Clinical Trial Phases

2.8 Clinical Trial Phases

Drug Development at Large

There is a rather fixed pattern in the stages of drug development process which a test treatment must pass before it can reach the market. Before a new drug application can be filed with drug regulatory authorities, it needs to go from pre-clinical stage to the clinical stage with three phases of clinical trials. The fourth and final trial phase represents post-marketing research.

A clinical trial is one of the final stages of a long and careful research process. The search for new treatments begins in the laboratory, where scientists first develop and test new ideas. The next step is to try a test article – molecules, vaccines, or medical devices – in animals to see how it affects, for example, cancer in a living being and whether it has harmful effects. During pre-clinical drug development, a sponsor evaluates the test article's toxic and pharmacologic effects through in vitro (Latin meaning within the glass), such as test tube testing, and in vivo (Latin meaning within the living) such as animal testing. It includes investigations on drug absorption and metabolism, toxicity of the drug's metabolites, and the speed at which the drug and its metabolites are excreted from the body.

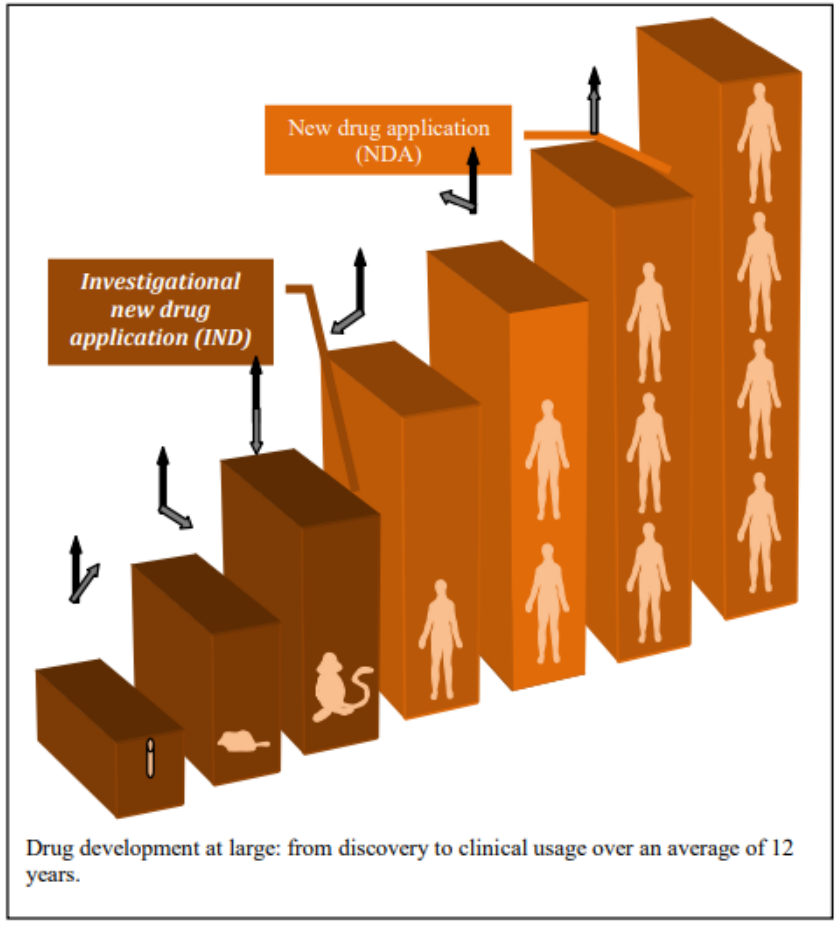
Drug Development at Large (2)

At the pre-clinical stage, the regulatory authority will generally ask the sponsor to:

- Develop a pharmacological profile of the drug.
- Determine the acute toxicity of the drug in at least two species of animals.
- Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical trials.

After completing pre-clinical testing, the company files an **investigational new drug application (IND)** with the drug regulatory authority in the country where the product will be marketed.

