Regulatory control of clinical trials

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11 April 2014

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Why do we need a robust regulatory approval system for CTs?

On the first page of the new Clinical Trials Regulation:

„ (1) In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests.

(2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation.”

If we go back 67 years in history...

Nuremberg Trials

- military trials held by the Allied forces after World War II
- in their occupation zone in Nuremberg, Germany
- for the prosecution of prominent members of the political, military, and economic leadership of Nazi Germany

If we go back 67 years in history...

Doctors' Trial

- first of 12 trials for war crimes of German doctors
- officially *United States of America v. Karl Brandt, et al.*
- trials held before US military courts

Doctors' Trial

- 20 of 23 defendants were medical doctors (other 3 were Nazi officials)
- accused of having been involved in Nazi human experimentation and mass murder under the guise of euthanasia
- Josef Mengele, one of the leading Nazi doctors, had evaded capture

Nuremberg Code

- 20 August 1947 verdict was delivered in the Doctors' Trial
- during the Trial several of the accused argued that their experiments differed little from pre-war ones and that there was no law that differentiated between legal and illegal experiments
- Counsel for War Crimes adopted 10 points defining legitimate medical research in the trial verdict

Nuremberg Code

Outlined the most important ethical aspects of conducting clinical trials, eg.

- voluntary consent of the human subject is absolutely essential
- anticipated results should justify the performance of the experiment
- all unnecessary physical and mental suffering and injury should be avoided
- no experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur
- degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved
- proper preparations should be made and adequate facilities provided
- the experiment should be conducted only by scientifically qualified persons
- subject should be at liberty to bring the experiment to an end
- scientist in charge must be prepared to terminate the experiment at any stage if the continuation is likely to result in injury, disability, or death to the experimental subject

Declaration of Helsinki

- set of ethical principles developed by the World Medical Association
- adopted in June 1964, revised 7 times, last in October 2013
- developed based on the Nuremberg Code
- "*Even though the Declaration of Helsinki is the responsibility of the World Medical Association, the document should be considered the property of all humanity*"

Good clinical practice (GCP)

- International Conference on Harmonisation (ICH) guideline
- international ethical and scientific quality standard for designing, conducting, recording and reporting trials
- compliance with this standard provides public assurance
  - that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki
  - that the clinical trial data are credible

Current directives

Directive 2001/20/EC

- „Clinical Trials Directive”
- describes the requirements for the conduct of clinical trials in the EU
- as a directive, had to be individually implemented in national legislation of the Member States
- implemented in 2004

Primary purpose of the Clinical Trials Directive

- protect the health and safety of participants in clinical trials
- ensure the reliability and robustness of data generated in clinical trials
- simplify and harmonise the administrative provisions governing clinical trials in order to allow cost-efficient clinical research

Current legislation

Commission Directive 2005/28/EC „GCP directive”

- „GCP Directive”
- concretises the Clinical Trials Directive
- implements principles and detailed guidelines for GCP
- regulates requirements for authorisation of the manufacturing/ importation of investigational medicinal products (IMPs)

Primary purpose of the GCP Directive

- describes procedures for applications to conduct a clinical trial and authorisation of a clinical trial by the national competent authority (NCA) and Ethics Committee
- regulates requirements for a clinical trial, including rules for protection of participants
- describes rules on reporting adverse events, in particular ‘suspected unexpected serious adverse reactions’ (SUSARs) during the clinical trial
- sets rules on the manufacturing, importation and labelling of the IMP
- sets rules of clinical trial sites’ inspections

Guidelines

further specifying aspects of clinical trials:

- information to be submitted to the competent authorities and to the ethics committees
- requirements on safety monitoring and the reporting of adverse reactions
- requirements regarding Good Clinical Practice, including the documentation, of the clinical trials
- specific requirements regarding the products
- inspections of competent authorities and the applicable procedures

Guidelines and groups of different bodies in the EU

EudraLex - The rules governing medicinal products in the European Union (EC)

Volume 10: Clinical trials guidelines

Volume 3: Scientific guidelines for medicinal products for human use

Inspection procedures and guidance for GCP inspections conducted in the context of the Centralised Procedure (EMA)

Clinical Trials Facilitation Group „CTFG” (established by HMA)

EudraLex Volume 10: Clinical trials guidelines

Chapter I

The dossier for the competent authority (CT1)

The dossier for the ethics committee

Chapter II Safety reporting (CT3)

