An Overview of Clinical Trials and the Drug Discovery Process

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The drug discovery process is the cornerstone of the pharmaceutical industry. Its purpose is to ensure that a drug or medicinal product is as safe and effective as possible for its indicated use in humans before being authorized for marketing. Even though this process is not perfect, it is still critical to drug approval because regulatory authorities, including the U.S. Food and Drug Administration and the Federal Institute of Drugs and Medical Devices in Germany, require successful human clinical trials before a drug, procedure, or medicinal product can receive marketing authority. It is essential for translators and interpreters working in the medical field to have an understanding of this process. Even those working outside the medical field might still encounter situations were terminology related to the pharmaceutical industry is used, so familiarizing yourself with the processes involved in drug discovery is worthwhile. The following is intended as an introduction to how drugs are developed and tested for safety and efficacy.

What’s Involved

Clinical trials involving drugs are the most common; however, clinical trials can involve new medicinal products such as blood glucose monitoring devices, new diagnostic procedures, and even the discovery of new uses for traditional medicines. Perhaps the best example of new uses for traditional medicines is aspirin. It was originally used as an analgesic, but, as a result of clinical trials, aspirin is also approved to treat and prevent cardiovascular disease, strokes, and heart attacks.

The majority of current clinical trials involves a drug used to treat a specific illness, and are thus known as treatment studies. Other types of clinical studies include:
• Genetic studies, which investigate the relationship between genes and illnesses, with the goal of developing individual treatments based on an individual’s genetic makeup.

• Epidemiological studies, which attempt to identify the patterns and causes of illnesses in groups of people.

• Observational studies, which involve the comparison of subjects against a control group.

There are three other types of studies that are often conducted as part of a larger trial, but that can also be conducted on their own: pharmacokinetic, pharmacodynamic, and pharmacogenomic studies.

• Pharmacokinetic studies investigate how the body affects a specific drug after administration (i.e., how it is taken into, moves around, and is eliminated from the body). This involves four components that can be summarized using the acronym ADME (absorption, distribution, metabolism, and excretion).

• Pharmacodynamic studies investigate how drugs affect the body (e.g., biochemical and physiological effects). Common drug actions studied include stimulating and/or depressing action through direct receptor agonism and downstream effects (i.e., how a drug affects chemical signals to cells).

• Pharmacogenomic studies investigate the influence of genetic variation in patients. The aim of such studies is to develop optimized drug treatments taking into account patients’ genotypes, which maximize efficacy and minimize adverse effects.

While any type of drug can theoretically be tested during a clinical trial, the following four types are the most common:

• Small molecule drugs (e.g., aspirin). These usually have a molecular weight between 500 and 600. Thus, the molecules can pass through the walls of the stomach and duodenum easily and enter the bloodstream. These drugs are usually taken orally, but other routes of administration are also possible.

• Proteins (e.g., insulin). These drugs are too large to pass through the stomach and duodenum, so they must be administered by injections or other suitable means.

• Vaccines (e.g., human papilloma virus vaccine).

• Nucleic acids (e.g., DNA and small interfering ribonucleic acids). These drugs seek to selectively stop the expression of a certain gene whose expression causes a specific disease.

Cost and Attrition
A new chemical entity, that is, a drug that has just been synthesized in the laboratory, can cost over $800 million and take as long as 15 years to develop, sometimes even longer. This amount includes the cost of development programs that failed and/or were terminated. Not surprisingly, given the major importance of clinical trials to the marketing approval of a drug, the majority of a drug’s development budget is spent on clinical testing.

Millions of dollars are invested into a clinical trial with no guarantee that the drug will ultimately receive marketing authorization. Many drugs begin the drug development process, but many of them fail—a process known as attrition. Approximately 62% of Phase II drugs undergo attrition. In addition, approximately 23% of drugs that enter the registration phase will not receive marketing approval. This leaves a very low overall success rate of about 11%.

Stages of Drug Discovery
The drug discovery process is very involved, and the familiar clinical trial phase is only one component of this process. The stepwise nature of this approach is significant because the number of test subjects increases at each phase, as does the probability for more subjects to be harmed or to not experience any benefit from the drug being investigated. A drug’s development can be terminated (e.g., by the pharmaceutical company or the authorities) at any point in this process if it has been shown that the drug is neither safe nor effective for its proposed indication in humans.
**Prediscovery:** In the prediscovery phase, scientists gather as much basic information about the illness as possible in an attempt to understand its underlying cause(s) and potential treatment(s). Then, a drug target, which is a key molecule for a particular signaling or metabolic pathway specific to a particular disease, is selected and validated.