Drug Development at Large (3)



Drug development at large: from discovery to clinical usage over an average of 12 years.

Drug Development (4)

The IND provides the results of pre-clinical experiments, the chemical structure of the compound, how it is believed to act in the body, any toxic effects discovered during the animal studies and how the compound is manufactured. The IND should also describe how and where the compound will be tested in humans. Approval is needed from an independent EC to undertake human studies.

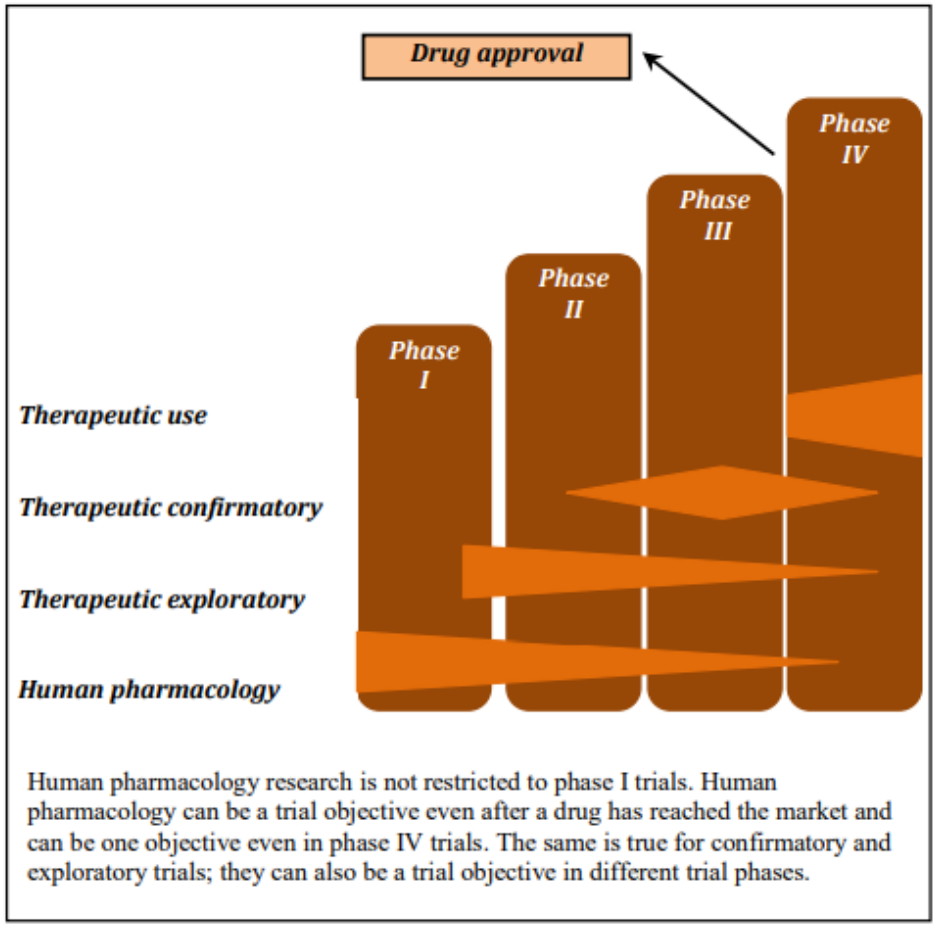
In a clinical trial, results from a limited sample of participants are used to infer how treatment will work in a general population of participants requiring treatment in the future. Most clinical trials are carried out in steps called phases. Each trial phase is designed to discover different information. Participants may be eligible for studies in different phases, depending on their general condition, the type and stage of their disease, and what therapy, if any, they have already received. The participants are seen regularly to determine the effect of the treatment, and treatment is always stopped if side-effects become too severe. After completion of the clinical testing, the company reports all the findings from all pre-clinical and clinical trials on the specific test article. If the results clearly demonstrate safety and effectiveness, the company files a **new drug application (NDA)** with the drug regulatory authority. The application includes all the results obtained. It takes a year or more to learn the endpoint of the review of an NDA submission.

