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Clinical Trials – application process, legislation & guidelines

IMB Clinical Trials Seminar 19th 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 1st 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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European Commission Website

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

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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’

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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

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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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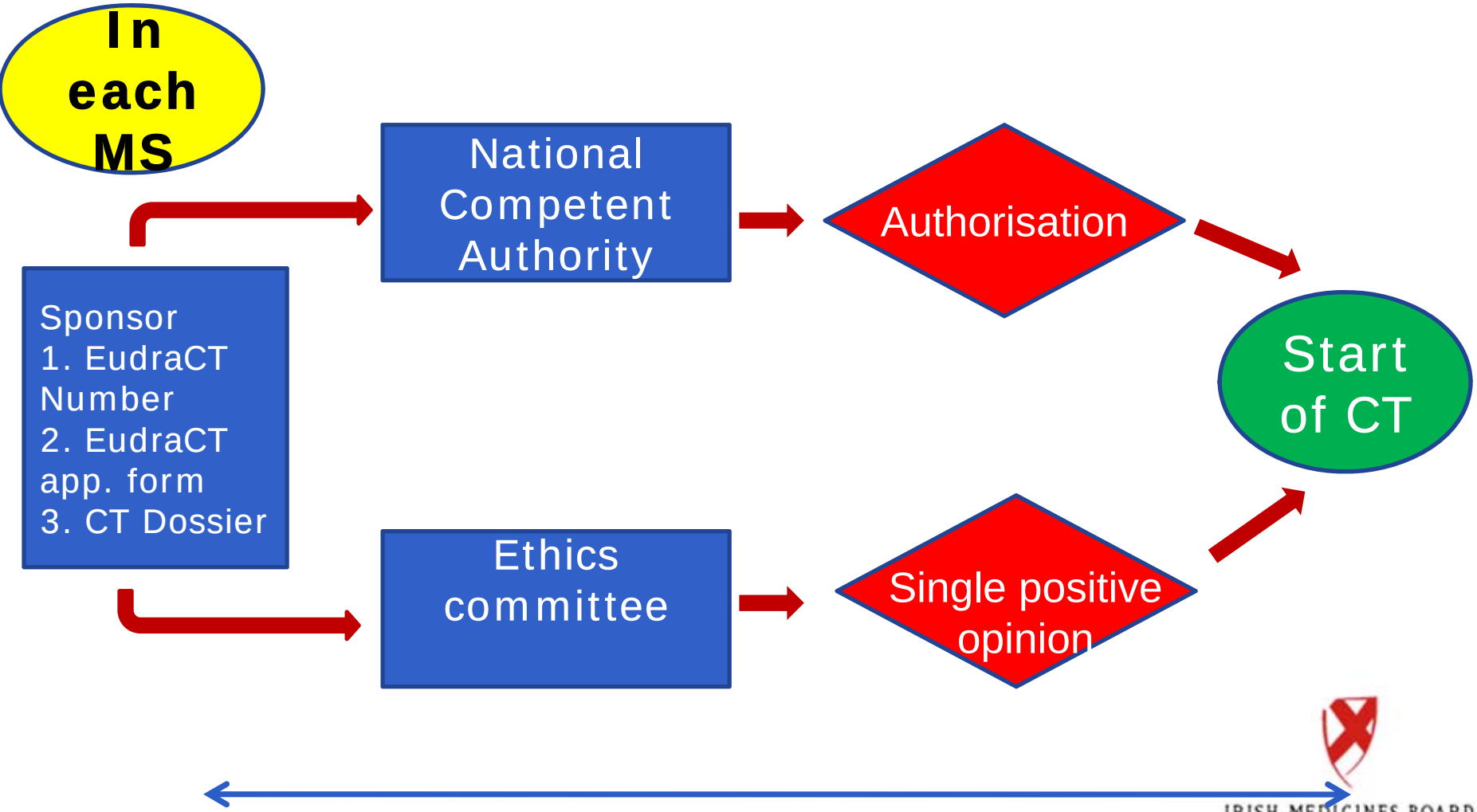
Clinical Trials - Regulatory framework



Parallel procedure is possible/fixed time frame

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)

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EudraCT

- 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

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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