**Drug Discovery:** The next phase is drug discovery, and it can last up to six years. Scientists use high-throughput screening to identify quickly the antibodies, genes, or active compounds that alter a certain biomolecular pathway. Anywhere from 5,000 to 10,000 compounds may be tested during this phase. These results are then used as starting points in the development of the drug. Due to the extremely expensive and long process before a drug can be marketed, usually no more than five molecules from the thousands of compounds tested will be the “candidate drugs” studied in clinical trials.

**Preclinical Testing:** The preclinical testing phase begins once the candidate drug has been identified. During this phase, researchers try to understand how the drug works and determine its safety profile for possible testing in humans. The U.S. Food and Drug Administration, as well as most international authorities, requires thorough testing before the candidate drug(s) can be studied in humans. Currently, the only viable ways this can be done is by animal, in vitro, and in vivo studies. If these tests demonstrate the safety and efficacy of the drug, then the drug can move into the familiar clinical research phase. The preclinical testing phase brings together many scientific disciplines, including physiology, chemistry, biology, biotechnology, and statistics.

**Phase I:** The next phase in the drug discovery process is the clinical research phase. Due to the fact that the number of subjects increases at each stage, this phase can last anywhere from six to seven years. The primary purposes of Phase I trials are to determine the effects of the drug on the human body, assess the dose and safety of the drug, and obtain a safe and optimal dose that is likely to be effective for the proposed indication. These trials typically include between 20 and 100 healthy volunteers and are designed to test how well the drug is tolerated in small numbers of people. Phase I trials typically last anywhere from several days to several weeks.

**Phase II:** The next step in the drug discovery pipeline is Phase II, and these trials are designed to observe the efficacy of a drug. These trials also refer to the actual testing of the proof of concept (PoC); in other words, does the drug actually work against the disease it was designed to treat? The frequency of adverse events is also measured during this phase. Phase II trials answer the question, “What is an appropriate dose for the drug to be effective?” Since different treatment regimens were likely studied during a particular drug’s Phase I trial, the Phase II trial often involves at least one treatment regimen for the drug. Phase II trials usually include between 100 and 250 subjects.

**Phase III:** If a drug has succeeded in the first two phases, Phase III is the next stage, which typically includes anywhere from 1,000 to 5,000 participants. These trials are designed to determine whether a drug is both safe and effective. In addition, adverse reactions resulting from long-term use of the drug are monitored during this phase. If a drug has advanced to Phase III, its study population should be defined in advance by inclusion and exclusion criteria, which is a set of medical criteria determining who can (and cannot) participate in a clinical trial. Phase III trials usually take years to complete. The marketing application is submitted to the national supervising authority during this phase. In the U.S., this form is called a New Drug Application (NDA) and is submitted to the U.S. Food and Drug Administration. In Europe, it is known as a Marketing Authorization Application (MAA).

**Phase IV:** These trials, commonly called post-marketing studies because they usually take place after a particular drug has received marketing...
authorization, represent the last step in the drug discovery process. Phase IV trials can take years to complete and can have patients numbering in the hundreds to thousands. They are designed to provide more data about a drug in real-life situations. In addition, special and at-risk populations, such as pregnant women, may be studied during this phase.

**Continuous Learning Curve**

The area of drug development can be an intriguing one for translators seeking to be part of the exciting medical advancements taking place. To be successful, however, translators must have a firm grasp of the processes and protocols involved that are essential to the industry. They must also be familiar with how to search for the latest information about clinical trials in clinical trial registries, such as the EU Clinical Trials Register and the U.S. National Institutes of Health. These registries typically contain specialized information about a particular study, including inclusion and exclusion criteria, detailed information about a study population, and primary and secondary outcome measures.

Understanding the clinical trials process and the procedures required to obtain marketing authorization for the drug approval process will serve translators wishing to specialize in pharmaceutical translation well.

**Notes**


3. EU Clinical Trials Register (www.clinicaltrialsregister.eu) and U.S. National Institutes of Health (www.clinicaltrials.gov).

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**Additional Reading**


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