The Basics of Clinical Trial Phases

The trial phase classification proposed by ICH – in the ICH E8 Guide – is based on the objective of the trial and not just a sequential number ranging from I-IV: **human pharmacology**, **therapeutic exploratory**, **therapeutic confirmatory and therapeutic use.**

On the other hand, drug development traditionally consists of four different phases (phases I-IV), But it is important to understand that those four phases do not necessarily have to follow a sequence and they are not mandatory for inclusion in a medicinal product development plan. In addition, sometimes the phase of development provides an inadequate basis for the classification of clinical trials, because one trial may combine several phases with **different fundamental objectives**. Despite this, the phase I-IV classification is still the only one generally recognised and adopted on a global basis.

The Basics of Clinical Trial Phases (2)



Human pharmacology research is not restricted to phase I trials. Human pharmacology can be a trial objective even after a drug has reached the market and can be one objective even in phase IV trials. The same is true for confirmatory and exploratory trials; they can also be a trial objective in different trial phases.

The Basics of Clinical Trial Phases (3)

Because of their multi-objective characteristics, trials are often labeled not just as phase I, for instance, but alternatively early phase I (IA) or late phase I (IB), or perhaps phase I/II or phase II/III, since they aim to study **several different fundamental aspects**. Human pharmacology research is not restricted to phase I trials. It can be a trial objective even after the drug has reached the market or an objective even in phase IV trials. The same is true for confirmatory and exploratory trials; they can also be a trial objective in different trial phases.

The number of phase I-IV trials per test article varies vastly from compound to compound and especially between therapeutic areas. An average of 25 and 35 trials are conducted for a single test article, with more early than late phase trials.

The variation between drugs and therapeutic areas is large so it is not easy to picture all possible scenarios, but a realistic average estimate is conducting 20 phase I trials, four phase II trials, three phase III trials and two phase IV trials – making a total of 29 individual trials for one test article. The average number of participants included in all trials for one and the same test article is 2,000, with around 10% healthy volunteers and the rest mostly patients with the disease under trial; those figures are based on the GlaxoSmithKline publicly available clinical trial database.

The Basics of Clinical Trial Phases (4)

