ERICA

European Rare Disease Research Coordination and Support Action

Essential requirements before thinking about a clinical trial

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European Reference Networks

Outline

- Overview of the minimal requirements before starting a clinical trial in a study site
- Applicable rules
- Possible roles of the investigator in the trial
- Guidance and sources

Clinical research for rare diseases

Small number of patients

need for getting reliable evidence

need for protecting participants

methodologically and ethically well-conducted

1- to know what is a clinical trial

What is a clinical trial?

investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to an investigational product(s), and/or study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy

- ICH E6(R1) Guideline for **Good Clinical Practice -**

Clinical studies vs clinical trials

STUDIES

(1) 'Clinical study' means any investigation in relation to humans intended:

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining the safety and/or efficacy of those medicinal products;

TRIALS

(2) 'Clinical trial' means a clinical study which fulfils any of the following conditions:

(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

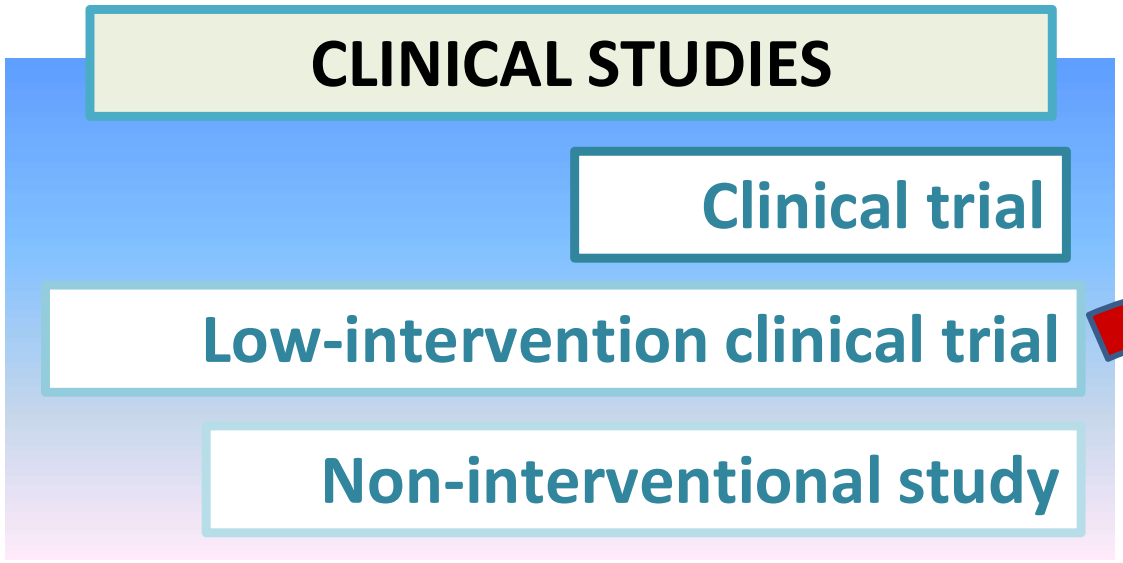
(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

- Regulation (EU) 536/2014 -

What makes a clinical trial different from the standard clinical practice?

CLINICAL TRIALS	STANDARD CLINICAL PRACTICE
AIMS: to investigate PK, PD, efficacy, safety	AIMS: to treat, prevent and diagnose
Interventions: investigational drugs either new or already available	Existing (marketed) drugs
Experimental use: drugs used according to the research plan to respond to experimental questions and participants are assigned to a specific intervention	**The use of drugs falls within the current practice**: drugs prescribed in the usual manner in accordance with the terms of the Marketing Authorisation
Eventual additional diagnostic or monitoring procedures	Diagnostic or monitoring procedures fall within the current practice

Clinical studies vs clinical trials



(3) 'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions:

(a) the investigational medicinal products, excluding placebos, are authorised;

(b) according to the protocol of the clinical trial,

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

- Regulation (EU) 536/2014 -

2- to know which rules apply

Which rules?

