

TEDDY Scientific Meeting and General Assembly
The paediatric theme in the forthcoming clinical
research scenario

Rome, December 19th 2016

The new clinical trials Regulation to
improve clinical research in Europe: the
ECRIN contribution

www.ecrin.org

Need for international clinical trials

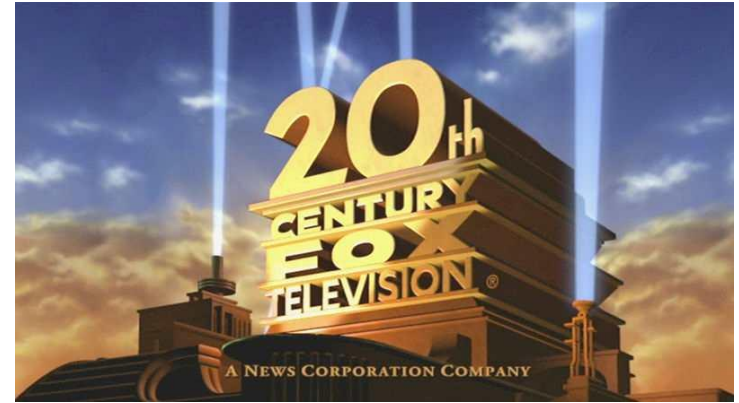
Added value :

- access to patients
- access to medical expertise
- unlock scientific potential
- methodological standards
- avoid duplication of trials
- share costs, tools, procedures
- better generalizability
- foster implementation

Obstacles :

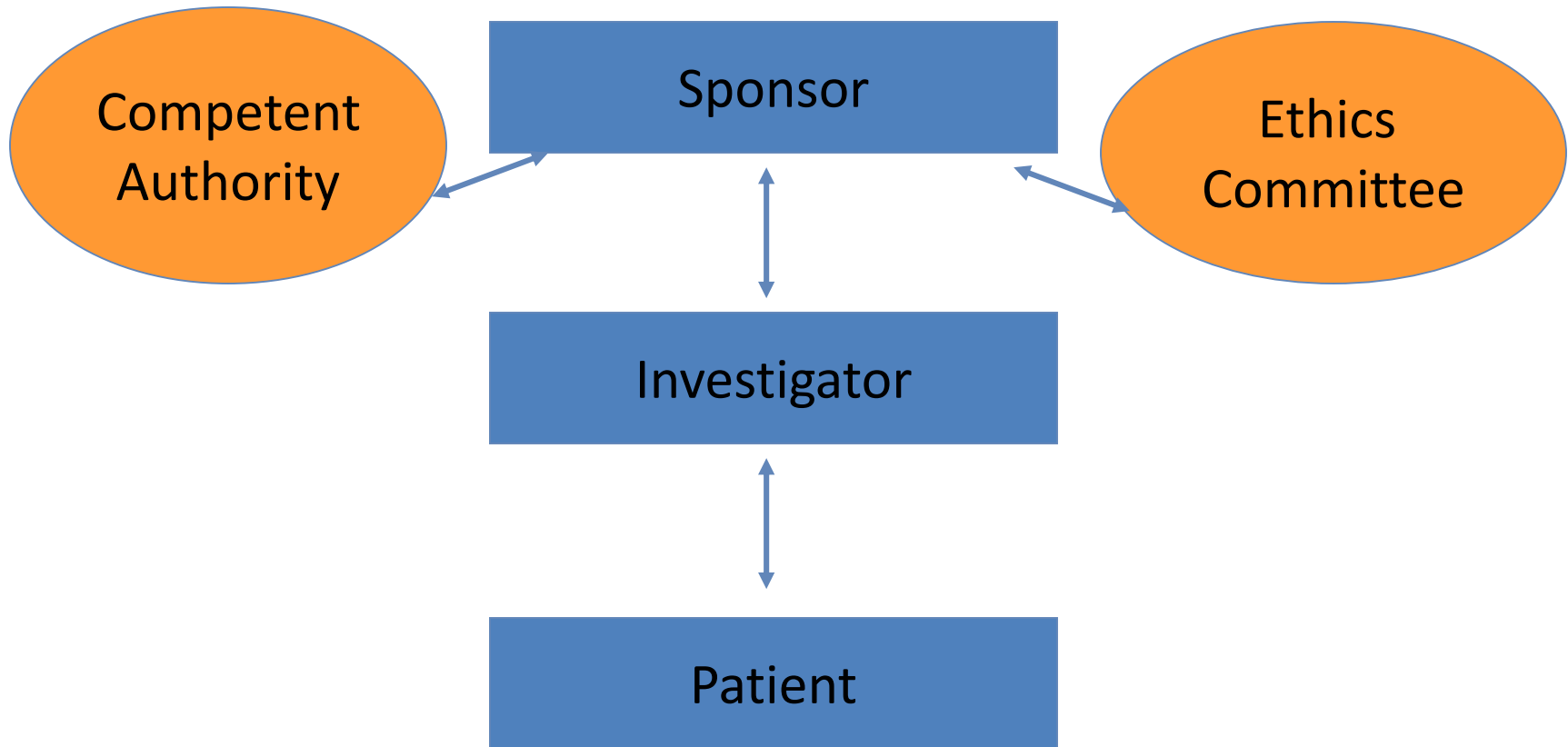
- infrastructure, interoperable tools and procedures
- regulation (medicines, medical devices, nutrition, other)
- ethical review
- insurance
- contracts
- cost models
- funding opportunities
- language