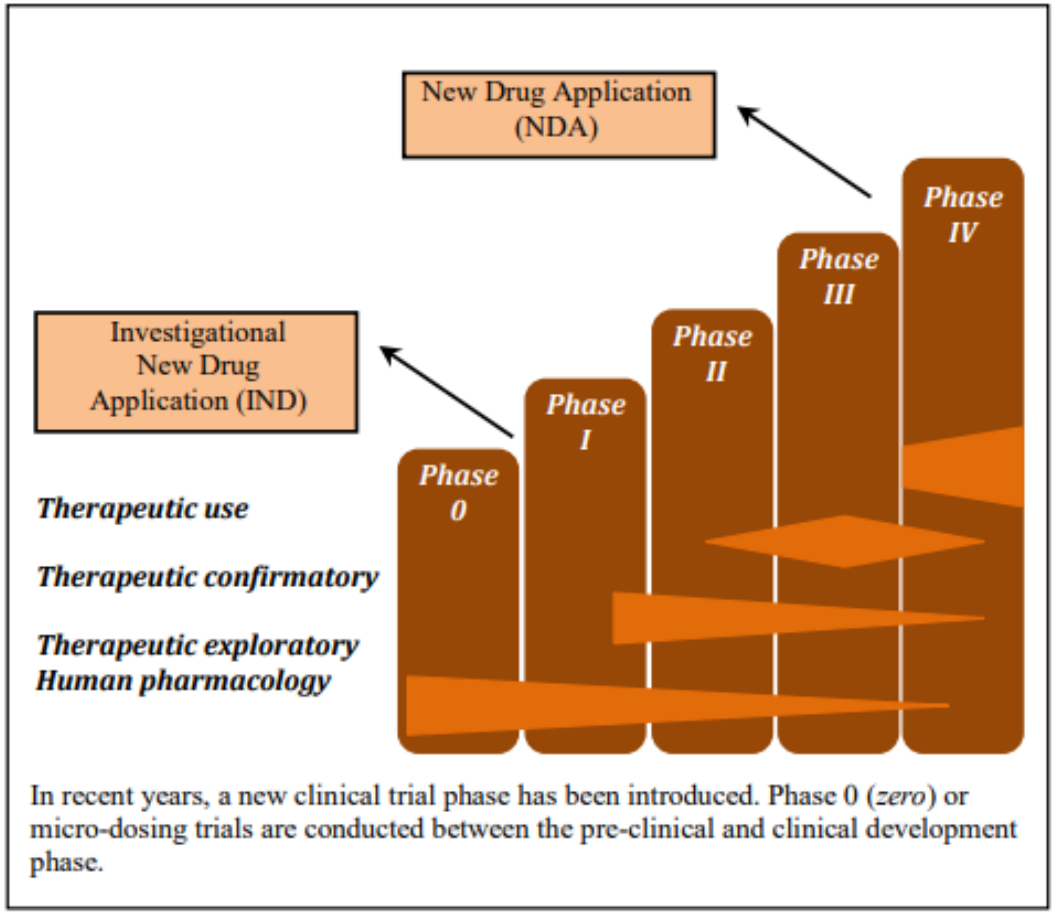
It is estimated that the industry needs to identify around 50,000 sites for some 2,500 trials annually. Most of these trials are phase I. They can be associated with higher risk of harm than late phase trials and are therefore conducted in dedicated phase I units in established clinical trial regions. It should be noted that the majority of phase I trials are simple and involve a low risk of harm. Phase III trials are confirmatory and have the largest sample size and consequently the largest number of investigators/sites. They are the predominant type of trials in both established and emerging clinical trial regions, frequently conducted in outpatient clinics or wards. The ECs of emerging regions will usually review trials of predominantly late phase characteristics – the confirmatory type of trial aiming at comparing a test article with standard treatment. These trials also frequently have other objectives including human pharmacology and exploratory research in new age groups or diseases. They may also address therapeutic usage based on safety endpoints, quality of life improvement and health economic comparisons with standard available treatments.

Phase 0 Trials

In recent years, a new trial phase term has emerged – the so-called phase 0 (zero) or micro-dosing trials. They are not frequently utilised but may become an important instrument for studying some essential elements of human pharmacology towards the latter part of the pre-clinical drug development phase. Such studies thus precede the traditional human pharmacology dose escalation, safety, and tolerance phase I trials that ordinarily initiate a clinical drug development programme.

The concept of a phase 0 trial is an interim step between pre-clinical research and phase I studies, where a small number of human volunteers take small doses of experimental test article so there is little risk of toxicity. A phase 0 trial has no therapeutic intent; the objective is human pharmacology, rather than identifying any toxic effects. Because participants receive sub-therapeutic doses, this means their risk of harm is much less than in conventional phase I trials, but they still need close monitoring.

Phase 0 Trials (2)



In recent years, a new clinical trial phase has been introduced. Phase 0 (*zero*) or micro-dosing trials are conducted between the pre-clinical and clinical development phase.

The Scientific Rational for Phase 0 Trial

The scientific rationale for phase 0 trials is to find out whether a new drug can modulate its intended target in humans, identifying its distribution in the body, or describing the metabolism of a drug. This knowledge is often critical in drug development and may avoid larger phase I and II trials for drugs shown to have unfavourable pharmacologic properties. However, the results of phase 0 trials do not always predict the human pharmacology for the intended dosage. This is probably the main reason that micro-dosing has yet to become very popular, since it may incorrectly terminate the development of a test article.

