Clinical Research: An Overview

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Clinical research is a complex and highly regulated area of medical science, involving a large number of individuals and organisations, including pharmaceutical companies, contract research organisations, and clinical trial centres. This article answers some basic questions about the pharmaceutical and clinical research industries, including drug development in humans, and gives an overview of the ever-changing regulations governing such research.

What is clinical research?

Clinical Research is a division of science that assesses the safety and effectiveness of new medications and medical devices in animals (preclinical) and humans (clinical). The term 'clinical research' encompasses the entire lifecycle of an investigational product or device, including its discovery and development in the lab (preclinical), through phases I-III of human development, regulatory assessment, and product approval and marketing. Clinical research is a highly regulated, multidisciplinary, global industry, involving large number of highly skilled research professionals.

How are new pharmaceuticals developed?

Drug discovery can take between 3 to 6 years and is aimed at detecting new compounds, also known as new chemical entities (NCEs). Target identification is the first step. A target can be any molecule, such as a protein or gene, which is involved in a particular disease. Target validation follows, whereby scientists have to prove that the target is actually involved in the disease and can be acted upon by the drug[1]. After a target has been identified and validated, many potential compounds will be tested to see if they can act on or modify the target. High-Throughput Screening (HTS) is a technique used to screen a large number of potential drug compound quickly and effectively. New compounds may also be identified from existing molecules, naturally occuring compounds or even create molecules from scratch.

Drug discovery teams will work together to identify a number of lead candidates, compounds which have the required biological activity, from which the best will be selected. These lead compounds will go through early safety tests to assess the absorption, distribution, metabolism, excretion and toxicological properties. These lead compounds will then undergo lead optimisation, i.e. altered to make them more effective. Many different variations of the lead compounds are made and tested. A huge team of discovery chemist and biologists work together making and altering molecules, and testing their effects in biological systems. The most promising lead compounds are then selected for progression into preclinical testing. When a promising new compound is found, companies must apply for a patent, which gives 20 years of exclusivity, and ensures any financial rewards from selling the compound are obtained (1). This is the classic route for small molecule drug discovery.

Biological drugs, or biopharmaceuticals, are well established in medicine and make up around one third of drugs currently in development. Biopharmaceuticals are produced using biotechnological techniques, such as recombinant human technology, gene transfer and antibody production methods, as well as methods involving microorganisms, genetically modified organisms or substances that living organisms produce (2). These large, complex molecules, are very different from small molecule chemical drugs, and include molecules such as cytokines, enzymes, hormones, clotting factors, vaccines, monoclonal antibodies, cell therapies, antisense drugs and peptide therapeutics. Human monoclonal antibodies (mAbs) are a particularly interesting group of biopharmaceuticals, and have seen rapid growth in recent times, with six having received US FDA approval since 2002 and another 7 in phase III development (3).

Another group of interesting compounds are orphan drugs, pharmaceuticals to treat rare diseases, for which regulations have recently changed in order to promote their development. Approximately 7000 rare diseases have been identified, of which many have a genetic basis, affecting children and young patients (4). Due to technological and scientific advances, for example, gene and cell-based therapies, new drugs are emerging to treat these rare diseases. The Orphan Drug Act was introduced in 1983 in the U.S., and then later in Europe and Japan, with the aim of promoting the development of chemical and biological drugs, and providing financial and regulatory incentives for development. The Act defines orphan drugs as "promising therapies intended to treat diseases affecting fewer than 200,000 people in the U.S." A pharmaceutical company will be granted orphan drug designation for the product by the U.S. FDA, if it meets the strict disease prevalence criteria (5).

The next stage is laboratory and animal testing of the lead compounds. The aim is to investigate the safety of the drug, how the drug works, and then decide if the compound(s) should progress into human testing. This stage of clinical development is tightly regulated, with the NCE undergoing a large number of tests, including carcogenicity, genotoxity, pharmacokinetic, reproductive and immunotoxicological studies, in line with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Safety Guidelines (6).

What are the phases of human drug development?

Drug discovery and development is a very long and expensive process, with on average, one new medicine taking 10-15 years to develop. The average cost to research and develop each successful drug is estimated to be $800 million to $1 billion, and by 2004, it was estimated that U.S. drug companies were spending as much as 37% of their total R&D budgets on clinical trial activity (7). For every 5000 to 10000 compounds that enter the R&D pipeline, one receives approval (8).