- Good Clinical Practice (GCP) – *ICH E6(R1)*
- EU Clinical Trials Regulation (CTR) - *(EU) 536/2014*
- Good Manufacturing Practice (GMP) - *Directive 2001/83/EC; Regulation (EU) No 1252/2014*

Strong regulatory knowledge!

Which rules?

(Legislative acts)

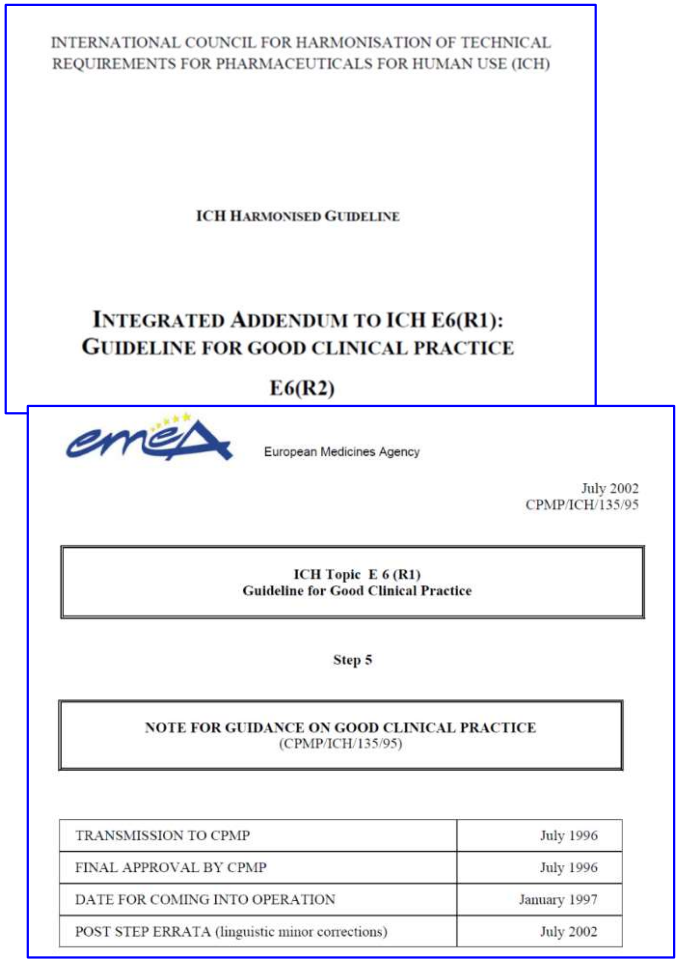
REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
(Text with EEA relevance)

Specific provisions on

- trial registration
- submission & authorisation
- modifications
- consent ⇨ *also for special populations*
- assent
- monitoring
- reporting
- archiving
- IMPs handling
- termination

Which rules?



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

European Medicines Agency

July 2002
CPMP/ICH/135/95

ICH Topic E 6 (R1)
Guideline for Good Clinical Practice

Step 5

NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE
(CPMP/ICH/135/95)

TRANSMISSION TO CPMP	July 1996
FINAL APPROVAL BY CPMP	July 1996
DATE FOR COMING INTO OPERATION	January 1997
POST STEP ERRATA (linguistic minor corrections)	July 2002

Introduction

1. Glossary
2. The principles of ICH GCP
3. IRB/IEC
4. Investigator
5. Sponsor
6. Protocol
7. Investigator's Brochure
8. Essential documents for the conduct of a clinical trial

Which rules?

