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# **Clinical Trials – application process, legislation & guidelines**

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*IMB Clinical Trials Seminar 19<sup>th</sup> June 2012*

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# IMB Mission

**To protect and enhance public and  
animal health through the regulation of  
medicines,  
medical devices  
and healthcare products**



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# Legislation

- The IMB is responsible for the authorisation of clinical trials and the inspection of compliance with ‘good clinical practice’ (GCP)
- Legislation:
  - Control of Clinical Trials Acts 1987 and 1990
  - **Directive 2001/20/EC** implemented nationally as SI No. 190 of 2004 on 1<sup>st</sup> May 2004



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# European Clinical Trials Directive 2001/20/EC

- Established to:
  - provide greater protection to subjects participating in clinical trials
  - ensure quality of conduct
  - harmonise regulation and conduct of clinical trials throughout Europe
- Review ongoing...



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# European Clinical Trials Directive 2001/20/EC

Amendments...

- Implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use.

The Good Clinical Practice Directive 2005/28/EC

- Requires good manufacturing practice (GMP) to ensure product quality

The Good Manufacturing Practice Directive  
2003/94/EC

...also implemented nationally



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EudraLex (rules/regulation for medicines) :

- Volume 10: Notice to Applicants
  - Questions and Answers, Feb 2012
  - Guidance CT-1, March 2010
- ICH Topic E6, Guideline for Good Clinical Practice

[http://ec.europa.eu/health/human-use/clinical-trials/index\\_en.htm](http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm)



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# Clinical Trials Guidelines - Volume 10



## Chapter I

- The dossier for the competent authority (CT1)
- The dossier for the ethics committee

## Chapter II

- Safety reporting (CT-3)

## Chapter III

- Pharmaceutical data

## Chapter IV

- Inspections

## Chapter V: GCP, EudraCT

## Chapter VI: Legislation



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# What is a clinical trial?

- study to investigate the clinical, pharmacological, pharmacodynamic or pharmacokinetic effect or to identify adverse reactions to investigational medicinal products (IMPs)
- IMPs include authorised, unauthorised medicines, placebos, comparators, blinded test and comparator medicines
- Questions? See decision tree in the Annex to Volume 10 Q&A document



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# What is not a clinical trial?

Outside the scope of the Regulations (SI No 190 of 2004):

- Non-interventional trials...medicine used within terms of its authorisation, usual clinical practice, no randomisation, prescription independent of decision to include patient in trial, no additional diagnostic or monitoring procedures
- Medicine administered to study physiology of the body (not pharmacology of medicine) e.g. diagnostic or challenge agents
- Clinical trials involving only medical devices, food supplements, or other non-medicinal therapies (such as surgical interventions).



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# Non-commercial Clinical Trial

- Trial is not part of the development programme for a marketing authorisation of a for-profit organisation (e.g. pharmaceutical industry)
- Investigator/sponsor has no commercial or financial interest in the outcome of the trial
- Designed, conducted and reported under the control of the researchers
- Data issued from the clinical trial are owned by the researchers (as per *Eudravigilance registration*)
- No requirement to provide medicines/devices free of charge
- IMB: '900' trials = sponsor or applicant is 'non-commercial'

# Sponsor

- person who takes responsibility for the initiation and management (or for arranging the initiation and management) of, and the financing (or arranging the financing) for that clinical trial;
- based in EU or legal rep. in EU or EEA
- every trial must have a sponsor
- IMB/EC communication is with sponsor



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# Can a sponsor delegate?

