



Clinical Research White Paper

Understanding the Clinical Research Process

The evolution from scientific hypothesis to approved and marketed medicine is a lengthy and arduous process that typically spans many years of research and development. To understand clinical research and data flows, one must understand what medicines are, how they are created, how they are tested and monitored, and how they are approved.

Preclinical Studies

Described in its most basic form, a drug is a chemical compound or biologic product designed to affect a process in the body. Before a drug is tested in humans, it goes through several types of preclinical research in a laboratory. Preclinical research could include research in (i) test tubes to analyze the biochemical interactions of the drug with other molecules, (ii) non-animal systems such as cell and tissue cultures, (iii) computer models, and (iv) animal research to evaluate physiological responses.

Once a compound shows, via such non-human research, promise of safety and effectiveness in potentially addressing a particular need in humans, it may then be considered for human evaluation, or clinical development. Prior to initiating research in humans, the pharmaceutical sponsor must make appropriate regulatory filings and obtain the appropriate government's agency permission and independent ethics committee approval to initiate clinical studies, *i.e.*, studies involving humans.

Clinical Studies

There are traditionally four phases to clinical drug research. The objective of Phase 1 studies is to understand how the investigational compound is handled / metabolized by the body and to assess whether the compound is generally *safe* and tolerable for use in humans. Researchers typically conduct studies in a small number of healthy volunteers to answer this question. These volunteers are typically paid for their participation and often the studies are conducted in specialized clinical units to allow close monitoring. For certain types of investigational compounds, such as anticancer agents, Phase 1 studies may be conducted using participants who have the type of disease the compound is intended to treat. Phase 1 studies indicate whether the investigational compound is well tolerated, and researchers gain a better understanding of the safe dosage range for the potential new medicine and possible side effects.

The objective of Phase 2 studies is to evaluate whether the investigational compound has the desired effect in the target patient population in the identified safe dosage range. In contrast to Phase 1, Phase 2 studies typically are conducted with



volunteer participants who have the disease or condition under consideration. It is common in clinical studies to randomly assign some of the volunteers to receive the compound being evaluated (the “treated group”) and to give the other volunteers (the “control group”) either a placebo or an active control that is formulated to resemble the compound. A placebo lacks any active ingredient(s), while an active control is an existing treatment to which the proposed drug will be compared in effectiveness and safety. In the majority of Phase 2 studies, neither the volunteer nor the investigator know the treatment that the volunteer participant is receiving during the conduct of the study, i.e. the study is conducted in a double-blind fashion. To ensure a fair and meaningful comparison, the participants in the treatment and control groups are closely matched in age, gender, race, health condition, life-style habits and other characteristics that may impact the outcome of the study. Comparing the study results from the group who received the compound with results from the control group assists researchers, drug developers, and later the regulator reviewers, in assessing whether the compound is having the desired effect.

The objective of Phase 3 studies is to firmly establish the safety and efficacy of the investigational compound through randomized, controlled, double-blind trials conducted in larger groups of volunteer participants. Where appropriate, further studies may evaluate the compound in special populations, or assess the effects of its prolonged use. At the conclusion of successful Phase 3 studies which show that the compound is effective and well tolerated at the suggested doses, the sponsor of the research will submit an application to the appropriate regulatory body seeking approval to market the product.

Once the drug is marketed, it may be further studied in post marketing research, or Phase 4 studies. The objective of these studies may be to learn more about the safety and efficacy profile of the drug by studying it in broader populations, assess real world experiences with the drug, study the medicine in different healthcare settings, or to satisfy any applicable post-marketing requirements for final approval of the drug.

Study Preparation

Clinical studies are designed to specifically address and meet the objectives of each Phase of research. Designing studies to meet these objectives is a complex endeavor, and planning is essential to successfully navigate the clinical research process. Filing the appropriate applications with regulatory bodies and independent ethics committees is a prerequisite to conducting research in humans with an investigational compound. As part of the approval process, sponsors of research compile a clinical development plan, preliminary protocol, preclinical data, chemical composition and information on the manufacturing process.

Central to all studies is the sponsor’s and researcher’s focus on protecting the rights, safety, and well-being of research participants. Many factors go into the preparation for a study, ranging from protocol development, to investigator and site



identification, to appropriate monitoring of participants' responses to treatment. Many of these processes involve an assessment of appropriate research participant populations and their ability to meet the rigorously established inclusion criteria, which determine whether a potential participant qualifies to participate. Inclusion and exclusion criteria are carefully developed for each compound individually by the sponsor company in consultation with the appropriate regulatory agency. The selection of participation criteria is driven by the need to document with scientific rigor the drug's effect on humans, and depends on the investigational compound's proposed indication for use, intended patient population, incidence of the pertinent medical condition, and other factors.

The sponsor of drug research, either independently or in conjunction with the independent researchers who will ultimately conduct the clinical studies, works to finalize the clinical development plan to address the types and design of studies to be undertaken and the precise questions to be addressed. The sponsor may also seek outside researchers' input to finalize the protocol, which is a written plan describing in detail the planned conduct of the study. The protocol is prepared in accordance with the internationally accepted guidelines, the International Conference on Harmonisation / Good Clinical Practices Guidelines (ICH/GCP).

