Clinical Trial Approval in Europe

What is a clinical trial?

Clinical research is an important part of the process of gaining better knowledge and understanding of human health and disease as well as the development of new and effective therapies for treating these diseases. Clinical trials represent an essential component of evidence based medical research.

Clinical trials are research studies involving people (healthy volunteers or patients) that test the safety and efficacy of a new treatment. A ‘treatment’ in this context could mean:

- A medicine.
- A medical device – such as a hearing aid.
- A surgical procedure.
- A test for diagnosing an illness.

A clinical trial can also compare whether a new treatment is better than existing alternatives. No matter how promising a new treatment may appear during initial laboratory tests, clinical trials are necessary to prove and identify benefits and risks in humans. ‘Better’ in this context does not necessarily mean ‘with a better efficacy’ but may also signify ‘fewer side effects (Adverse Drug Reactions, ADRs)’ or ‘better handling, less burden’ and more. This is sometimes reflected in clinical trial designs which look for equivalence or non-inferiority to an existing treatment.

Clinical trials are designed by groups of doctors, scientists and other specialists. The trial design is usually based on a thorough analysis of existing research, and the recognition that certain questions about treatment, symptom control or

side effects need to be answered. To draw up the best possible trial design, discussions involve medical staff, nurses, patients, statistical experts and support staff, as well as representatives from companies or funding agencies. The background, design and plan for the study are contained in a document known as the **protocol.**

How are clinical trials conducted?

For clinical trial approval, a Clinical Trial Application (CTA) must be submitted to regulatory bodies called competent authorities. A Research Ethics Committee (REC) also reviews the protocol and gives a positive or negative opinion. This is to ascertain that the research respects the dignity, rights, safety and well-being of the people who are participating. In order to ensure compliance with ethical standards, the majority of clinical trial protocols are developed in line with the 'Declaration of Helsinki', a set of ethical standards for research involving human beings, human material or identifiable data, developed in 1964 by the World Medical Association (WMA) and revised several times.

Clinical trials on medicines are conducted in the European Union (EU) in compliance with regulations, directives and guidelines. The standard to which clinical trials are conducted is called Good Clinical Practice, as defined in a guideline by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP). This is an international quality standard that must be applied in all member states of the EU and describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and ethics committees. GCPs cover aspects of monitoring, reporting and archiving of clinical trial data and incorporating supplements on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process.

Who conducts clinical trials and why?

Clinical trials typically involve a number of different parties. It is helpful to understand who is leading the creation and the conduct of a trial and why they are doing it:

- A **sponsor** is the body (usually a company, university or hospital) that takes responsibility for organising the trial and often funds the trial.
- An **investigator (or investigators for multi-centre trials)** – the doctor responsible for the performance of the trial.
- Sometimes the sponsor will engage a **contract research organisation** (CRO) to help with the logistics (organisation) and the conduct of the trial.

Sponsors can be companies or government funded institutions/agencies. Both may perform trials in order to use the gathered data to support applications that will allow promotion and marketing of products for the approved indication(s).

They may also undertake studies in the best interests of the community to understand diseases. Occasionally they will collaborate with other partners to explore a particular problem, perhaps one that is not of commercial interest but is of interest to patients and the healthcare system.

History of clinical research legislation in Europe

As in the US, disasters in Europe have in several cases

prompted change in legislation. The thalidomide disaster contributed to the publication, in 1965, of the first European Directive, known as 65/65/EEC, enacted by the Council of the European Economic Community. It stated that no medicine could be placed on the market in a member state unless authorisation had been issued by the competent authority in that member state. In essence, pharmaceutical manufacturers had to seek approval for their medicines from each country before marketing could begin in that country.

In 1995, the European System for Marketing Authorisation of Medicinal Products as well as the European Medicines Evaluation Agency (EMEA), was established. Evaluation of applications and elaboration of guidelines was undertaken through the incorporation of the Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal Products (CVMP). The centralised procedure eliminated the need for individual member state review – as one approval is given to cover all member states.

The mutual recognition procedure (MRP) and the decentralised procedure (DCP) are used for those medicines not authorised by the centralised procedure. They are similar to the former procedure where an applicant goes directly to a single member state. Once the medicine is approved by that authority, the applicant then seeks to have other member states recognise the approval and grant their own marketing authorisation (MRP) or member states collaborate directly on an application submitted (DCP). In 2004, the full name of the agency was shortened to the European Medicines Agency (EMA). The CPMP was renamed the Committee for Medicinal Products for Human Use (CHMP).

The ICH-GCP guideline sets an international harmonised quality standard that protects the rights, safety and welfare of human participants. It minimises human exposure to investigational products, and improves quality of data, with the aim of speeding up development of new medicines and decreasing the cost to sponsors and to the public. Compliance with this

guideline provides public assurance that the rights, safety and well-being of trial participants are protected and consistent with the principles of the Declaration of Helsinki. It also assures that the clinical trial data are credible.

There are 13 core principles of ICH-GCP as cited below:

1. Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety and well-being of the trial subject are the most important considerations and should prevail over interests of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. A clinical trial should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of subject should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subject should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Current European legislation situation

Prior to 2001, each EU member state had its own national clinical trials regulations and approval systems, (e.g. Clinical Trials Act 1987 and 1990 in Ireland). This increased the complexity of multi-national European clinical research, primarily due to differing requirements and approval mechanisms between countries. In an attempt to standardise and harmonise clinical trial approvals amongst member states the European Commission introduced the first European Clinical Trials Directive. In Europe clinical trial approval is granted by a regulatory authority and requires favourable opinion by a Research Ethics Committee (REC). The CT Directive set out the minimum requirements for clinical trials with a specific sub-category of medicines called ‘investigational medicinal products’ (IMPs). This had to be implemented into national law in each European country by May 2004.

These requirements included:

- Protection of trial participants as stated in the Declaration of Helsinki.
- Regulatory authority approval per member state, within specific timelines.
- A single REC opinion (per member state), within specific timelines.
- Common quality standard of GCP (ICH-GCP).

[glossary_exclude]To find out about the requirements of individual countries please visit the EMA website, where a list of National Competent Authorities (NCAs) in the EU member states can be found: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human[/glossary_exclude]

The clinical trials directive has been replaced by the clinical trials regulation (Regulation (EU) No 536/2014) it will apply no early than 28 May 2016. The new regulation ensures that the rules for conducting clinical trials are identical throughout the EU.

The main characteristics of the new Regulation are:

- A streamlined application procedure via a single entry point, the EU portal.
- A single set of documents to be prepared and submitted for the application.
- A harmonised procedure for the assessment of applications for clinical trials.
- Strictly defined deadlines for the assessment of clinical trial application.
- The involvement of the ethics committees in the assessment procedure in accordance with the national law of the Member state concerned but within the overall timelines defined by the Regulation.
- Extension of the tacit agreement principle to the whole authorisation process which, without compromising

safety, will give sponsors, in particular SMEs and academics, increased legal certainty.

- Simplified reporting procedures which will spare sponsors from submitting broadly identical information separately to various bodies and different Member States.
- Increased transparency as regards clinical trials and their outcomes.
- Control in Member states and third countries to ensure that clinical trials rules are being properly supervised and enforced.

Clinical trials conducted outside the EU, but referred to in a clinical trial application within the EU, will have to comply with regulatory requirements that are at least equivalent to those applicable in the EU.

A2-4.14-v1.1