WMA

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

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COUNCIL OF EUROPE
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European Treaty Series - No. 164

Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine

Oviedo, 4.IV.1997

ADDITIONAL PROTOCOL
TO THE CONVENTION
ON HUMAN RIGHTS
AND BIOMEDICINE,
CONCERNING BIOMEDICAL RESEARCH

Strasbourg, 25.I.2005

EN Official Journal of the European Union

I

(Legislative acts)

REGULATIONS

REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 27 April 2016
n the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

..In case of paediatric trials

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 September 2017
EMA/CPMP/ICH/2711/1999
Committee for Human Medicinal Products

ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population

Step 5

INTERNATIONAL COUNCIL ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

Current *Step 4* version
dated 20 July 2017

Ethical considerations for clinical trials on medicinal products conducted with minors

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

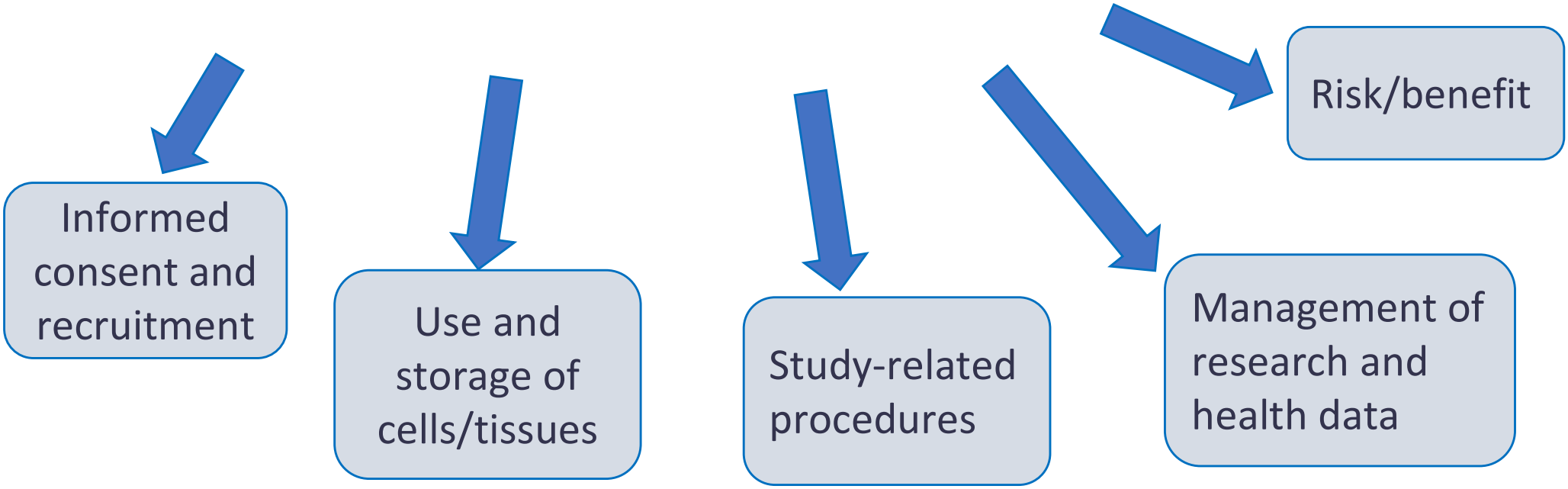
Revision 1

18 September 2017

3- to well-set up the protocol

Clinical trial protocol – key points

- Strong rationale, availability of supporting evidence
- Contents according to ICH-GCP



