patients or patients' organisations.
- ✓ the necessary expertise is available.
- ✓ In accordance with international guidelines the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience

(Art. 9)

Ethics Research Committees (5)

Requirements of members:

- ✓ **Expertise** (with the exception of lay member(s): collectively
- ✓ A **reasonable number** of members
- ✓ **Independence** of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence and
  - having no conflict of interest
  - Transparency of affiliations, declaration of financial interests

(Art. 9)

European Medicines Agency

- The Agency has to deliver, control and maintain the IT platforms (Portal and Database) needed for the implementation as required by Regulation
- It shall be responsible for avoiding unnecessary duplication (Art. 81.1)
- EU Portal and database project (Art. 80, 81, 82 and 84)
- Safety Reporting project (Art. 40 to 44)
- EudraCT and EU Clinical Trial Register Legacy project (Art. 98)
- A data warehouse is part of these developments to facilitate the reporting tools between the different systems

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Self assessment questions with answers

1. Does the new EU **Regulation require a single opinion by each MS**? **TRUE**

2. **Shall ERC assess scientific related issues** (ie., on methodology, adequate design of the project in relation to the implication of human beings, the use of personal data, human biological samples and animals) **in addition to the purely ethical and legal issues**? **TRUE**

3. Should **independence of ERC** be **understood** also as a conflict of interests? **TRUE**

My take home messages

- A common EU regulation on CT will promote a strongest and more competitive research by European scientists and promotors
- An ethically-oriented research is consistent with European values and human rights
- Dialogue between stakeholders and between them and society is necessary to develop an ethical awareness of biomedical research

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Thank you for your attention!!!

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