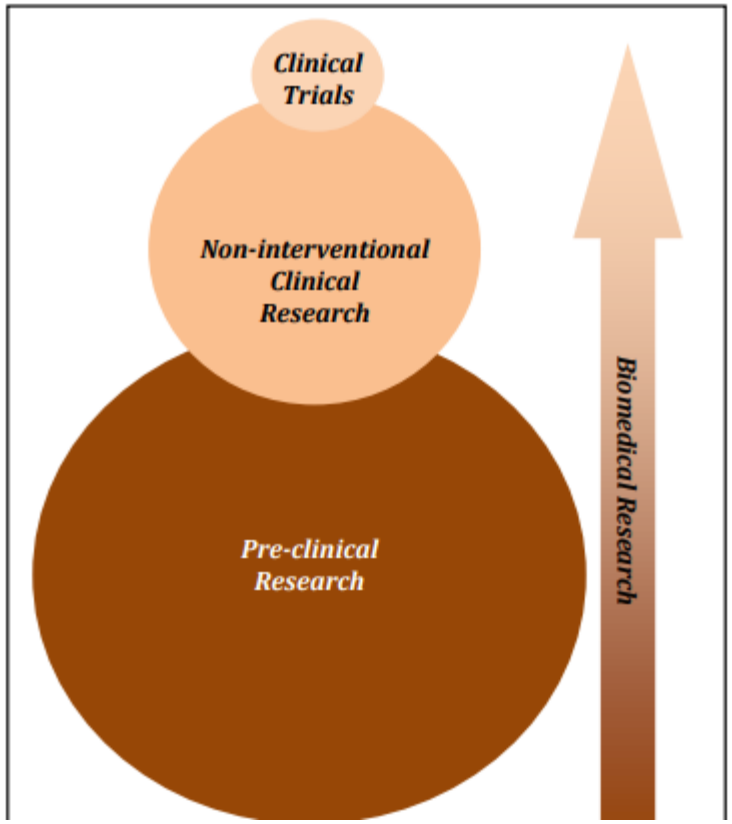
Fundamentals of Clinical Research

1.2 Clinical Trials in the Context of Biomedical Research

Biomedical research can be sub-classified as basic/pre-clinical research and clinical research. Pre-clinical biomedical research is important for expanding the knowledge of basic biological mechanisms. Studies are commonly conducted in pre-clinical departments or institutions in fields such as anatomy, biochemistry, cellular biology, immunology, microbiology, molecular biology, neuroscience, pharmacology, and physiology. Pre-clinical research can contribute to the discovery of new medical treatments.

Clinical research ranges from clinical laboratory or investigational studies to testing of new clinical procedures, new clinical diagnostic tools, and new medicinal products in humans.

Clinical Trials on Medicinal Products



Biomedical research and experimental medicine are terms used interchangeably and are known as medical research. It is sub-classified as basic/pre-clinical research and clinical research. Clinical research includes non-interventional research and interventional research or clinical trials.

Clinical Trials on Medicinal Products (2)

There is a persistent demand, in addition to a great need, to develop new medical treatments that are as effective and safe as, or more effective or safer for specific types of patients than, treatments already on the market. Research also enables discovery of new therapeutic uses for currently available medications, as well as enabling development of innovative treatments for currently untreated conditions. New medicinal products are commonly discovered by means of laboratory research and animal studies before they can be tested in humans – through clinical trials – and eventually used in medical care.

Clinical Trials on Medicinal Products (3)

Clinical trials are the mandatory bridge between pre-clinical discovery of new medicinal products and their general uses. This means that clinical trials must take place before new research treatments can be made available to the public, whether for prescription, over-the-counter sale or for use in a clinic.