Sponsor, investigator, patients





*European legislation on clinical trials:
2001/20/EC Directive for clinical trials on
medicinal products*





2001/20/EC Directive

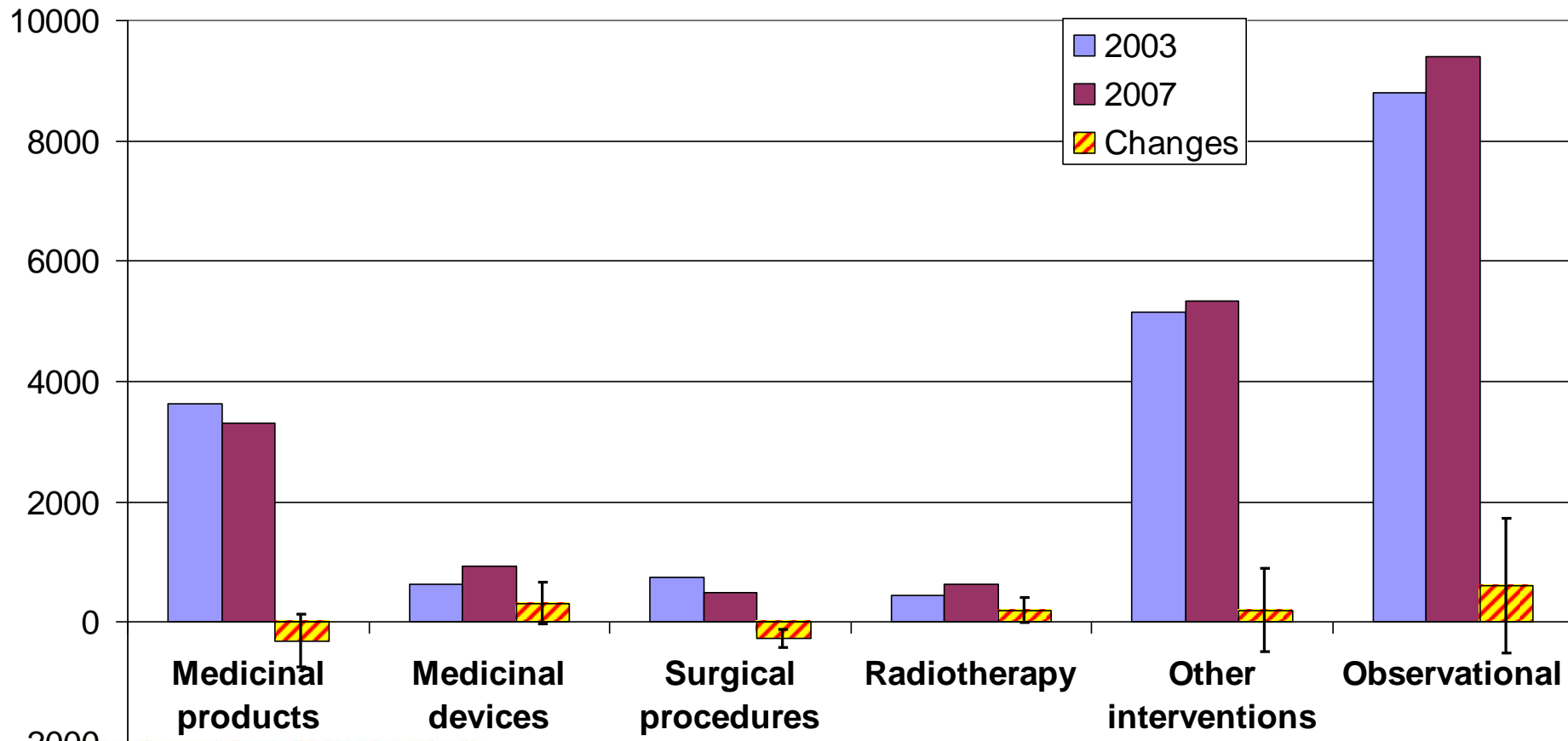
- ✓ “Directive” (not “Regulation”) : requires transposition into national legislation → divergent implementation
- ✓ Focus on clinical trials on medicinal products
- ✓ Definition of “intervention” and of “clinical trial” (!)
- ✓ Similar requirements whatever the sponsor, the risk and the marketing authorisation status, no distinction between IND and non-IND studies
- ✓ Single sponsor in EU (and sponsor’s representative in the EU when trial initiated outside the EU)
- ✓ Insurance/indemnity