Chapter III Pharmaceutical data

Chapter IV Inspections

Chapter V GCP, EudraCT

Chapter VI Legislation

EudraCT
European Union Drug Regulating Authorities Clinical Trials

- database of all clinical trials commencing in the Community from 1 May 2004 onwards
- established in accordance with CT Directive
- access to EudraCT database itself is confidential and remains accessible only to the Competent Authorities of the Member States, the EMA and the Commission
- EudraCT number
  - unique identifier for each clinical trial with at least one site in the European Union (EEA)
  - must be included on all clinical trial applications

EudraCT
European Union Drug Regulating Authorities Clinical Trials

- gives the competent authorities of the Member States, the EMA and the Commission the necessary information to communicate on clinical trials and to maintain oversight of clinical trials and IMP development
- provides for enhanced protection of clinical trial subjects and patients receiving IMPs
- BUT! does not contain results

Effect of EU directives and guidelines

- harmonized legislation, guidelines and systems ensure that clinical data generated anywhere in the EU
  - is accepted for registration
  - subject rights and safety are respected
  - generated data is robust and reliable

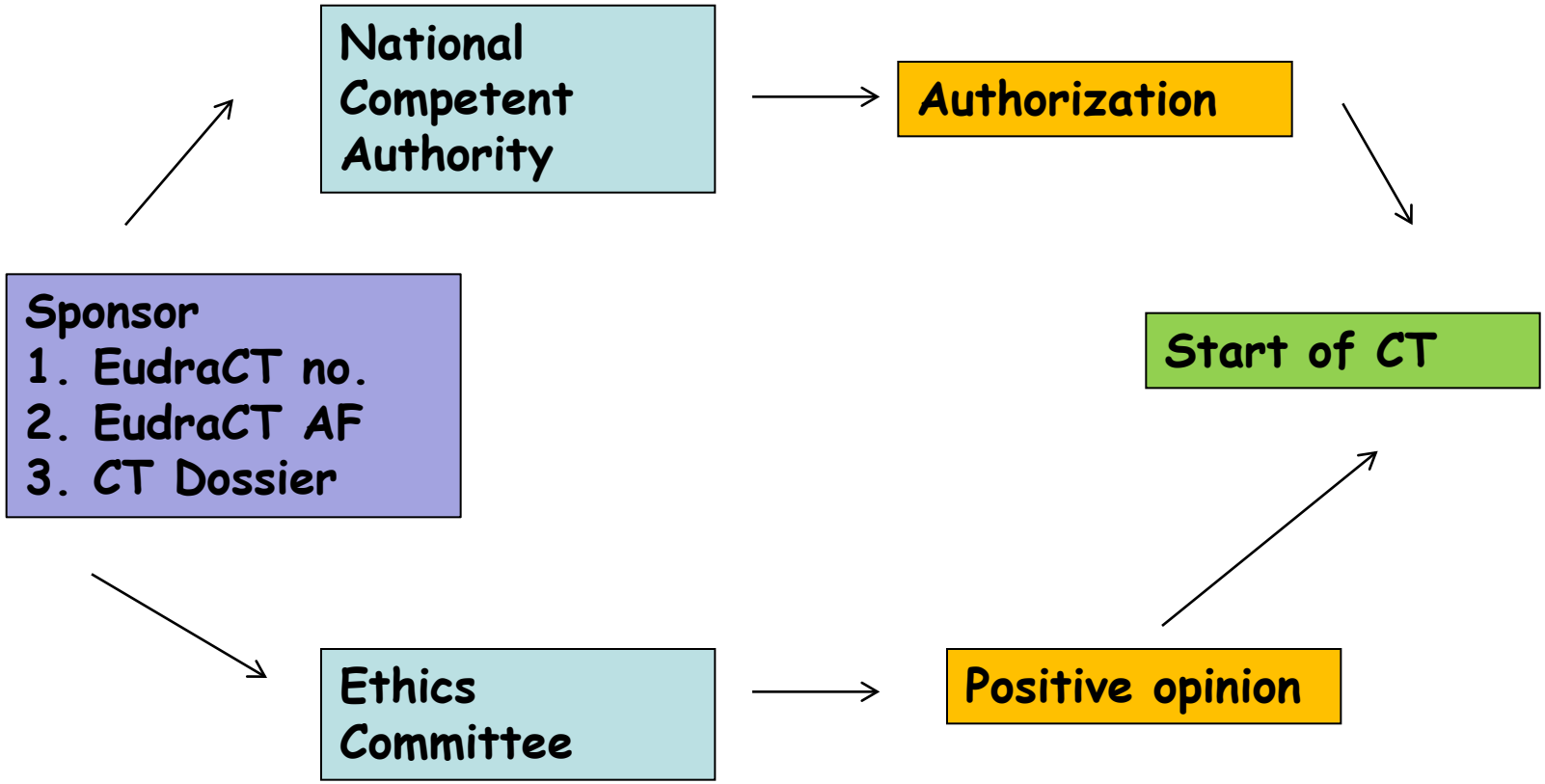
Clinical trials conducted outside the EU have to follow the Clinical Trials directive in order to be eligible for registration.

