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Clinical trials in Ireland Regulatory Framework.

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Agenda

- IMB Background
- Clinical Trials - Regulation
- Clinical Trial Statistics
- Conducting a Clinical trial
- IMB Evaluation of Adverse Events
- IMB Aims
- Web links / Contact email Addresses



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IMB - Background

- 1996 (formerly National Drug Advisory Board)
- Competent authority for
 - Medicinal products (including herbals and homeopathics), blood and blood components, tissues and cells, advanced therapies
 - Medical devices
 - Veterinary medicines
 - Cosmetics



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Clinical Trials Regulation

- Control of Clinical Trials Acts 1987 and 1990
- Directive 2001/20/EC
 - Implemented nationally into SI 190 of 2004, May 2004
 - Amended SI 878 of 2004, December 2004
- Directive 2005/28/EC
 - Implemented nationally into SI 374 of 2006, July 2006



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Clinical Trials

- + Good Clinical Practice (GCP)
- + Licensing
- Human Medicines
- Veterinary Medicines
- Manufacturing
- Wholesale Distribution
- Controlled Drugs and Precursor Chemicals
- Classification of Medicines
- Export Certification

Clinical Trials

The role of the Irish Medicines Board is to assess applications from sponsors to conduct clinical trials with medicinal products. The types of trials assessed range from first-in-man studies for new compounds to studies with products which already have marketing authorisations.

Clinical trials are undertaken to allow data on the safety and efficacy of new products to be collected. These trials can be conducted using healthy volunteers or patients, depending on the type of product and its stage of development. Information on the quality of the product and its non-clinical safety will have been obtained before the clinical trial programme commences.

Clinical trials begin with small studies in a controlled population of volunteers or patients and, as data are gathered, expand to large scale studies in patients. These large scale studies will often investigate the new product and the currently used treatment to see how these two compare. As information is obtained, larger numbers of patients are exposed to the new product and safety data can be collected showing the safety of the product in the intended patient population.

Submission of Academic Clinical Trial Investigation Applications

When submitting academic led clinical trial investigations in circumstances where there is no financial support for the conduct of the clinical trial, the investigator

Latest Information

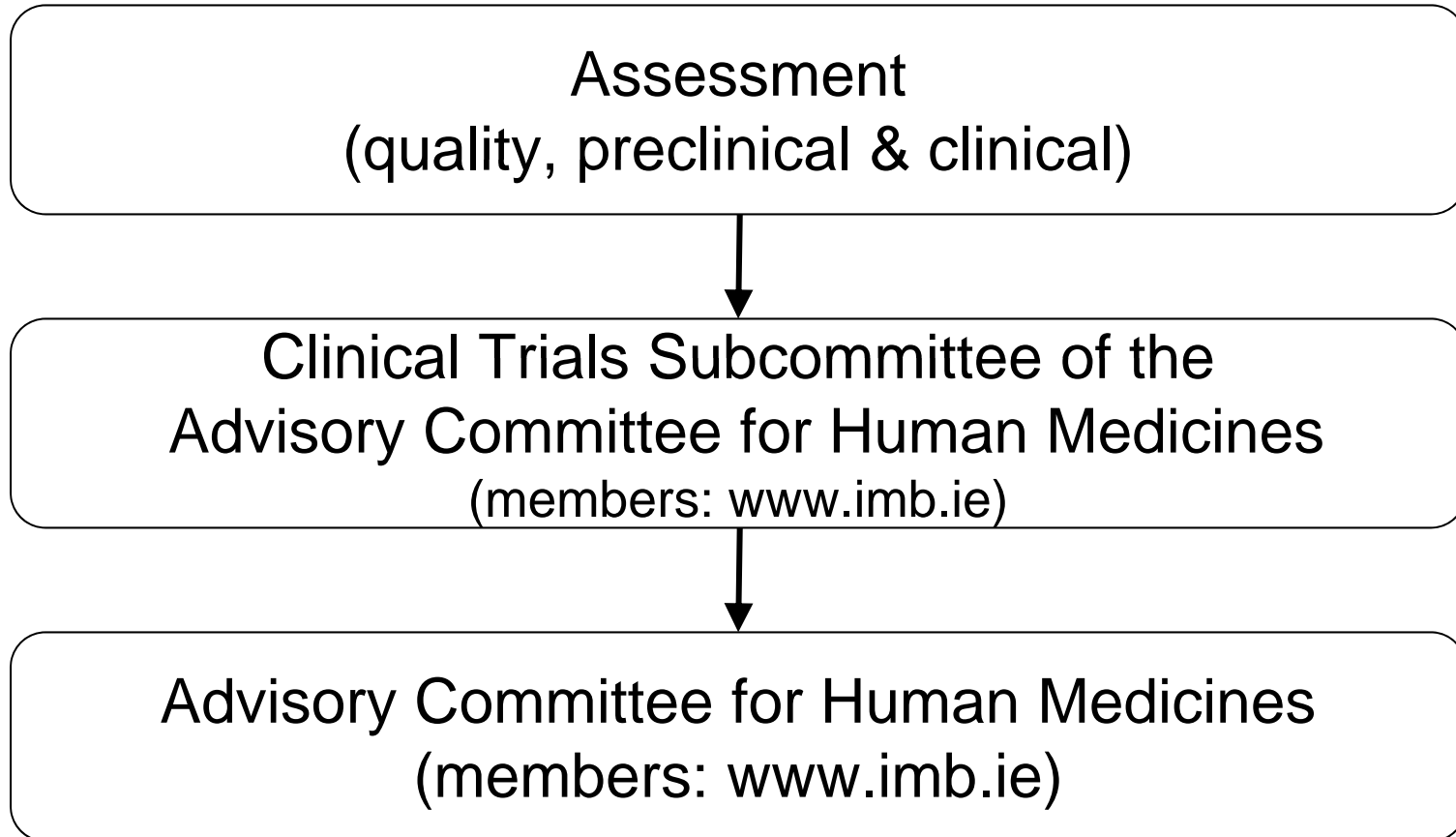
Publications - (13)