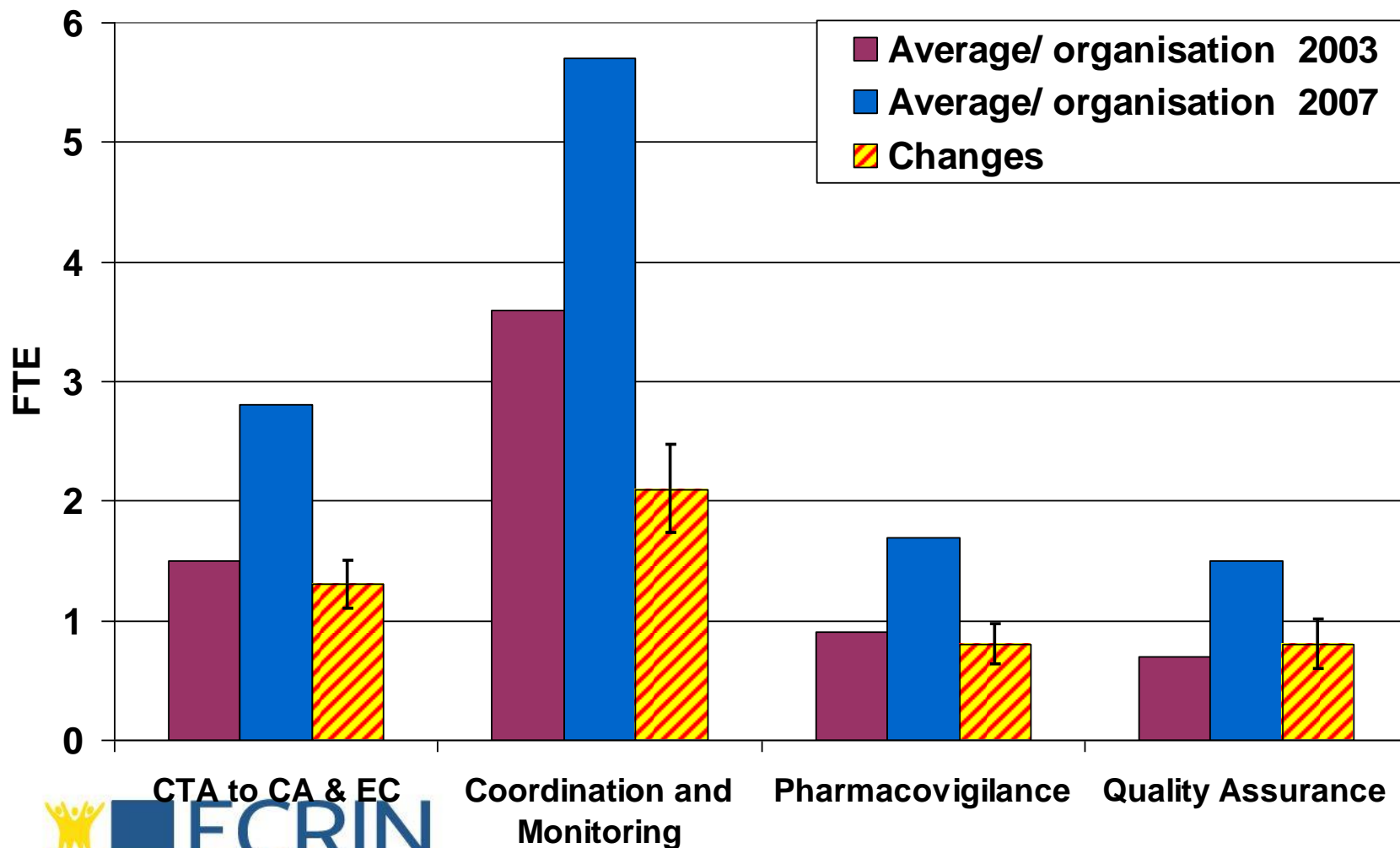
2001/20/EC Directive

- ✓ Parallel clinical trial authorisation (by national competent authorities and ethics committees) process in involved countries, multiple dossiers / languages
(simplification through Voluntary Harmonisation Procedure: coordination of competent authorities)
- ✓ Single ethical opinion in each country
- ✓ Symmetrical role for EC and CAs (SUSAR reporting)
- ✓ Partial harmonisation for clinical trials on medicinal product, no harmonisation for other categories of clinical research
- ✓ Poor alignment with non-EU systems