Criticism for Clinical Trials Directive

- creating barriers to the conduct of clinical trials in Europe
- allows Member States to introduce additional requirements
- costs for conducting clinical trials in the EU increased
- delay for launching clinical trials increased

Regulatory approval procedure for CTs

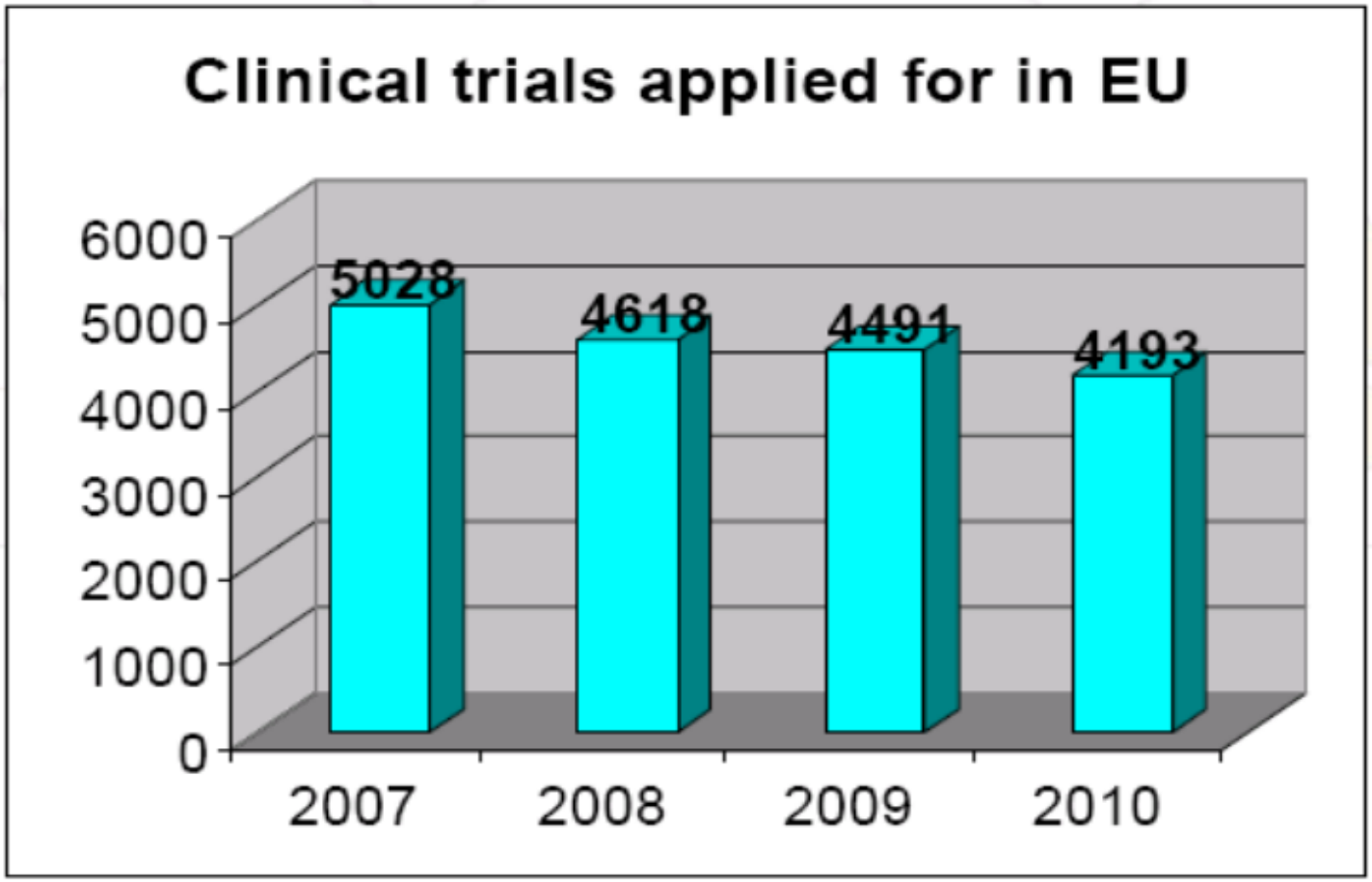
Separately in each Member State...