…if applicable…

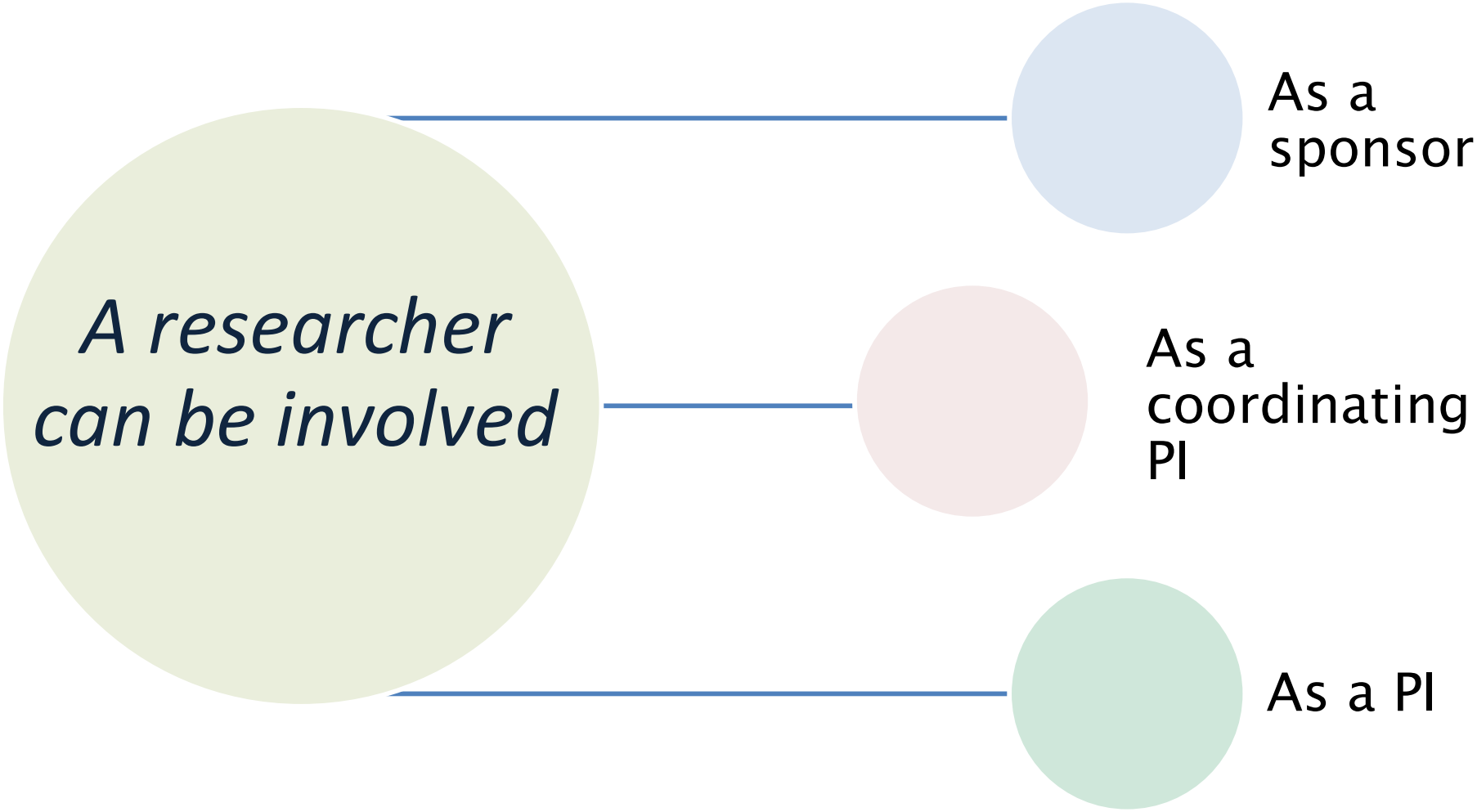
- *Involvement of children* ⇨ specific provisions, informed assent, ad hoc endpoints and procedures, etc
- *Genetic tests* ⇨ specific aims and endpoints, provisions for informed consent, recruitment
- *ATMPs* ⇨ handling according to Reg 1394/2007/EC

4- to know which responsibilities everyone involved has

Steps of a clinical trial

- Protocol preparation
- Site identification
- Clinical Trial Application
- Site Initiation and Recruitment
- Study Management: data management, drug management, clinical and technical operations, communication, procedures and plans
- Monitoring
- Pharmacovigilance
- Site and data closure
- Data analysis and trial report

Roles and responsibilities



4- to know which responsibilities everyone involved has

SPONSOR

SPONSOR

- Sites identification
- Registration in clinical trial databases
- Authorisation and Ethics approval
- IMPs manufacturing & distribution
- Pharmacovigilance and monitoring activities
- Management of personal data
- Transfer/sharing of data/samples
- Management of financial issues
- Follow on (amendments, study end, annual reporting)

All activities can be delegated!