- Yes!
- Activities delegated must be specified in writing on application form (Section G.5) and records
- Sponsor is ultimately responsible for ensuring conduct of trial (e.g. compliance with protocol) and data generated comply with legislation
- Non-commercial, multi-centre CT: local and international sponsor



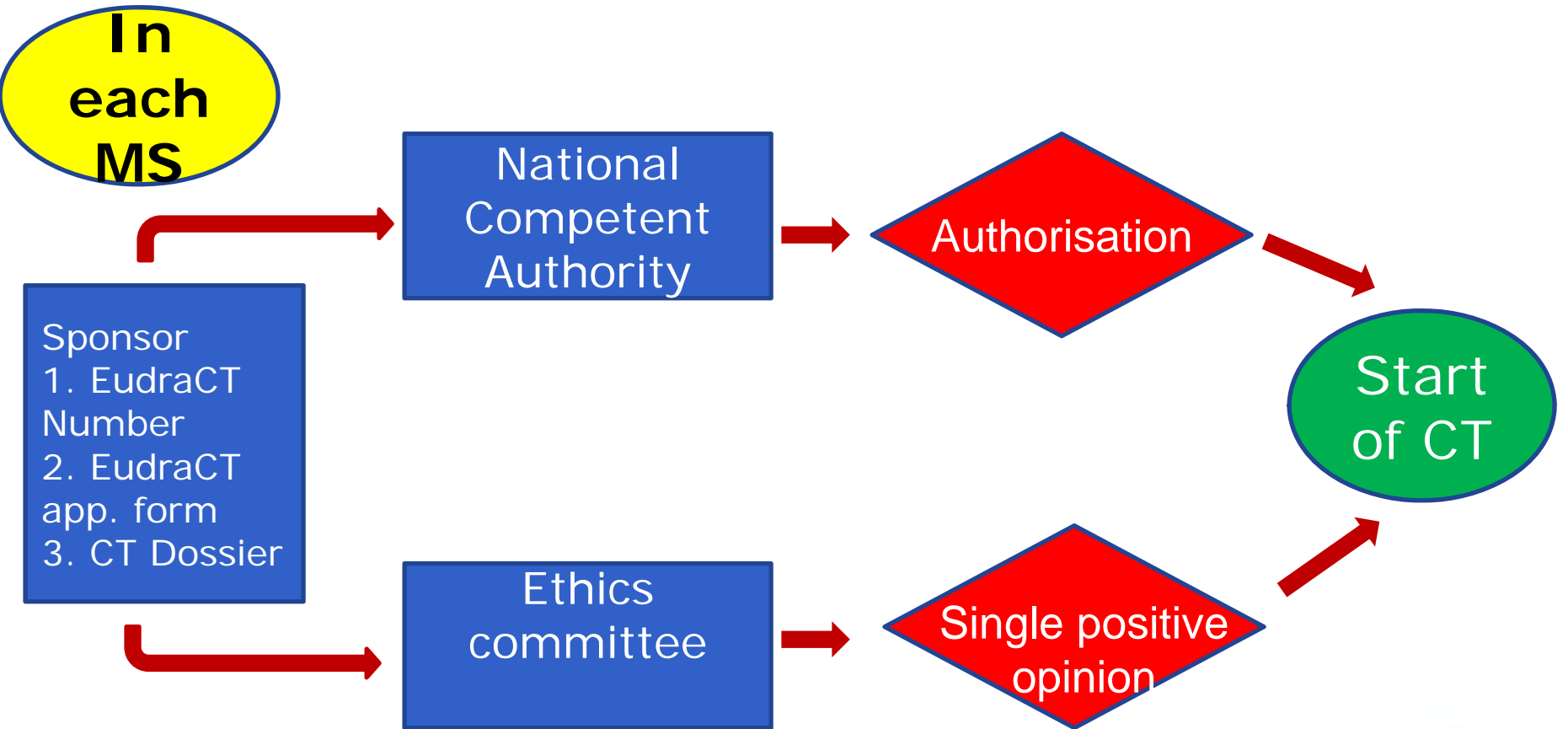
# Investigator

- the authorised health care professional responsible for the conduct of a clinical trial at a trial site and if a trial is conducted by a team of authorised health care professionals at a trial site, the investigator is the leader responsible for that team;
- Co-ordinating (multicentre) and principal (single-centre) listed on EudraCT application form
- ‘investigator-sponsor’ is the chief investigator who is also acting as the sponsor for that clinical trial;



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# Clinical Trials - Regulatory framework



← Parallel procedure is possible/fixed time frame →



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# Trial can start...