CTs performed before and after the CTD implementation



Workload before and after CTD implementation



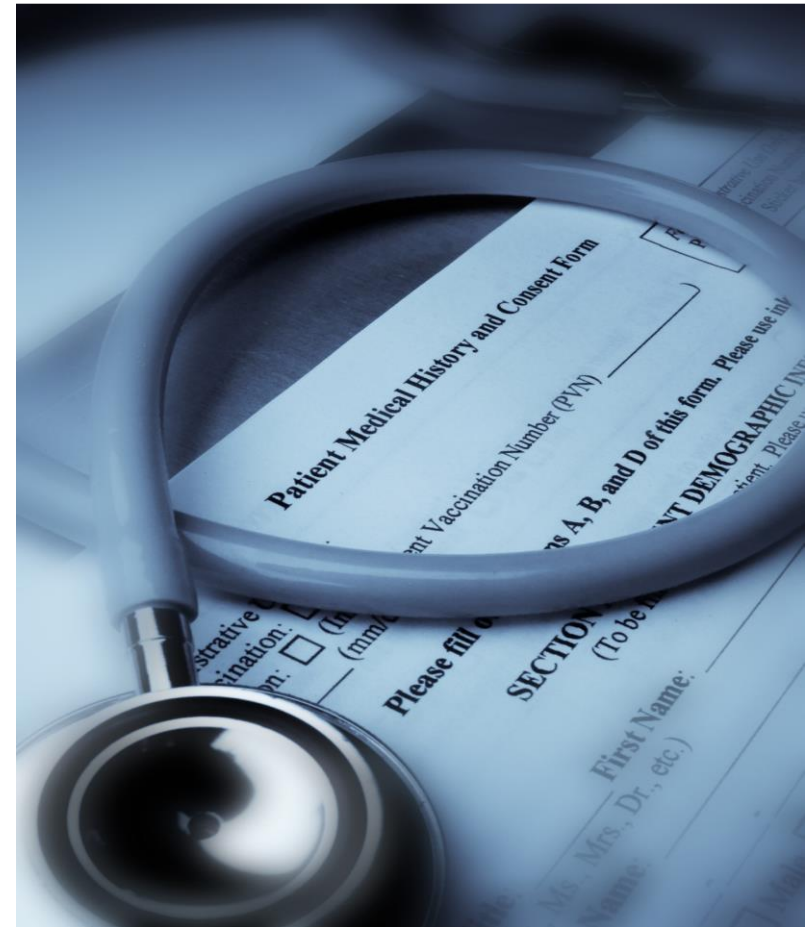
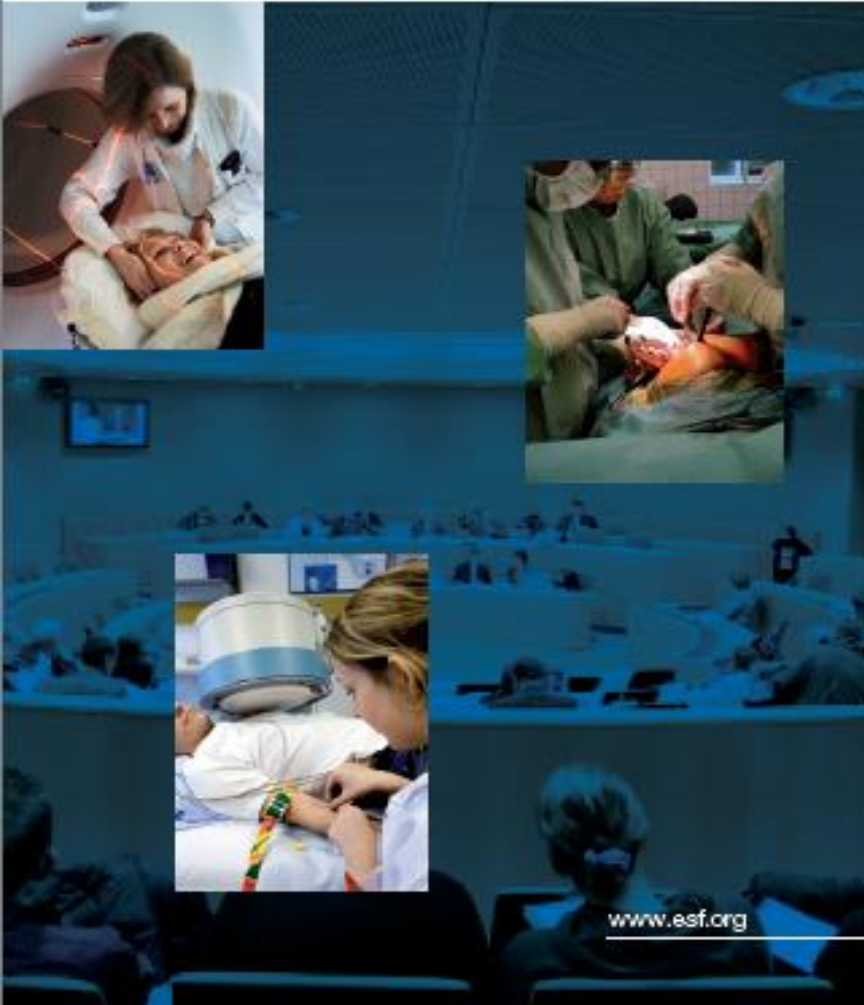


2005/28/EC Directive

- ✓ Art 11 : provisions for non-commercial trials ?
- ✓ Guidance never published
- *Protection of participants should not depend on the commercial or non-commercial objectives, but on the risk associated with the trial*
- *Risk-based approach*