Utilisation of micro-dosing is claimed to reduce overall drug development costs because the microgram amounts of compounds required do not need to be scaled up to an expensive and time-consuming manufacturing level. Other arguments in favour of its usage are that fewer animal studies are needed to support micro-dosing studies, compared to phase I trials, so there are ethical as well as financial advantages.

Given the design and purpose of phase 0 trials, there can be little expectation of either direct or indirect benefits from them, as is the case with phase I trials. Phase 0 trials should be reviewed by experts in clinical pharmacology and toxicology. Also, they should be conducted only at dedicated and experienced research units, such as high-quality inpatient phase I units.

The Scientific Rational for Phase 0 Trial (2)

The ICH recently released a guideline – M3(R2) – that has also been accepted by the European Union. It includes some guidance on micro-dosing trials, spelling out that the aim of micro-dosing, or rather "exploratory studies," is to collect human data early in development, as well as information about the characteristics of the candidate compound. These studies do not seek to investigate therapeutic effects or safety, and the dosage should have limited human exposure, namely less than 100 µg or less than 1/100th of the pharmacological active dose.

Human Pharmacology/Phase I Clinical Trials

A human pharmacology trial is typically a phase I trial, representing the first stage of testing in human participants. Phase II-IV clinical trials can also have components of human pharmacology, but these are not addressed in this section. As elaborated elsewhere in this Guide, certain phase I trials are generally associated with a higher risk of harm than any other trials, especially the so-called **first-into-man trials and dose escalating trials**. These studies are usually conducted on small populations of **healthy humans** to specifically determine a **drug's toxicity**, **absorption**, **distribution**, **metabolism**, **excretion**, **duration of action, drug-to-drug interaction**, and **drug-to-food interaction.**

Although the treatment will have been thoroughly tested in laboratory and animal studies, side-effects in participants cannot be completely known ahead of time. For this reason, phase I studies may involve significant risks. These trials are often conducted in a dedicated inpatient clinic, where the participant can be observed by full-time staff, usually until several half-lives of the drug have passed.

Human Pharmacology/Phase I Trials (2)

Example of sequential dosing in high risk Phase I trial

Day 1	Day 2	Day 3	Etc
	Review of data	Review of data	
One active	Two active	Three active	
One placebo	One placebo	One placebo	
In phase I unit*	In phase I unit*	In phase I unit*	

*Phase I trials should be undertaken in dedicated centres with appropriate facilities for emergency treatment and intensive care. The first study participant should be dosed in a hospital ward near the intensive care unit with a trial physician present.

Human Pharmacology/Phase I Trials (2)

About 20% of all phases I trials are conducted in patients rather than in healthy volunteers. The reason for this is that some **drugs are too toxic** – **e.g., anticancer drugs** – to be given to healthy participants. Such phase I trials may provide some early information about efficacy based on surrogate endpoints.

An example: A drug under development by a German company was tested in a commercial phase I unit in London UK. The pre-clinical data – including high dosing studies in primates – did not indicate any safety concerns, but the test drug was targeting the immune system, which should have raised concerns. But in this first-into-human trial, six healthy volunteers were simultaneously dosed with the test drug and within minutes they all experienced systemic inflammatory response. All suffered from multiple organ failure and required machine support. Fortunately, everyone recovered or recovered with sequelae after weeks of hospital care. The review of the incident revealed that the sponsor and the commercial phase I-unit provider had followed all regulations at the time with respect to pre-clinical testing and phase I trial operation. The side-effects could not have been predicted, and no misconduct was identified that could have caused the event.

Human Pharmacology/Phase I Trials (3)

The event triggered much press coverage and eventually also led to a new regulation in Europe for the conduct of phase I trials. The new regulation stresses sequential dosing – namely, start the dosing in one participant alone. It also insists on using a dedicated hospital ward or intensive care unit (ICU) for very high risk of harm phase I trials.