FAQs - (23)

Consultation - (1)

Provide Feedback

IMB Clinical Trial process.



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IMB Clinical trial Process

- Ongoing involvement and benefit/risk assessment until trial completion.
- Amendments to the clinical trial
 - Non substantial
 - Substantial



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IMB - EU Links

- EU Working Groups
 - Clinical Trials Facilitation Group (CTFG)
 - EU Commission (guidance etc)
 - Good Clinical Practice (GCP) Inspectors
 - Good Manufacturing and Distribution Practice (GMDP) Inspectors
- Databases
 - EudraCT and alert system
 - EudraVigilance (SUSAR reporting)



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Definition of an Investigational Medicinal Product

‘a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form’

Dir. 2001/20/EC



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What is a clinical trial ?

- Any investigation in human subjects other than a non interventional trial intended;
 - a) discover, verify clinical pharmacological or other pharmacodynamic effects of one or more IMP's.
 - b) Identify AR to one or more IMPs
 - c) study absorption, metabolism, distribution or excretion of such IMPs
 - d) discover, verify, identify or study any combinations of above.

IMB is responsible for authorisation of interventional clinical trials only.

Definition of a Non-interventional Trial

‘a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by the trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data’

Dir. 2001/20/EC

- *See volume 9 A guidelines on pharmacovigilance post authorisation safety study*



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IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				A NON-INTERVENTIONAL CLINICAL TRIAL?
Is it a medicinal product (MP)? ¹	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
<p>If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP.</p> <p>If you answer yes to <u>any</u> of the questions below go to column B.</p>	<p>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</p> <p>If you answer no to this question below go to column C.</p>	<p>If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column D.</p>	<p>If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column E.</p>	<p>If you answer yes to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC.</p> <p>If your answers in columns A,B,C & D brought you to column E and you answer no to <u>any</u> of these questions the activity is a clinical trial within the scope of the Directive.</p>
<p>A.1 Is it a substance¹ or combination of substances presented as having properties for treating or preventing disease in human beings ?</p> <p>A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?</p> <p>A.3 Is it an active substance in a pharmaceutical form?</p>	<p>B.1 Are you <u>only</u> administering any of the following substances?</p> <ul style="list-style-type: none"> • Human whole blood²; • Human blood cells; • Human plasma; • Tissues except a somatic cell therapy medicinal product³; • A food product⁴ (including dietary supplements) not presented as a medicine; • A cosmetic product⁵ • A medical device 	<p>C.1 To discover or verify/compare its clinical effects?</p> <p>C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?</p> <p>C.3 To identify or verify/compare its adverse reactions?</p> <p>C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?</p>	<p>D.1 To ascertain or verify/compare the efficacy⁶ of the medicine?</p> <p>D.2 To ascertain or verify/compare the safety of the medicine?</p>	<p>E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?</p> <p>E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation?</p> <p>E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol⁷?</p> <p>E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?</p> <p>E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?</p> <p>E.6 Will epidemiological methods be used for the analysis of the data arising from the study?</p>