Recommendations for a risk-based approach

OECD Recommendation on the Governance of Clinical Trials



Principles for risk assessment: **stratified** and trial-specific approaches

I - Risk to participant rights:

- I.1 patient information
- I.2 personal data protection

II - Risk to participant integrity and safety:

- **II.1 safety of the treatment intervention**
 - **New product**
 - **Modified use**
 - **Usual care**
- II.2 risk, burden and intrusion of invasive procedures
- II.3 vulnerability of patient population

III – Risk to data quality, results and public health:

- III.1 data quality
- III.2 credibility of results
- III.3 impact on healthcare practice and public health





EU clinical trial Regulation 536/2014

Journal officiel de l'Union européenne

L 158



Édition
de langue française

Législation

57^e année
27 mai 2014

Sommaire

I Actes législatifs

RÈGLEMENTS

- * Règlement (UE) n° 536/2014 du Parlement européen et du Conseil du 16 avril 2014 relatif aux essais cliniques de médicaments à usage humain et abrogeant la directive 2001/20/CE⁽¹⁾ 1
- * Règlement (UE) n° 537/2014 du Parlement européen et du Conseil du 16 avril 2014 relatif aux exigences spécifiques applicables au contrôle légal des comptes des entités d'intérêt public et abrogeant la décision 2005/909/CE de la Commission⁽¹⁾ 77
- * Règlement (UE) n° 538/2014 du Parlement Européen et du Conseil du 16 avril 2014 modifiant le règlement (UE) n° 691/2011 relatif aux comptes économiques européens de l'environnement⁽¹⁾ 113
- * Règlement (UE) n° 539/2014 du Parlement européen et du Conseil du 16 avril 2014 relatif aux importations de riz originaires du Bangladesh et abrogeant le règlement (CEE) n° 3491/90 du Conseil 125
- * Règlement (UE) n° 540/2014 du Parlement européen et du Conseil du 16 avril 2014 concernant le niveau sonore des véhicules à moteur et des systèmes de silencieux de remplacement, et modifiant la directive 2007/46/CE et abrogeant la directive 70/157/CEE⁽¹⁾ 131

DIRECTIVES

- * Directive 2014/56/UE du Parlement européen et du Conseil du 16 avril 2014 modifiant la directive 2006/43/CE concernant les contrôles légaux des comptes annuels et des comptes consolidés⁽¹⁾ 196

⁽¹⁾ Texte présentant de l'intérêt pour l'EEE

Les actes dont les titres sont imprimés en caractères maigres sont des actes de gestion courante pris dans le cadre de la politique agricole et ayant généralement une durée de validité limitée.
Les actes dont les titres sont imprimés en caractères gras et précédés d'un astérisque sont tous les autres actes.



FR



EU clinical trial Regulation 536/2014

- ✓ “Regulation”: no transposition into national legislation
- ✓ Focus on clinical trials on medicinal products
- ✓ Definition of “intervention” and of “clinical trial” (!)
- ✓ Provisions for “low intervention trials” : trials on authorized products, used either within their licensed indication, or off-label if this represents the established standard treatment.
- ✓ Co-sponsor, sponsor’s representative in the EU
- ✓ Possible insurance/indemnity by public health systems (for “low intervention”): country decision



EU clinical trial Regulation 536/2014

➤ ***Clinical trial authorization*** *(role of ethics committees ?)*

Part I : product and protocol:

coordinated assessment

(free circulation of goods -> EU treaties)

Part II : information, consent, site,
competencies etc:

no coordination, national assessment

(ethics -> national)





EU clinical trial Regulation 536/2014

- ✓ **Clinical trial application** through a single portal (operated by EMA) with a reporting Member State coordinating the authorisation process

- ✓ **Single, electronic dossier**
 - Part 1: product and protocol : coordinated
 - Part 2: “ethical” review (information, consent, site) : nationalEach country has its own organisation (CA vs. EC) to provide authorization