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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 ± additional data
  - Marketed products (blinding) ± 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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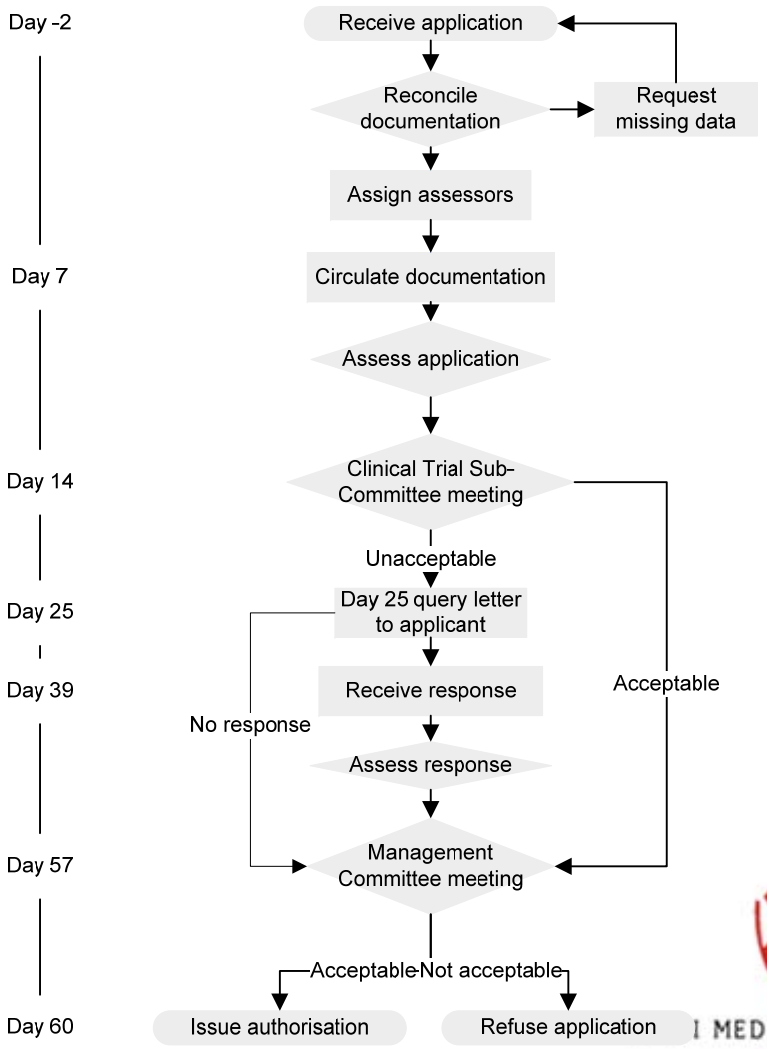
Clinical Trials – IMB Procedure

Procedure for authorization of a clinical trial by the IMB

NB: Max 60 days
No clock-stop



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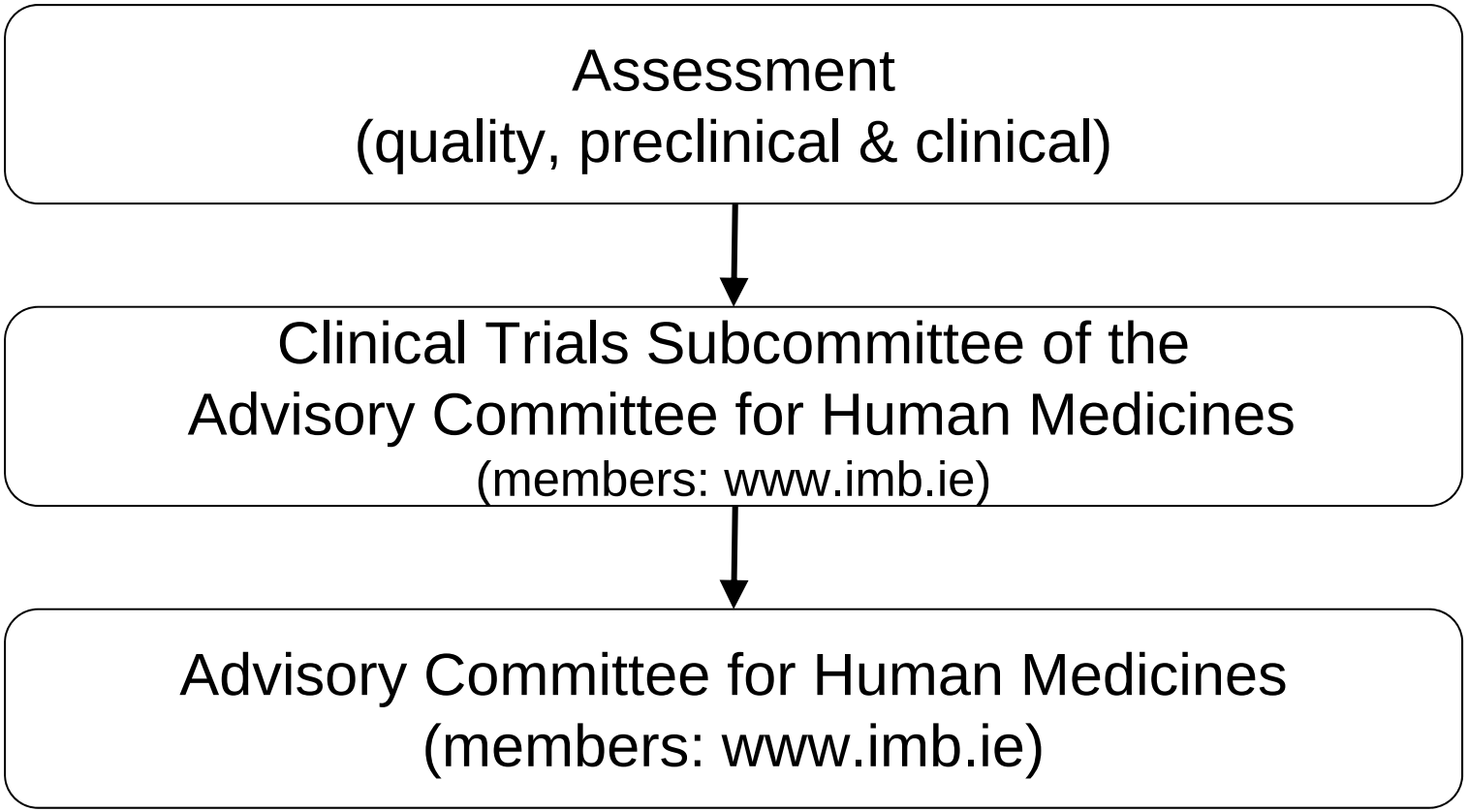
IMB Links