The protocol serves as the roadmap by which investigators will conduct the research. It includes details such as the method of assignment to treatment groups, dosage and duration of treatment, number of sites contemplated, and the number of participants sought. It also delineates inclusion and exclusion criteria. The protocol also provides the measurement parameters for safety and efficacy, general procedures such as the types and frequency of patient evaluations and visits, and appropriate processes to address participant withdrawal from the study.

Partnerships in Clinical Research

Drug developers serve as sponsors of clinical research, and as such, perform critical evaluations to identify appropriate sites and independent investigators to conduct the research. Interacting with site personnel and potential investigators is critical for sponsors. Sponsors must locate healthcare professionals who will have access to populations meeting enrollment criteria and who are appropriately trained to conduct studies, including knowledge of the many applicable regulatory requirements and privacy laws. Sponsors will then engage those sites and investigators to conduct the studies in accordance with the developed protocol.

To assist in the clinical research process, sponsors of research sometimes also engage contract research organizations (CROs) and/or field monitors, known as clinical research associates (CRAs) to undertake on the sponsor's behalf many of the research oversight functions.



Once investigators and sites are selected and approvals to conduct the study in humans have been obtained from the government agency and the relevant independent ethics committees, the study can begin. The success of a study ultimately hinges on the collection of accurate data, which the sponsor oversees through the use of study monitors, whose responsibilities include authenticating source data.

Data Collection, Processing and Transfer

As collection of medical information is instrumental to the conduct of clinical research, procedures to address data integrity and confidentiality are routinely implemented. Before each research volunteer is enrolled in a study, the researchers seek his or her informed consent to participate. The informed consent process, in addition to the other details of a proposed study protocol, are reviewed and approved by appropriately constituted independent ethics committees.

The independent ethics committees, typically constituted of medical professionals and non-medical members, are responsible to ensure the protection of the rights, safety and well-being of research participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s) facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. Once the independent ethics committee approves the study and documentation to be shared with potential research participants, the investigator is permitted to proceed.

During the informed consent process, the investigator and clinical study staff explain to the participants the purpose of the study, the expected procedures, the types and frequency of evaluations, the potential health and informational risks and benefits of the study, and the voluntary nature of their participation, including the participant's right to withdraw from the study after it has begun. The informed consent process also includes a description of the individuals and entities who will have access to study data, and the likelihood that such data will be shared with affiliates and regulators. Sponsors require potential participants to document their understanding of the information provided to them and encourage potential participants to ask any questions they may have. This deliberate process of explaining all key elements of the study and seeking a participant's permission to enroll is critical to assuring voluntary and informed participation.

The success of a clinical research project depends on the sponsor's ability to collect accurate and complete data for analysis. The critical mechanism by which clinical investigators communicate study results back to the drug sponsor is the case report form (CRF), which can be either a hard copy document or an electronic data record. The CRF is the primary data capture tool in clinical research studies. By completing the CRF, investigators are able to provide the sponsor with the necessary data that the sponsor will analyze. Use of the CRFs ensures consistency in reporting of



data across multiple studies. The length and complexity of a CRF may vary from study to study. However, regardless of a study's design or level of complexity, a sponsor, through the CRF, seeks to capture essential data, attempts to minimize data redundancy, and seeks to ensure data compatibility for analysis across multiple studies for an investigational compound. CRFs generally do not contain directly identifiable patient information, such as name and address, however, they may include patient initials as a mechanism to ensure the accuracy and integrity of the information gathered. Rather, CRFs are typically coded to protect the identity of participants, yet retain an ability to assimilate health and chronological data from the same participant for a meaningful analysis of the study results.

Data is collected from research participants at many different times throughout a study. Research participants' data and samples may be collected directly from them based on investigator interviews or physical examinations. Also, data may be sent to laboratories engaged to perform specific tests necessary for the study. These laboratories may be at the investigator site or at another location. A "central" laboratory, possibly located in another state or country, may be used to ensure consistency in tests or analysis of clinical measurements to permit more accurate comparison of results across several study sites.

Data collected at the study site and transmitted to the sponsor is typically entered into databases. It is then reviewed for accuracy and any anomalies. If, as a result of this data integrity review, certain data is questioned, the sponsor may direct one of its agents, such as a CRA, to review the source data and work with the investigator to correct the CRF if a transcription error is identified. Once the sponsor is satisfied that the data set is complete and accurate, it then begins the process of analyzing the data and assessing the results of the study. Upon conclusion of this analysis, the sponsor will take steps to prepare a study report, which may be included in submissions to various regulatory authorities.

Role of Government Regulatory Agency

The permission to market a drug is granted to drug sponsors by a government regulatory agency. The drug developer applying for marketing authorization must provide the agency with a comprehensive review of conducted clinical and non-clinical studies. If the presented results satisfy the requirements established by the government agency's scientists and policy-makers, the drug application may be approved. Otherwise, additional studies and supporting information may be required for approval.

This paper was prepared by the members of the International Pharmaceutical Privacy Consortium to provide basic background to privacy officials about the clinical research enterprise.

Drug Discovery and Development