- ✓ **Sponsor proposes the reporting MS**





EU clinical trial Regulation 536/2014

- ✓ Limited possibility to opt-out
- ✓ Timelines: 60 days for authorisation, tacit approval
- ✓ Transparency: publication of results
- ✓ Trials in emergency situation
- ✓ Need for adaptation of national legislation : procedure for approval (CA vs. EC), clinical research without medicinal products

ECRIN Campus : regulatory database

www.ecrin.org/en/tools/campus

Country-specific information on regulatory and ethical requirements for clinical trial authorisation, 23 countries

- ✓ Medicinal Products
- ✓ Medical Devices & Combination studies
- ✓ Nutrition studies
- ✓ ATMP/ gene therapy
- ✓ Radioactive compounds
- ✓ Rare diseases
- ✓ Blood and tissue samples



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Select the country and/or study type of interest

Country Study type Sub study type

Medical Devices

Clinical investigations of Medical Devices for human use (hereinafter referred to as MD) assess the safety and clinical performance and evaluate the suitability of an MD for the purposes and the populations(s) for which it is intended. With respect to the wide diversity of medical devices and their associated risks, different provisions may apply and must be complied with when planning and undertaking a clinical investigation of the MD in question. The comprehensive information compiled in this

[Read more](#)

[Study type per country >](#)

Nutrition Studies

In the field of human nutrition studies, a considerable body of research is being conducted across Europe, however, a harmonized regulatory framework with established operational principles and standards for high-quality design and conduct of human studies is not available (unless nutrition is considered as a medicinal product). There is some guidance for European researcher provided by international ethical guidelines and declarations. Given the heterogeneity of human nutrition

[Read more](#)

[Study type per country >](#)

Medicinal Products for Human Use

Clinical trials/studies with medicines are investigations in humans intended to discover, test or verify the effects of potential treatments with one or more investigational medicinal products (IMP), to identify any side effects, to evaluate the safety, pharmacokinetics or efficacy and/or to confirm the effectiveness of the IMP in question. The information covered in this section also includes relevant details of clinical trials of advanced therapy medicinal products (ATMP), such as gene therapy medicinal

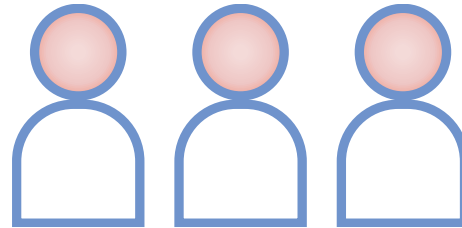
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[Study type per country >](#)

Total: 3 Entries

Simplified representation of the stratification and oversight requirements for clinical trials on medicinal products in various countries / regions

Marketing authorisation status of the medicinal products	Non- authorised medicine	Authorised medicine, treatment regimen outside marketing authorization		Authorised medicine tested within marketing authorisation
		not supported by established medical practice	supported by established medical practice	
USA		IND trials supervision by FDA approval by IRB		non IND studies approval by IRB
Japan		chiken trials supervision by PMDA approval by IRB		non-chiken studies approval by IRB
Australia	exemption scheme approval by CA (TGA) approval by EC			notification scheme approval by EC (EC decides if TGA should be involved, based on trial protocol)
2001/20/EC Directive	approval by CA approval by EC			
UK / 2001/20/EC Directive	approval by CA (MHRA) approval by EC	approval by CA (MHRA) approval by EC		notification to CA (MHRA) approval by EC
Draft EU Regulation 2012	coordinated approval by oversight bodies		low intervention trials coordinated approval by oversight bodies	
OECD Recommendation	approval by CA/regulatory authority approval by EC/IRB	approval by CA/regulatory authority approval by EC/IRB		approval by EC/IRB (notification to, or authorisation by CA is an option)
	<i>IND: investigational new drug</i> <i>EC: ethics committee</i> <i>IRB: institutional review board</i> <i>CA: competent authority</i>			marketing ↑ authorisation



Thank you!

Any questions?