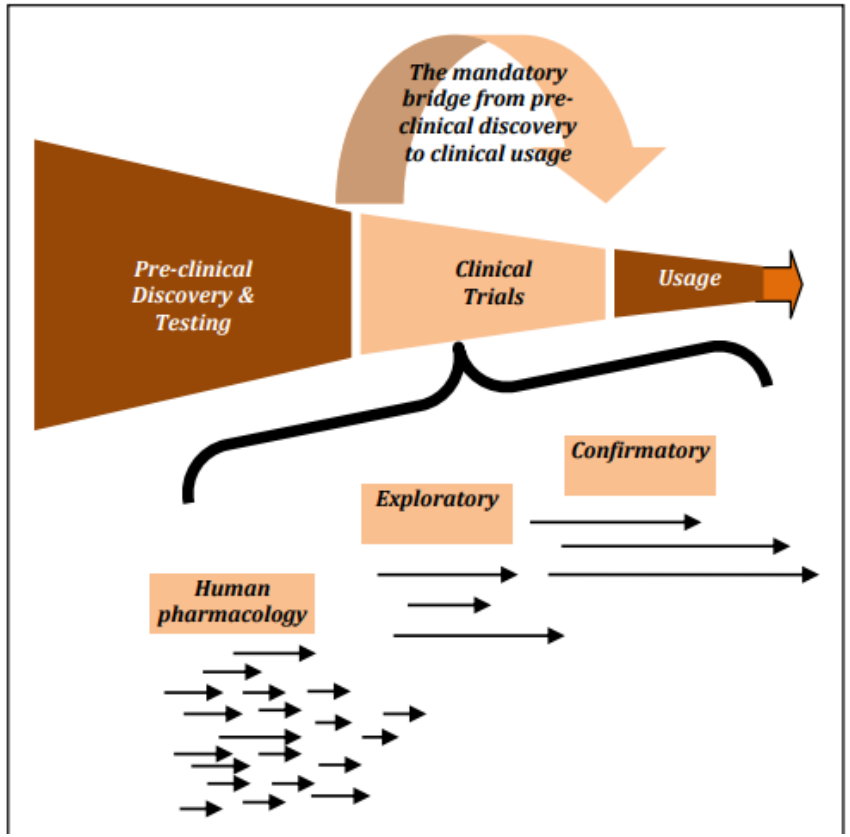
Pre-clinical testing of new medicinal products can only forecast their treatment and side-effects in humans. On average, only one out of 14 new drugs that enter clinical testing programs is eventually introduced for clinical use. The main reasons for the high drop-out rate are unforeseen side-effects or insufficient treatment effects. Pre-clinical laboratory and animal studies thus only partially indicate effects in humans.

During the clinical testing period, data are collected to support a subsequent marketing application for the new medicinal product (test article), whether a drug, vaccine, medical device, or diagnostic tool. A new drug application, for instance, will include all aspects of the test article, from pre-clinical information about the molecular structure and action, manufacturing information, formulation, and animal studies to test results in humans depicting the pharmacological action, dosage, preventive or curative effects, and potential side-effects.

Clinical Trials on Medicinal Products (4)

Pre-clinical and clinical developments are carefully monitored under strict government regulations in most countries to ensure that all aspects of the compound have been studied – and that research has used proper trial designs in a high-quality manner, in accordance with international and local human research ethical standards. Clinical testing of the product passes through different phases, from human pharmacology to exploratory research in participants with the target disorder, and eventually large-scale trials where the product's safety and effects are compared to the best current treatment on the market.

Clinical Trials on Medicinal Products (5)



On average, there are 25-30 different trials conducted on the same compound, each adding some essential information to the existing body of knowledge. The trials are conducted in a close to sequential manner, although the clinical development plan is altered and adjusted according to results obtained at certain points in time.