- IMB authorisation
- 'Recognised' Ethics Committee - positive opinion
- Sponsor or legal representative established in the Community

*SI No 190 of 2004*

- Sponsor/third party agreements in place



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# Application to the IMB

## **General information:**

- Covering letter
- EudraCT number
- EudraCT application form (signed by sponsor/applicant)
- IMP labelling in English
- EPA Certificate (for GMOs only)

## **Protocol-related folder:**

- Current protocol + synopsis (signed by sponsor & investigators)
- EC's opinion (when available)

## **IMP-related folder**

- Investigator's brochure
- Investigational Medicinal Products Dossier (IMPD)
- Non-Investigational Medicinal Products Dossier (NIMPD)





- **EudraCT** (**E**uropean **U**nion **D**rug **R**egulating **A**uthorities **C**linical **T**rials) is a database of all clinical trials commencing in the Community from 1 May 2004 onwards. It has been established in accordance with Directive 2001/20/EC.  
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** - Each clinical trial with at least one site in the European Union receives a unique number for identification, the EudraCT Number, must be included on all clinical trial applications

<https://eudract.emea.europa.eu>



# Protocol

- Document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial and includes any successive versions of the protocol and protocol amendments;
  - Definition of the end of trial
  - Provision for care of subjects after trial has ended, if necessary

**NB: Consent documents not reviewed by the IMB**



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# IMB Protocol Template

- Background and rationale
- Objectives & endpoints/outcome measures
- Trial design
- Treatment of trial subjects
- Safety reporting
- Statistics
- Data handling and record keeping
- Retention of essential documents – minimum 5 years
- QC & QA procedures
- Audits and inspections
- Ethics
- Financing and Insurance/indemnity
- Clinical Study Report and publication policy
- References



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# Investigator's Brochure

- Summary of the clinical and non-clinical data on the IMP which are relevant to the trial e.g. rationale for dose, safety monitoring
- Reference safety information for assessment of expectedness of adverse reactions
- Authorised IMP: use the Summary of Product Characteristics (SmPC):  
[www.imb.ie](http://www.imb.ie)



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# Investigational Medicinal Products Dossier (IMPD)

- Contains data from non-clinical studies and clinical use and provides information on the quality of test products, comparators and placebos to be used in the clinical trial
- Concise, data in tabular form
- Stand-alone or cross refer to Investigator's Brochure
- Simplified IMPD...
  - IMP authorised: use SmPC  $\pm$  additional data
  - Marketed products (blinding)  $\pm$  pharmaceutical data

See CT-1 for further examples



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# IMPD – Pharmaceutical Data

- Authorised
  - SmPC
  - If blinded / modified (e.g. over-encapsulation) – data to demonstrate that there is no significant effect on the quality of the product
- Unauthorised in EU/EEA/ICH or placebo
  - full IMPD is required.
  - **Substances of *chemical* origin**: Guideline: (CHMP/QWP/185401/2004)
  - **Substances of *biological* origin**
    - Guideline (EMA/CHMP/BWP/534898/2008)
    - Guideline on viral safety (EMEA/CHMP/BWP/398498/2005)
  - **Advanced Therapy IMPs**: medicinal products involving cell or gene therapy or tissue engineering (vaccines against infectious diseases are excluded): no guidance yet – **pre-submission meeting**
- Use of authorised products is highly recommended



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# IMP licences and labelling

- IMP licences / QP declarations are required for:
  - All sites conducting manufacturing activities related to the unauthorised IMP / placebo (e.g. manufacture, packaging).
  - Sites performing modification/ re-packaging of authorised products (dependent on the modification proposed).
  - Release of unauthorised IMPs / placebo and modified authorised products (IMP licence).
- Labelling:
  - The labels of the immediate and outer container should comply with the requirements of **Annex 13 to the EU Guide to GMP** on 'Manufacture of Investigational Medicinal Products'.
  - Label text must be in English.
  - Labels are not reviewed during assessment but could be subject to review during inspections.