The London incident was very rare. Most established phase I test units do not experience serious adverse events (SAEs) requiring ICU medical care of trial participants. However, since unforeseen risks are always present during the early clinical testing phase, the EC should be sure that all possible safety aspects are in place in the event of an unexpected SAE reaction.

Risk Assessment/Management of Human Pharmacology/Phase I Trials

The risks of harming participants must be fully assessed before each phase I trial, especially during the transition from the pre-clinical stage to the first-into-human trial. The trial sponsor must have the pre-clinical data reviewed by experts with technical, scientific, and clinical background. In assessing the risk of harm, the sponsor's designated expert(s) must consider all aspects of the test article, such as its class, novelty, species specificity, mode of action, potency, dose- and concentration response relationship for efficacy and toxicity, and route of administration. The following types of phase I trials are generally regarded as a higher-risk:

1. First-into-human trials

Risk Assessment/Management of Human Pharmacology/Phase I Trials (2)

2. Trials in a new population, new dosage or new formulation of a test article regarded as higher-risk biological product are elaborated below:

- Any agent that might cause severe disturbance of vital body systems.
- Agents with agonistic or stimulatory action.
- Novel agents or mechanisms of action for which there is no prior experience.
- Species specificity, making pre-clinical risk assessment difficult or impossible.
- High potency, e.g., compared with a natural ligand.
- Multifunctional agents, e.g., bivalent antibodies.
- Cell-associated targets. • Targets that bypass normal control mechanisms.
- Immune system targets. • Targets in systems with potential for large biological amplification in vivo.

Clinical Risk Management

The Association of the British Pharmaceutical Industry (ABPI) published a guideline for phase I clinical trials in 2007, which includes detailed guidance on risk management of various trial aspects. The aspects include, but are not limited to:

- Starting dose, increases in the dose, administration of doses.
- Safety records of phase I trials.
- Requirements of a protocol.
- Trial procedures.
- Administrations such as contracts between the sponsor and investigator
- Location, construction, space, facilities, and staff.
- Trial participant-related issues: recruitment, obtaining informed consent, screening.

Clinical Risk Management (2)

Some additional risk management issues should be considered, such as:

- An independent data safety and monitoring committee should be established by the sponsor to assess at intervals the safety data and to recommend to the sponsor whether to continue, modify or stop a trial.
- The first participant to be tested in a hospital ward close to the ICU.
- Dosing usually to be made in the morning, e.g., 8:00 am.
- A doctor should stand by in the hospital ward or phase I unit during the first 24 hours from the start of each trial.
- Night-shift back-up of the hospital resuscitation team should be available in the hospital ward or phase I unit. The resuscitation team should anticipate stabilising the participant before transportation to ICU.

Clinical Risk Management (3)

After the phase I incident in London, the European Medicines Agency (EMA) developed a guideline for phase I trials (EMA/CHMP/SWP/294648/2007). This guide addresses the essence of phase I. “It identifies factors influencing risk for new investigational medicinal products and considers quality aspects, non-clinical and clinical testing strategies, and designs for first-in-human clinical trials. Strategies for mitigating and managing risk are given, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the conduct of the clinical trial.” “Key aspects of the trial should be designed to mitigate those risk factors, including study population; trial sites; first dose; route and rate of administration; number of participants per dose increment (cohort); sequence and interval between dosing of participants within the same cohort; dose escalation increments; transition to next dose cohort; stopping rules; allocation of responsibilities for decisions with respect to subject dosing and dose escalation.”

Therapeutic Exploratory/Phase II Trials

After the successful completion of phase I, an experimental drug is next tested for safety and efficacy in a larger population of individuals afflicted with the disease or condition for which the drug was developed. If a significant portion of participants in the phase II trial respond to the treatment, the treatment is judged active. The aim is to assess the drug's effectiveness in about 3 to 6 phase II trials involving around 200 to 600 participants. The studies are short, usually lasting several weeks or months. In addition to effectiveness, they consider the drug's safety and require close monitoring of each participant. Often intermediate endpoints – surrogate endpoints – are used, rather than clinical endpoints since the objective is to show some sign of efficacy – proof-of-concept – rather than demonstrate efficacy.