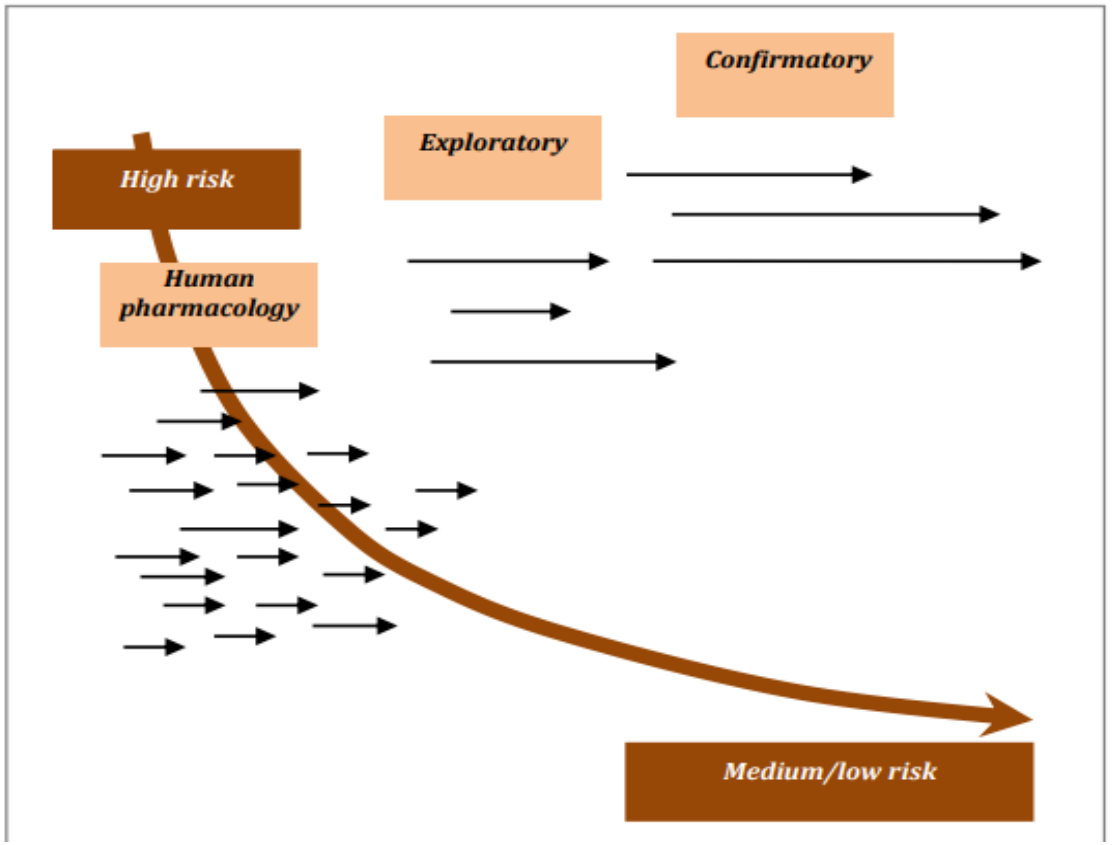
Low and High-Risk Clinical Trials

Three essential factors echo the risk of harm level of a clinical trial:

cumulative clinical experiences of the test article, targeted participant population and biological characteristics of the test article.

As clinical testing proceeds, more and more participants are exposed to the test article. The information gathered is used to evaluate the effects – negative as well as positive – of the product in humans. Accordingly, it follows that risk of harm in general is much higher during the initial clinical testing phase, i.e., human pharmacology, than during later stages. Thus, early phase clinical trials often need more oversight than later phase trials.

Low and High-Risk Clinical Trials (2)



The highest level of risk arises when the product is first tested in humans (first-into human trials), followed by trials with dose escalation and multiple dosing. Most of these trials are conducted in **healthy volunteers**, not participants with the target disease. Initial human pharmacology clinical trials, conducted mostly on healthy volunteers, are followed by exploratory trials where the test article/investigative drug is administered on target participant groups for the first time. The reactions from these participants may differ from those in healthy volunteers, so first-into-human trials are also often regarded as having a higher risk of harm and therefore need extra oversight.