Regulatory approval procedure for CTs

- localising submissions creates more bureaucracy with high resource needs
- timelines for approval can differ, but usually 60 days plus clock-stops - **delays**
- CTs assessed by several CAs and Ethics Committees
- can reach divergent decisions for the same trial
- fees apply separately in all Member States

Decrease in CT numbers



Ref: Clinical Trials – application process, legislation & guidelines, IMB Clinical Trials Seminar 19th June 2012

Why is this a problem?

- EU much less attractive for CTs
- huge financial and administrative burden for pharmaceutical industry...

...but also for EU itself:

EU Health Commissioner John Dalli said:

“Patients in Europe should have access to the most innovative clinical research. Clinical trials are crucial for developing new medicines and improving existing treatments. ... 800 million Euros per year could be saved in regulatory costs and boost research and development in the EU, thus contributing to economic growth.”

Steps taken by the Commission

- two public consultations in 2009 and 2011
- responses published by the Commission
- large stakeholder workshop in 2011
- impact assessment conducted and report published

Commission’s proposal

- harmonised authorisation
- single portal to submit an application
- flexible and swift assessment procedure
- clear mechanism to appoint ”reporting MS”
- clear timelines with a concept of „tacit approval” (if authority does not object, it should be considered to approve)
- creation of a Clinical Trials Coordination and Advisory Group (CTAG)

European Parliament's additional proposals

- ethics committees should consist of healthcare professionals, lay persons and patients or patient representatives
- full "Clinical Study Reports" to be published
- persons assessing the application should declare any financial and personal interests

Revision of the Clinical trials Directive

- 17 July 2012 the Commission adopted a "Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC”
- regulation: **directly** valid in all EU Member States

Creating the new Clinical Trials Regulation – main points

- single submission dossier to be submitted via a single EU portal
- assessment procedure where RMS leads the assessment of technical/scientific aspects and CMSs assess national/local and ethical aspects
- leads to a single decision
- within set timeframe

Creating the new Clinical Trials Regulation – main points

transparency

- new publicly accessible EU clinical trials register to be set up and run by the EMA
- a summary of the CT results should be published within a year of the trial's end
- a summary understandable to a lay person of what was found in the trial should be published
- Clinical Study Reports (detailed documents normally produced for regulatory processes) should be made publicly available

Creating the new Clinical Trials Regulation – main points

- rules for clinical trials based on the actual risk posed to the safety of participants
- increased emphasis on the protection of the interests of subjects, including in particular vulnerable populations with eg. more detailed informed consent requirements
- recognition that a withdrawal of consent generally does not affect the use of data obtained prior to the withdrawal

Creating the new Clinical Trials Regulation – main points

- possibility for the Commission to conduct controls in Member States and third countries to make sure the rules are being properly supervised and enforced
- financial penalties should be imposed on anyone running a clinical trial who does not adhere to these new regulations

Approving the new Clinical Trials Regulation

- 22 January 2014 - European Parliament's ENVI (Environment, Public Health and Food Safety) Committee voted in favor
- 2 April 2014 – European Parliament voted in favor
- Regulation has to be formally adopted by the Council of the European Union
- and published in the Official Journal

When will it become applicable?

- 2 years after publication in the Official Journal
- only 6 months after the notice by the European Commission that the EU CT portal and database have achieved full functionality
- expected to come into effect in mid-2016 at the earliest

So have we reached heaven with the new Regulation?

Richard Bergstrom, Director General of EFPIA

"The revised legislation is a good step towards more streamlined processes surrounding clinical trials in Europe, as well as towards a responsible transparency surrounding clinical trials -- one that I see as in line with EFPIA-PhRMA Principles for Responsible Data Sharing. **There is still work to be done. The success of this legislation will depend on how it is applied in practice.** It will be essential to collaborate with relevant stakeholders and ensure they have the opportunity to provide input. This is a must if we are to achieve a system that will foster the innovation we need to improve patient outcomes."

Summary

- current legislative environment in EU created huge financial and administrative burden for pharmaceutical industry
- number of clinical trials in EU decreased by 25% between 2007 and 2011
- new Clinical Trials Regulation was approved by European Parliament on 2 April 2014
  - streamlines approval process for clinical trials
  - single point EU submission
  - promotes transparency
- ...but the proof of the pudding is in the eating - good collaboration between industry and EU bodies is necessary for the successful implementation of the new system


THANK
YOU