Once a potential drug has progressed through preclinical testing, the Investigational Medicinal Product (IMP) will enter phase I studies. Generally, phase I studies are conducted in healthy subjects at specialist research centres, although some phase I studies are performed in patients, in particular oncology studies, where cytotoxic drugs are used. These studies investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of the IMP. Pharmacokinetics is the study of how the body absorbs, distributes, metabolises and excretes a drug. This process is also known as ADME. Pharmacodynamics describes how the body is affected by the drug. These processes have previously been described as 'Pharmacokinetics' may be simply defined as what the body does to the drug, as opposed to pharmacodynamics which may be defined as what the drug does to the body'. Phase I studies will provide information on the tolerability of a range of doses including multiple doses, the pharmacokinetics and pharmacodynamics of the drug including bioavailability, plasma binding, clearance, and also a safety profile of the drug. Once enough data and information has been gathered in phase I about the drug, a decision will be made to progress into phase II. Regulatory agencies will review all phase I data and give the go ahead to proceed.

Phase II studies are often the first trials where patients are treated, usually around 50 to 500 patients with the disease or condition under study, in anything from 5 to 100 sites. These trials are known as 'proof of concept' or 'pilot studies'. The principle aim of phase II studies is to demonstrate pharmacological activity, assess short-term safety, find out if the drug is improving the condition, and find what the optimum dose is. Phase II studies will attempt to identify the dose that produces efficacy with the fewest number of side effects. At the end of phase II, the important decision of progression into phase III must be made. This decision will be made once efficacy has been established, no significant safety problems have been found in the phase II programme, and the appropriate dose has been defined (9). This decision is not made lightly, as the cost of large, global phase III studies can be in the millions of pounds.

Phase III studies involve much larger numbers of patients, from 200 to 4000, with the disease or condition under study. Due to the size and duration of these studies, phase III studies are the most expensive and time consuming studies, as they involve many hundreds of hospital sites and research staff in many countries around the world. The aim of the phase III studies is to use large numbers of patients to generate statistically significant data about safety, efficacy and the overall risk-benefit relationship of the study drug. The efficacy of the drug must be compared with current treatments, and the use during the phase III programme should be as close to its clinical use as possible. This phase of clinical research is extremely important in determining whether the drug is safe and effective. It will also provide the basis for labelling instructions. If the phase III studies have been successful and have reached their primary outcomes, then the sponsors are likely to submit an application to the MHRA for a licence called a Marketing Authorisation (MA) (10). Some phase III studies will continue while the regulatory submission is pending which allows patients currently enrolled in the study to continue receiving medication. During the initial submission to the regulatory agency, other phase III studies may be ongoing which may be in a different indication to the submitted application. For example, the initial application may be for drug *xyz0123* in ovarian cancer, but phase III studies may be initiated and currently running with drug *xyz0123* in pancreatic and bladder cancer.

Phase IV studies are performed after initial approval of a drug for a MA. They may be known as Post-Marketing Surveillance Trials and involve the safety monitoring of a drug in current practice. They may be performed to look at the safety in a specific patient population, to compare the safety and effectiveness of similar drugs, or to look at drug interactions. Regulatory agencies may request a phase IV study be performed to answer certain questions in a particular market. These studies are normally performed in a large number of subjects and they collect less data compared to phase II and III studies.

How is the clinical research industry regulated?

The principle document underpinning clinical research is ICH-GCP, which originated from a number of requirements from the FDA in the 1970s. This table shows some of the milestones in clinical research regulations:

Date	Event
1947	The Nuremburg Code
1964	Declaration of Helsinki (WMA)
1968	Medicines Act 1968 (UK)
1990	ICH established
1996	ICH-GCP Guideline E6
2001	EU Clinical Trials Directive (2001/20/EC)
2004	The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031)
2005	GCP Directive (2005/28/EC)
2005	Update to EU Clinical Trials Directive (2001/20/EC)
2006	The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (SI 2006/1928)
2006	The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 (SI 2006/2984)
2008	The Medicines for Human Use (Clinical Trials) Blood Safety and Quality (Amendment) Regulations 2008 (SI 2008/941)
2009	The Medicines for Human Use (Miscellaneous Amendment) Regulations 2009 (SI 2009/1164)
2010	The Medicines for Human Use (Advanced Therapy Products and Miscellaneous Amendments) Regulations 2010 (SI 2010/1882)

The history of clinical trial regulations begins with the Nuremberg Code and Declaration of Helsinki, which were developed as a result of two historical events. The first event was the horrific experiments carried out on humans during the Second World War. Concentration camp prisoners were subjected to experiments without their consent. The Nuremburg Code was developed by the judges at the Nuremburg Trials and covers 10 points including informed consent, properly designed experiments performed by qualified persons, and voluntary withdrawal at any point. The second event involved Thalidomide, which was first used in 1957 as a sedative and for morning sickness in pregnant women. The drug was withdrawn in 1961 as it was found to cause birth defects (11). Around 10,000 babies were born with disabilities. Thalidomide did undergo testing but the tests did not identify the teratogenicity of the drug.