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# Non-investigational Medicinal Products

- Products which are not the object of investigation (i.e. not test product, placebo or active comparator)
- Examples: rescue medication, challenge agents, medications to assess endpoints e.g. radiopharmaceuticals and background medicines
- Strongly recommend that authorised medicinal products are used

See Guidance in Vol. 10



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# IMB does not assess...

- Indemnity/insurance matters, facilities and staff-related issues including the suitability of investigators and other ethical issues
- Patient information and consent form - significant issues relevant to patients may be highlighted to ethics committee
- Statistical plan should be included in the study protocol however detailed assessment is not performed
- Labelling – may be examined at inspection

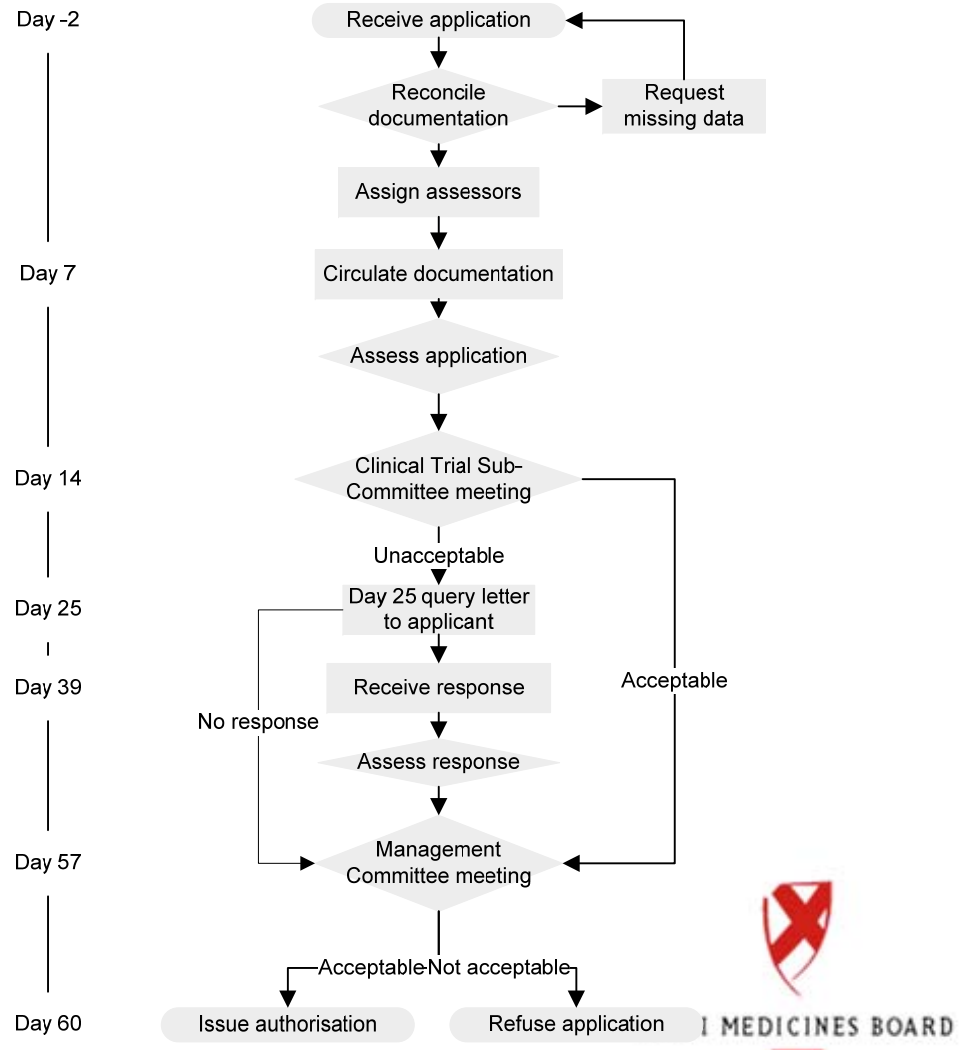


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# Clinical Trials – IMB Procedure