Clinical Trials Statistics

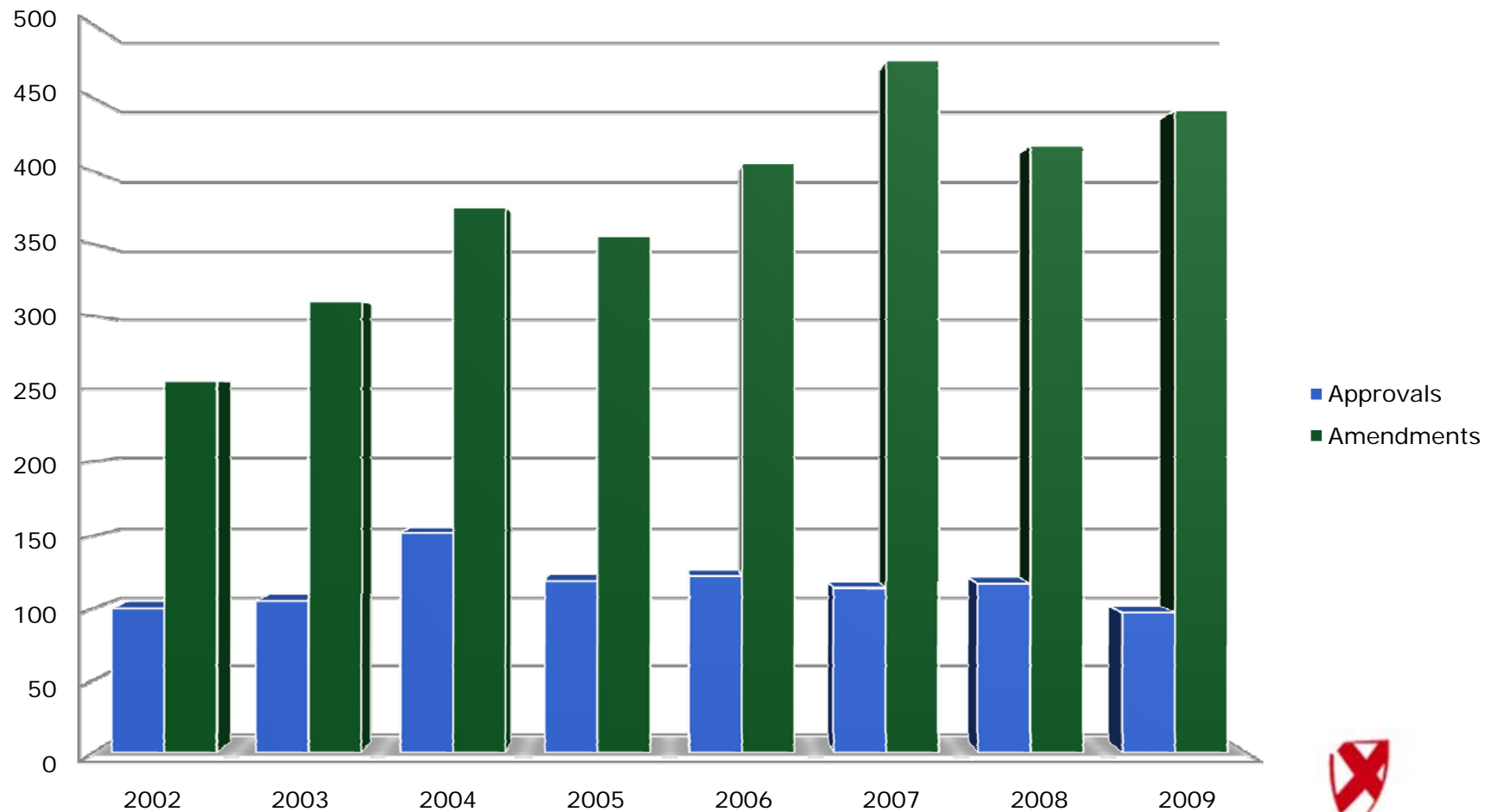
- Approx 390 trials ongoing
- Average 114 applications/year (2005- 2009)
- Approx 140 sponsors
- Approx 500 investigators
- Approx 20% non-commercial trials
- 100% compliance with timelines



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IMB CT statistics

Applications authorised 2002-2009



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Conducting a Clinical Trial

- All staff assisting in a clinical trial should clearly understand the protocol.
- Should be clear on their trial related duties and functions & follow the approved protocol.
- Highlight any practical issues, minimise potential protocol violations for patients and trial staff.
- Review the patient information



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Conducting a Clinical Trial

- Trial staff should be familiar with the expected adverse events, ensure that information to patients is sufficiently detailed and clearly informs them to report any adverse events
- Question subjects about clinical status/symptoms in accordance with protocol and remind subjects to inform them about new AE's
- Adverse events should not be ignored even if minor as they may be a sign of a more significant or evolving clinical significant issue.