Low and High-Risk Clinical Trials (3)

Clinical testing of medicinal products that are ineffective and/or have unreasonable side-effects is terminated early. This means that late exploratory and confirmatory clinical trials are performed on a subsample of products confidently expected to have a reasonably low risk of inducing side-effects in relation to the treatment effect, since the safety profile is acceptable.

The targeted patient population may also influence the degree of risk of a medicinal product. For instance, life-threatening diseases such as cancer usually call for stronger and thus potentially more toxic drugs with a different risk of harm acceptance from, for instance, anti-flu drugs. Likewise, young children may have a higher risk of side-effects than adults, due to their ongoing organ growth and the body's functional development in early life. Participants in need of multiple drug treatments, such as psychiatric patients or drug abusers, have a risk of harm from drug-to-drug interaction, which may be higher than for participants given the test drug who have no other significant medical conditions.

Low and High-Risk Clinical Trials (4)

Proper risk assessment of a trial can be made only with detailed access to the results of previous testing of the product, in animals and humans, as well as details of the target population and knowledge about the characteristics of the test article. Such information should be included in any trial protocol. For trials overseen by a regulatory authority, additional details are documented in a mandatory **investigator's brochure. Both the trial protocol and the investigator's brochure for a trial**, should be submitted to an (Ethical Committee) EC for review.

Sponsors of Clinical Trials

Sponsors of a clinical trial can be either a commercial company (industry-sponsored trial) or a clinical investigator/physician (non-industry trial). The former comprises pharmaceutical and biotechnology companies, while the latter comprises medical schools, biomedical research institutes, government institutions or clinical trial networks. Depending on the body, non-industry trials are referred to as non-profit, non-industry-sponsored, investigator-initiated, or institutional-initiated trials.

Most industry-sponsored clinical trials are registered with the US national clinical trials registry (ClinicalTrials.gov) because registration is a mandatory requirement by the US government for filing a **new drug application (NDA)** in the US. The US trials registry is a database of privately and publicly funded clinical studies conducted around the world.

Sponsors of Clinical Trials (2)

The overall objective of a commercial life-science company in conducting clinical trials on a medicinal product is to collect information about the safety and efficacy of the product in human participants, i.e., to take the test article from pre-clinical discovery and testing to usage.

The data collected and analysed from trials eventually represent an important and mandatory body of information for the application to a government drug regulatory authority for market acceptance of the product. The commercial company is therefore concerned that the trial follows international and local regulations – from scientific, ethical, and quality assurance viewpoints – so government market approval can be achieved in a timely and undisputed manner. The main objective here is thus primarily commercial.

Sponsors of Clinical Trials (3)

In contrast, an investigator acting as sponsor of a clinical trial may primarily be involved for scholarly reasons, rather than to bring a new medicinal product to the market. Often, the investigator's motive is scientific achievement, leading to published findings, advancing knowledge among peers, and many times also improvement of patient care, health care or population health. Such trials may compare new surgical procedures, health interventional programs or clinical diagnostic tools. They may also test combination therapies or new indications of already approved commercial medicinal products. A smaller number of investigator-initiated trials test new medical products that an investigator or institution has invented, with the primary objective being commercial.

Whether the sponsor of a clinical trial is a commercial or non-commercial body, the same scientific, ethical, and quality standards should apply, and the EC review process should be identical. Industry-sponsored trial protocols have commonly been subject to third-party review because the clinical development plan of products is continuously monitored by drug regulatory authorities. Investigator-initiated trials, on the other hand, may lack the review of an independent third party before they are submitted to the EC. The EC may request details of the third-party review and details of the protocol development team.

Sponsors of Clinical Trials (4)

Regardless of who the sponsor may be, the clinical trial protocol should detail the same aspects: the scientific rationale behind the protocol, the rationale behind the trial design and sample size, treatment blinding, the risk-benefit balance, participant compensation, informed consent, insurance/indemnity, any conflicts of interest that may influence the collection of data or results, and essential quality assurance measures.