Procedure for authorization of a clinical trial by the IMB

NB: Max 60 days  
No clock-stop



# IMB Links

Assessment  
(quality, preclinical & clinical)



Clinical Trials Subcommittee of the  
Advisory Committee for Human Medicines  
(members: [www.imb.ie](http://www.imb.ie))



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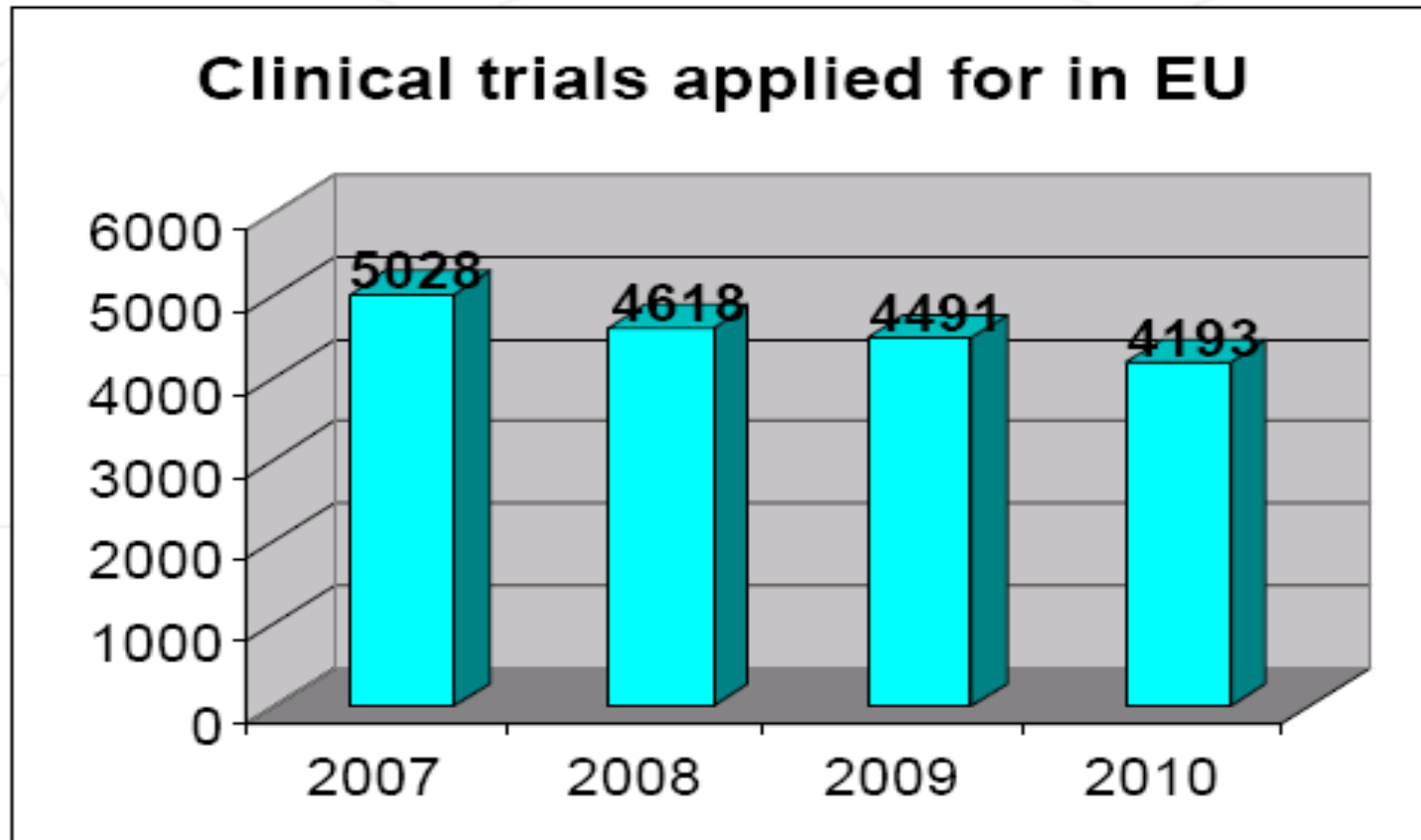
# Clinical Trials Statistics