Phase II trials primarily aim **to explore therapeutic efficacy in target patients**. They also aim to estimate **the proper dosage** for subsequent studies and provide the basis for confirmatory trial design, endpoints, and related methodologies. Initial phase II trials use various trial designs, while subsequent trials are usually randomised using concurrent controls to evaluate the efficacy of the test drug and its safety for a particular therapeutic indication. Phase II trials are typically conducted in a small, well-defined group of participants, leading to a relatively homogeneous population.

Therapeutic Exploratory/Phase II Trials (2)

An important objective of exploratory trials is to define the dose(s) and formulation for subsequent phase II/III trials. Dose escalation trial designs can be used for this purpose, and later studies may confirm the dose response relationship for the specific indication. Phase II trials are also important for evaluating potential trial endpoints, therapeutic regimens, concomitant medications, and target populations – e.g., age, gender, disease stage/degree.

Therapeutic Confirmatory/Phase III Trials

Therapeutic Confirmatory/Phase III Clinical Trial After a drug is shown to be reasonably effective, it must be compared with current standard treatments for the relevant condition in a large trial involving a substantial number of participants. Phase III trials – major randomised controlled trials – usually involve 500 to 3,000 participants. Some, such as prevention trials – e.g., vaccine, osteoporosis, and cardiovascular trials – may require as many as 20,000 participants. There is usually more than one phase III trial owing to different indications. The duration can vary from a week to many years. For instance, an influenza treatment phase III trial may last for less than a week for an individual trial participant, while a growth promotion trial in children can last for 10 years, i.e., until final adult height has been reached.

The primary objective of a confirmatory phase III trial is to demonstrate or confirm the therapeutic benefit from using important clinical endpoint(s), rather than surrogate endpoint(s). Those trials are designed to confirm preliminary evidence collected during the exploratory phase of clinical testing, i.e., that the drug is safe and effective for use in the specific indication and patient population. These studies provide the basis for marketing approval. Other aims could be to study the test article's extended patient populations, in different disease stages, or as a combination therapy with another drug.

Therapeutic Use/Phase IV Clinical Trials

Therapeutic use/phase IV trials begin after a drug has been approved for distribution or marketing. In phase IV trials or post-marketing surveillance trials, safety surveillance – pharmacovigilance – is conducted and ongoing technical support of that drug is provided. Other phase IV trials aim to study the effectiveness of treatment after approval. Such trials are becoming more and more common and represent an area of outcome research. In the past, phase IV trials were frequently marketing trials with the aim of introducing a new drug to a new market. Such trials had little scientific value owing to the lack of good study design as well as quality assurance and would not today be seen as ethically sound trials.

Medications such as cerivastatin under the brand names Baycol and Lipobay, and the medications troglitazone and rofecoxib, known respectively as Rezulin and Vioxx, were approved for sale, but later recalled due to the severe health risks they posed on patients. As such, these phase IV trials are usually required by regulatory authorities, or they may be carried out voluntarily by the sponsor.

Therapeutic Use/Phase IV Clinical Trials (2)

Therapeutic use trials are not necessary for approval but are regarded as important for optimising usage of the drug. Examples are additional drug-drug interaction, dose response or safety studies and studies designed to support use under the approved indication, e.g., mortality/morbidity studies.

Post-marketing trials can also be critical for exploring new uses for a therapy, as well as acquiring a full understanding of the capability and uses of a drug. After initial approval, drug development may continue with studies of new or modified indications, new dosage regimens, and new routes of administration or additional patient populations. If a new dose, formulation, or combination is studied, additional human pharmacology studies may be indicated, necessitating a new development plan. These new therapeutic use studies of an approved drug are under the drug regulatory authority's area of responsibility, likewise pre-marketing phase II or III trials.