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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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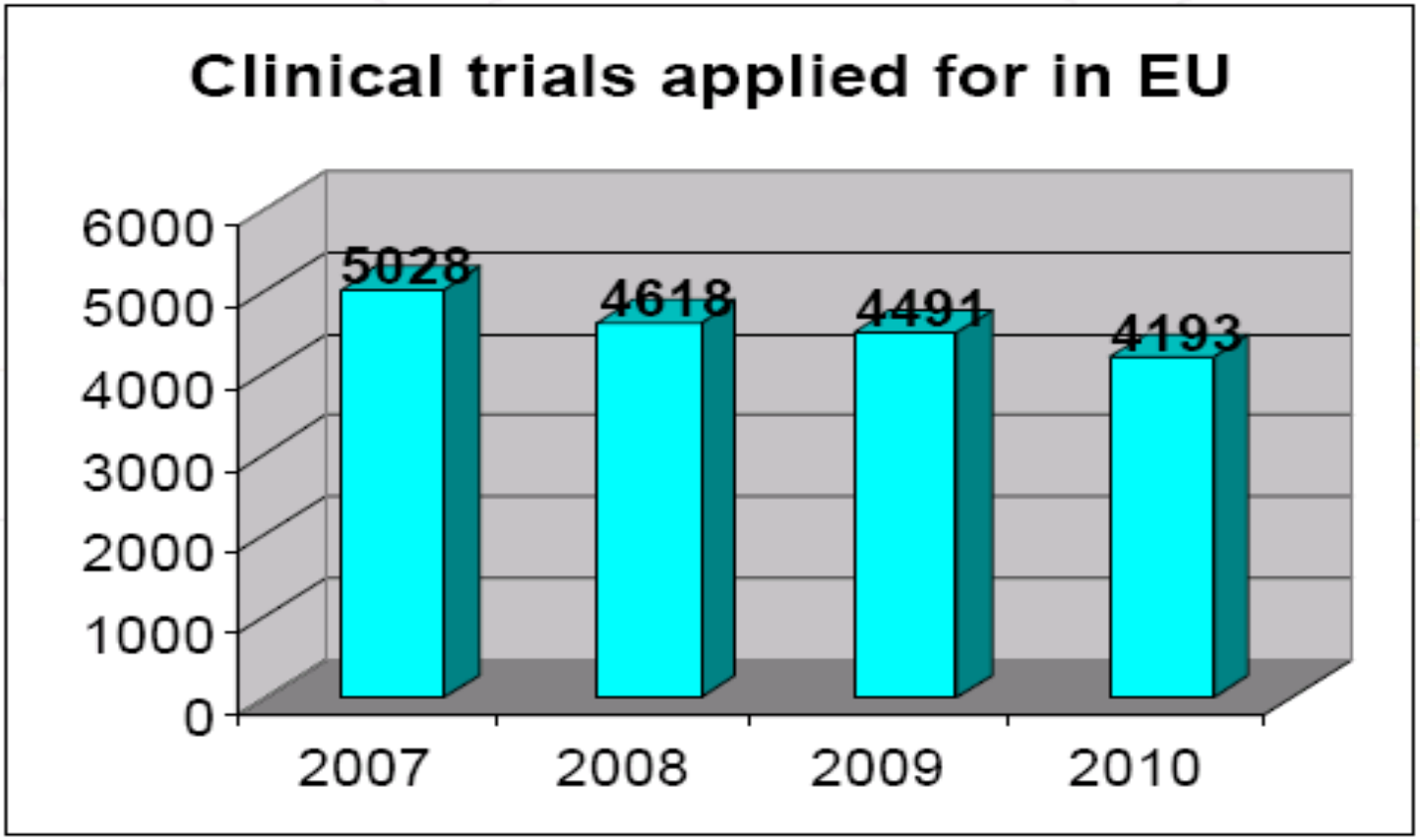
European Commission Clinical Trial Statistics



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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

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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

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EU Clinical Trials Register

- Public face of EudraCT
- 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
  - Guide to clinical trial applications
  - Application forms, links to EU sites etc
- Protocol template – available on request
- Queries

  clinical.trials@imb.ie

  IMBPharmacovigilance@imb.ie

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European Commission Website

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THANK YOU !

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