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Conducting a Clinical trial

- Serious Adverse events (SAE) are very important- as emerging safety data.
- SAE reports must be timely, factual and consistent with medical record and case report forms.
- Follow up SAE is important for both incomplete initial reports and to provide information on resolution of any SAE's.



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Conducting a Clinical Trial

- Safety of clinical trial participants is dependent on
 - Protocol compliance (staff and subjects),
 - Timely reporting and recording safety information,
 - Management of ongoing expected and unexpected safety issues
- Adhering to the approved protocol and GCP principals will generate high quality safety and efficacy data and provide reassurance that the trial was conducted to the highest ethical and scientific standards.
- Clinical trial data influence decisions on medicinal product development, (e.g. form the basis for medicinal product authorisation, highlight or refute safety concerns, etc.)

Adverse Events

- Adverse Events vs Adverse reactions
 - Duration from signing informed consent to end of trial
- Serious adverse event

Sponsor

- Causality (is it a reaction to a trial medicine or not?
Probable, possible, unrelated)
- Expectedness (is the reaction a recognised adverse effect of the medication or is it unexpected?)
- Severity (Mild, moderate or severity).-



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SUSARs

- An investigator shall report any serious adverse event which occurs in a subject at a trial site immediately to the sponsor.

SUSARs: Both unexpected and serious (SUSARs) are subject to expedited reporting -unblinded unless SUSAR is an endpoint of the CT. (e.g. mortality/morbidity outcome study).

- Fatal or life threatening SUSARS:
Not later than **7 days** and any follow up information within a further 8 days.
- All other SUSARs: not later than **15 days**
(Directive 2001/20EC)



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IMB – Evaluation of Adverse Events 1

Adverse events become ICSR (Individual case safety reports)

- **Initial Report Review**

- Case validation
- Assessment of report status (initial/follow-up)
- Preliminary review of case details, reactions, (seriousness/expectedness etc.)
- Compliance review (report quality/timelines)

- **Data Processing**

- IMB case ref number assigned
- Database entry
- Acknowledgement of IE cases
- Follow-up information requested, as required
- Onward reporting to EudraVigilance, as required



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IMB – Evaluation of Adverse Events 2

- **Additional Report Review**
- Detailed review of case, background data, i.e. medical history, con meds, risk factors etc.
- Consideration of single case, in context of other data, i.e. further case reports, cases with related symptoms, class related effects.
- Impact of case against background data/cumulative safety information
- Medical review, as necessary
- Discussion at monthly expert CT subcommittee meeting, as required



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Additional IMB Safety Evaluation

- Review of Annual Safety Reports (ASRs) & Line Listings for national SUSARs, with cross-check for relevant cases
- Review of cumulative safety data by medical assessor and highlighted for discussion at CT meetings, as necessary
- Consideration given to need for regulatory action/communication, e.g. Clinical trial amendment, GCP site inspection, PV system inspection (MAH), letter to Health Care Professionals, updates to Investigators Brochure etc.



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Compliance Monitoring

- Ensure receipt of appropriate, high-quality reports, submitted in accordance with specified timelines
- Assess consistency/completeness of reporting across individual and cumulative safety reports
- Consider issues indicative of system-related problems, i.e. inadequate oversight of data
- Assess progress with regard to implementation of electronic reporting



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Regulatory Action/Communications

- Regulatory actions discussed and agreed by CT Assessors/CT Committee
- Finalisation of letter to healthcare professionals (HPC) should be agreed with IMB.
- Submit
 - Draft texts
 - Overview of proposed recipients
 - Timelines for finalisation/distribution

NB – Letters to HPCs issued on IMB website



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Safety Summary & Conclusions

- Timely and comprehensive CT reporting and evaluation of safety data essential to:
 - Facilitate identification of new safety concerns
 - Establish safety profiles of medicinal substances
 - Ensure timely and appropriate regulatory action
 - Support prompt communication to the CT community and wider healthcare professional groups, as necessary



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IMB Aims

- Facilitate positive research environment
 - clear administrative procedures
 - efficient, quality assessments
 - training of assessors/inspectors
 - ensure compliance with GCP
 - Adhere to timelines
- Ensure protection of subjects
- High quality research data
- Availability of safe and effective medicines



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Links

- <http://www.imb.ie>
- [EudraLex - Volume 10](#)
[Clinical trials guidelines](#)
- clinicaltrials@imb.ie
- imbpharmacovigilance@imb.ie
- compliance@imb.ie



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Thank You
Comments/Questions



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