4- to know which responsibilities everyone involved has

Coo PI

In multi-centre trials ⇨ the same study conducted at more than one site, one or more countries

❖ **COORDINATING INVESTIGATOR**

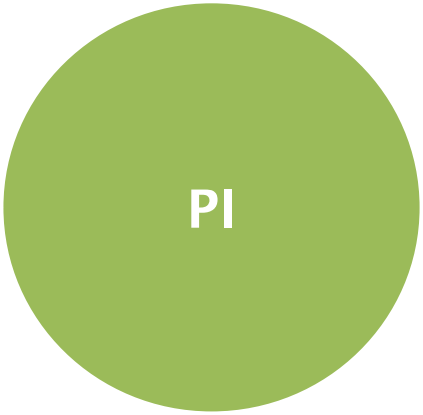
an individual responsible for the coordination of investigators at different centres in the same country participating in a multicenter trial

- ICH E6(R2) Guideline for GCP, Regulation (EU) 536/2014 -

Coo PI

- Usually collaborates with the sponsor to
- prepare the protocol and related docs
- follow up, manage outcomes

4- to know which responsibilities everyone involved has



❖ **INVESTIGATOR**

an individual responsible for the conduct of a clinical trial at a clinical trial site

❖ **PRINCIPAL INVESTIGATOR (PI)**

an investigator who is the responsible leader of a team of investigators who conduct a clinical trial at a clinical trial site

- ICH E6(R2) Guideline for GCP, Regulation (EU) 536/2014 -

What should be able to demonstrate before participating in a clinical trial?

PI

To have

- potential for **recruiting**
- **time**
- adequate **facilities**
- an adequate qualified **staff**

PI

- Check of needed **expertise and facilities** (according to the protocol) to carry out informed consent, collect samples, perform tests, record data, manage IMPs, process data (collect, analyse, store, share) etc.
- Local documents preparation
- Check of COI
- Management of financial issues and insurance
- IMPs management (receiving, storing, dispensing, inventory, disposing)
- Adverse events reporting

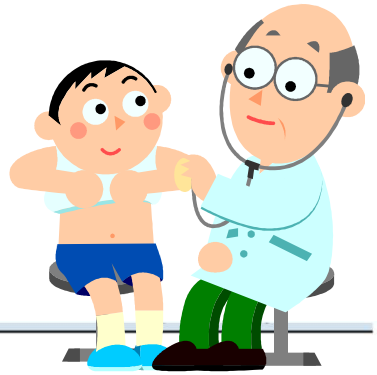
…In case of paediatric trials

PI

Further **competences** and **facilities** required for:

- Informed consent and assent
- Ability to collect samples from children
- Measures for storage of biosamples

Guide for informed consent and assent



Tool of the contents for informed consent and assent forms across all paediatric age groups

Symbol	Description
✖	Does not have to be included in the assent/agreement/informed consent process for this age group
✔	Should be included and discussed during the assent/agreement/ informed consent process for this age group
◎	May be included/optional to include in the assent/agreement/informed consent process for this age group

Age Group in years 0<2	2<6	6<10	10<18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
✖	✖	◎	✔	✔	**Explanation of the concept of a clinical trial and the methodology used.**	• What is a clinical trial? • How does the clinical trial differ from normal routine care? • What is randomisation / double-blind / open label etc.?	NOTE: **Explain only the relevant methodology – a short version - used according to the current protocol. Avoid complex terms and flowcharts with too much detail.**

Lepola, Kindred, Giannuzzi et al, Arch Dis Child 2021

EnprEMA NETWORK

Guide for managing paediatric samples

- Easy-to-use tool
- for managing biological samples and associated data in the design and conduct of paediatric trials

PedCRIN

Giannuzzi et al, CTS 2023 in press; [ECRIN website]

TEDDY NETWORK
European Network of Excellence for Paediatric Research

- The preparation and conduct of a clinical trial on drugs must comply with a well-defined set of rules
- The trial protocol must be well-set up
- Before starting a trial, all the requirements apply according to the role an investigator may have in a trial
- An investigator should
  - be aware of what is a clinical trial
  - apply the required rules
  - have the specific competences and facilities to comply with the protocol

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