- Average 109 authorisations/year ('07-'10)
  - 27% oncology
  - 11% cardiology
  - 7% each: CNS, anaesthesia, endocrine
  - 10% non-commercial trials



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# European Commission Clinical Trial Statistics



# Clinical Trials Facilitation Group (CTFG)

- Established by Heads of Medicines Agencies (HMA)
- Representation: 27 national Competent Authorities, European Commission and European Medicines Agency
- Sharing of scientific assessment of multinational clinical trials – **voluntary harmonization procedure (VHP)**
- Harmonizing processes and practices relating to clinical trials mainly in the fields of clinical trial applications, clinical trial amendments and safety procedures
- Developing data sharing and participating in the improvement of information systems
- Developing communication with stakeholders and co-operating with other EU working groups



# Voluntary Harmonisation Procedure (VHP)

- Co-ordinated assessment of a clinical trial that is to take place in several European countries (3) - short, predictable timelines.
- Submission of a common dossier to the VHP Co-ordinator and a simultaneous assessment by the national competent authorities concerned, common position within 60 days
- National phase abbreviated: no further changes to documents.
- 144 applications since 2009, 90% positive opinion
- 86% commercial; 14% non-commercial
- Competent authorities only not ethics committees
- Further information: [www.hma.eu](http://www.hma.eu)



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# EU Clinical Trials Register



- Public face of
- Information on clinical trials in EU and EEA and those conducted outside the EU/EEA if they form part of a paediatric investigation plan (PIP).
- Information: title of protocol, sponsor, medical condition, dates, population age and gender, status in countries participating
- WHO - 'primary registry' – registration prior to publication
- Launched on 22 March 2011
- Future: publication of results of studies

<https://www.clinicaltrialsregister.eu>



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# Clinical Trials – useful references

- IMB Website [www.imb.ie](http://www.imb.ie)
  - Guide to clinical trial applications
  - Application forms, links to EU sites etc
- Protocol template – available on request
- Queries

[clinical.trials@imb.ie](mailto:clinical.trials@imb.ie)

[IMBPharmacovigilance@imb.ie](mailto:IMBPharmacovigilance@imb.ie)



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# European Commission Website

The screenshot shows a Windows Internet Explorer browser window displaying the European Commission website. The address bar shows the URL: [http://ec.europa.eu/health/human-use/clinical-trials/index\\_en.htm#geninf](http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm#geninf). The page title is "Medicinal products for human use - Clinical trials | Public health, European Commission".

The website layout includes a blue header with the European Commission logo and the text "PUBLIC HEALTH". Below the header is a navigation breadcrumb: "European Commission > DG Health & Consumers > Public health > Medicinal products for human use > Clinical trials".

The main content area features a search bar, a "Print version" link, and social media icons. The central heading is "Medicinal products for human use". Below this, there is a "Hot topics" section with two entries:

- [Draft template for the written confirmation for active substances imported into the European Union for medicinal products for human use](#)  
Released 16 April 2012
- [Delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use - concept paper submitted for public consultation](#)  
Released 20 January 2012

A "More" link is provided for the hot topics section. Below this is a "Related information" section with links to "Press material", "Key documents", "Videos", "Events", "Consultations", and "News and updates".

The "Clinical trials" section includes a "General Information" link and a "Major developments" link. A small image of a laboratory setting is visible next to the "Major developments" link.

The "General Information" section contains the following text:

Clinical trials are investigations in humans intended to discover or verify the effects of one or more investigational medicinal products ("IMPs").

Requirements for the conduct of clinical trials in the EU are provided for in " [Directive 2001/20/EC](#) of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" (" [the Clinical Trials Directive](#) ").

The Clinical Trials Directive is concretised further by " [Commission Directive 2005/28/EC](#) of 4 April 2005 laying down principles and detailed guidelines for good clinical practice on records



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**THANK YOU !**



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