The 1960s and 1970s saw an increase in the laws, regulations and guidelines for reporting and evaluating the data gathered during the clinical trials of new medicinal products. As clinical trials became more and more global, countries were developing their own regulatory requirements, which meant that the pharmaceutical companies had to duplicate many time-consuming and expensive test procedures, in order to market new products internationally (6). There was therefore a need to harmonise regulations.

In the 1980s, the European Community (EC), which is now the EU, started to work towards developing a single market for pharmaceuticals. At the same time, discussions started between Europe, Japan and the US, about the potential harmonisation of regulations. During the World Health Organisation (WHO) Conference in Paris in 1989, further, more detailed discussions were had, and soon after, in 1990, the International Conference on Harmonisation (ICH) was formed. Over the last 20 years, the ICH have developed a number of guidelines on Safety, Quality, Efficacy and Multidisciplinary topics, including the Medical Dictionary for Regulatory Activities (MedDRA) and the Common Technical Document (CTD), and now the electronic CTD (6).

International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines were published in 1996, which is now the core document underpinning all clinical trials. Although this document has no legal status in its own right in the EU, and is still classified as a scientific guideline, the document is referred to in both EU directives 2001/20/EC and 2005/28/EC, which is where the legal framework for ICH-GCP now sits.

The EU Clinical Trials Directive (2001/20/EC) was introduced to increase harmonisation across the EU and to provide a legal basis for ICH-GCP. This began development in 1995, and was transposed into UK law in 2004 as The Medicines for Human Use (Clinical Trials) Regulations 2004. A directive provides a legal framework and core requirement, which then the member state must adopt into law, although flexibility allows for the member state to include their own legislation. A further step forward was taken by the EU in 2005, when the EU GCP Directive (2005/28/EC) was introduced, which confirmed ICH-GCP as a basis of clinical research in the EU and EEA, states trials are to be conducted in accordance with the Declaration of Helsinki, defines content of the Investigators Brochure, and provides guidance on the structure of the Trial Master File (TMF) and study archiving requirements (10). The GCP Directive was transposed into UK law by The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, which came into effect on 29th August 2006. The regulations were later amended and The Medicines for Human Use (Clinical Trial) Amendment (No. 2) Regulations 2006, came into effect on 12th December 2006. This second amendment allows the inclusion of incapacitated adults into trials in emergency situations, prior to consent being obtained from a legal representative.

Prior to any human clinical trial, Regulatory and Ethics Committee approval must be obtained. In the UK, regulatory approval must be obtained from the Medicines and Healthcare Regulatory Agency (MHRA). Each country has their own competent authority, who reviews all documentation from a regulatory and safety perspective, prior to the initiation of a clinical trial, and also review Marketing Authorisations for new medicines. In addition, if research is being conducted at any NHS hospital site, NHS Research and Development (R&D) approval must also be obtained from each NHS Trust.

How are clinical research organisations (CROs) involved in the drug development process?

Clinical or Contract Research Organisations (CROs) provide services to the pharmaceutical, biotechnology, medical device and healthcare industries. These services can include any or all of the following; study management and monitoring, data management, central laboratory, regulatory, medical writing, biostatistics, ECG, pharmacovigilance, training, commercial and preclinical. There are a number of CROs, including large, global CROs offering the full range of development services, and there are the smaller, niche CROs, offering highly specialised services, for example, staffing solutions, and medical imaging management and interpretation. Pharmaceutical companies outsource to CROs for a number of reasons, including:

- *Cost*. It is cheaper for pharmaceutical companies to outsource some services to a CRO as the fixed cost of an employee can be transferred to a variable cost of a CRO. Large pharmaceutical companies therefore tend to outsource large parts of clinical trials, which give them the flexibility with internal staff headcount.
- *Location*. Large CROs often have a global footprint with a presence in 50+ countries so may be able to conduct a fully global study. This will help smaller pharmaceutical and biotechnology companies who want to run global studies.
- *Services and expertise*. Small Pharmaceutical and Biotechnology companies may not have access to all the required services to conduct a clinical study and a CRO will often have specific expertise in certain areas.

A recent report found that projects with high CRO involvement were associated with shorter development times (12). Strategic partnerships have emerged recently, whereby one pharmaceutical company will partner with a CRO in a specialist area. For example, all data management may be outsourced to CRO *x*, and central labs services to CRO *y*, or even all phase II and III development to CRO *z*. Large CROs are now often offering the full range of services, from preclinical, through to marketing.

The contract research industry is a multi billion pound industry, with revenues for 2010 totalling $21.69 billion (13), and the top 5 CROs holding a 55% share of the total market (12). Pharmaceutical companies are continuing to outsource all stages of the drug development process, with a new report by Visiongain, predicting that world pharmaceutical clinical trial service revenues will reach $32 billion in 2015 (13).

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