Researchers must have a thorough understanding of the clinical trial process before they begin going down the long road of bringing a drug or device to market.

By Aron Shapiro

The medical community relies on clinical trials to help guide treatment decisions and to answer clinical and medical questions. Questions may be related to the safety and efficacy of therapies or to the natural course and causes of diseases. For retina specialists, making the decision to partake in clinical trials is a hefty one; although there is a significant amount of work that goes into a study, the benefits of participation are plenty. New Retina MD’s newest column, Clinical Trials, aims to speak to the many intricate pieces of partaking in clinical research, from the requirements to qualify as a site and submitting an investigational new drug application to recruiting patients for clinical trials and choosing proper endpoints. In this installment of the column, the main characters of clinical trials, their roles, and the phases of clinical development are introduced.

**KEY PLAYERS**

The successful completion of a clinical trial is a product of many individuals, groups, and organizations working together.

The **study sponsor** is the party funding the research, and this entity is in many ways the “owner” of the protocol and its design. **Contract research organizations (CROs)** may be hired by the sponsor to manage the trial. CROs will likely facilitate regulatory relations regarding the protocol and other aspects of the study.

An **institutional review board (IRB)** conducts regulatory and ethics reviews of study materials and ongoing study issues. IRBs may exist within specific institutions (eg, hospital IRBs) or as independent entities. Regardless, IRB approval of all study materials is required prior to commencement of a study.

**Data management groups** are charged with the proper handling of the plethora of data generated during a trial. **Reading centers** provide centralized evaluation of retinal imaging outputs (eg, optical coherence tomography, fundus photography, and fluorescein angiography), and **central laboratories** provide centralized laboratory assessment, such as blood counts or electrocardiogram readings. Lastly, the **site** is where the actual study takes place—in our world, this is frequently the office of the retina specialist.

When it comes to the actual execution of the study, several other key players come into the mix. The **principal investigator (PI)** is responsible for the study conduct at his or her particular research site. Although staff members and subinvestigators may conduct certain procedures, the PI has the overall responsibility for oversight of all duties.

The **study coordinator, or clinical research coordinator** (CRC), is responsible for performing the daily operations at a particular site. Many sites conducting retinal clinical studies actually have dedicated CRCs within research departments whose only responsibility is to conduct studies. Duties often include interaction with the CRO, sponsor, central laboratories, monitors, and study subjects, as well as completing study logs (eg, screening/enrollment, adverse events, protocol deviations, etc.) and performing other tasks (eg, data entry into case report forms) as applicable.

The CRC role requires dedication, attention to detail, and the ability to multitask.

**Site operations associates (SOAs)** work under the supervision of the PI during the course of the study, performing assessments and procedures. **Monitors** are individuals from either the sponsor or CRO who visit sites periodically throughout the study to review data collected, perform quality assurance checks, and to gauge study progress.

**Auditors** are responsible for examining data collection and study conduct in order to assure subject safety and compliance. Auditors may be representatives of the sponsor, an IRB, or regulatory authorities such as the US Food and Drug Administration (FDA). Sponsor audits are mock audits that follow the FDA manual for an inspection plan. Audits conducted by an IRB are either routine or for-cause audits: Routine audits ensure that the site is conducting studies correctly, and for-cause audits review a study for ethical or regulatory compliance concerns. FDA audits are conducted “to determine validity and integrity of the data,
to assess regulatory adherence, and to ensure that rights and safety of human subjects are properly protected.\(^4\)

**CLINICAL TRIAL PHASES**

Clinical trials are often described by phase and generally consist of three premarketing clinical development phases and a fourth phase of trials that provide postmarketing information regarding the product’s quality, safety, or effectiveness.

**Phase 1**

A phase 1 trial usually includes a small group of approximately 20 to 60 subjects\(^5\) and is the first time an experimental therapy is tested in humans. The goal is to determine the drug’s safety, identify its most frequent side effects, explore the drug’s metabolism and pharmacokinetic and identify its pharmacodynamic profiles. Typically, a phase 1 study is a single ascending dose or a multiple ascending dose open-label clinical trial. In trials with multiple ascending doses, dosing frequency is typically short and sufficient so that researchers gain a firm understanding of systemic pharmacokinetic differences between a single dose and multiple doses.

It is important to note that healthy subjects are generally enrolled in trials testing systemically administered drugs. For retina studies investigating intravitreally administered drugs, a phase 1b/2a study is typically conducted, as dosing with an injection should not be conducted on a subject without disease. Although the primary focus of a phase 1b/2a study may still be safety, efficacy can also be evaluated because subjects with disease are enrolled.

**Phase 2**

Phase 2 trials enroll approximately 80 to 200 subjects with disease and aim to obtain preliminary efficacy data. These trials also provide supplementary data on safety.\(^5\) Generally these studies track patients for 6 to 12 months, which is usually the timeframe the study sponsor requires to see a change from baseline and sustained efficacy. Most phase 2 trials are randomized and double-masked, and are designed to compare a group of subjects receiving an investigational treatment with a group of similar subjects receiving an active control or placebo.

This stage of development is sometimes divided into phase 2a and phase 2b trials, which are specifically designed to assess dosing and to determine efficacy, respectively. Dosing is the largest variable that is evaluated at this stage, and questions include the ideal concentration or amount of drug, proper frequency of treatment, and the best route of administration. If there are several successful formulations in a phase 1 trial, phase 2 trials may also evaluate multiple formulations to determine the best candidate. Additionally, trials at this stage are also useful for endpoint evaluation and for selecting optimal endpoints moving forward based on the mechanism of action of the drug.

**Phase 3**

In phase 3 clinical trials, the drug under investigation is tested in a very large group of subjects with disease to confirm the treatment’s efficacy, compare it with commonly used therapies, monitor side effects, and evaluate the overall benefit-risk relationship of the intervention to provide an adequate basis for physician labeling.\(^2\) A broader study population is typically used to gather a more comprehensive view of safety and efficacy. If the results from phase 3 trials demonstrate that the drug is both safe and effective, a new drug application (NDA) may be submitted to the FDA for review. The FDA will typically require two pivotal trials to support the approval of a product. Depending on the disease, the FDA may have a requirement for a longer-term endpoint in order to evaluate and confirm the sustainability of a response. For example, drugs designed to treat wet age-related macular degeneration typically require a 9-month visual acuity efficacy endpoint.

Studies that are performed after an NDA submission are loosely termed phase 3b studies and typically run parallel with the regulatory process to further expand the knowledge about the product. These trials may be used to supplement earlier trials, for marketing claims against other approved products, or for additional label indications.

**Phase 4**

Even after the FDA has approved a drug, research on the effects of a product continues via postmarketing surveillance. These trials are used to gain additional information such as long-term safety and efficacy data (additional benefits or risks), optimal dosing schedule, and impact on a patient’s quality of life, or to test the product in various populations. Phase 4 trials may be mandated by the FDA or pursued by the sponsor.\(^5\)

**CONCLUSION**

Although the road to FDA approval is long and winding, it is important to become familiar with the approval requirements of each stage of product development. Knowing who to rely on and how the drug development process works will help retina specialists on their way to successful clinical trial participation.

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