Department: **UAMS Institutional Review Board**
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Section: **Drugs and Devices**
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SUBJECT: Drug Trials

Drug trials provide the transition from promising basic or laboratory research to helpful therapeutic or diagnostic procedures for patients. New drugs that offer the hope of some beneficial response in afflicted patients are first tested in animal models. But animal trials do not necessarily demonstrate what the physiological, pharmacological, or toxicological effects of a new drug will be in human beings. Only by careful testing in human subjects can the safety and effectiveness of a new drug be evaluated. The Food and Drug Administration (FDA) is responsible for monitoring the testing of new drugs in humans, for determining whether a new drug can be marketed, and for observing drugs after marketing to be sure that they are safe, effective, and properly labeled (21 CFR 312 and 21 CFR 314).

DEFINITIONS

FDA Clinical Investigation: Any experiment that involves a test article (drug, device, biologic, radiopharmaceutical) and one or more human subjects and the data wherefrom is intended to be submitted to the FDA as part of a marketing application. [21 CFR 50(c)]

Drug: Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

Investigational New Drug or Device: A drug or device permitted by FDA to be tested in humans, but not yet determined to be safe and effective for a particular use in the general population, and not yet licensed for marketing.

Investigator: An individual who actually conducts an investigation.. Any interventions (*e.g.*, drugs, devices, biologics) involved in the study are administered to subjects under the immediate direction of the investigator.

Phase 1, 2, 3, 4 Drug Trials: Different stages of testing drugs in human, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to post marketing studies (Phase 4).

> **Phase 1 Drug Trial:** Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is

to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

Phase 2 Drug Trial: Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

Phase 3 Drug Trial: Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects at multiple sites.

Phase 4 Drug Trial: Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain post marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time (21 CFR 312.85).

Principal Investigator: The scientist or scholar with primary responsibility for the design and conduct of a research project.

Sponsor: A person or entity that initiates a clinical investigation of a drug — usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation but rather distributes the new drug to investigators and physicians for clinical trials. The drug is administered to subjects under the immediate direction of an investigator who is not also a sponsor. A clinical investigator may, however, serve as a sponsor-investigator. The sponsor assumes responsibility for investigating the new drug, including responsibility for compliance

with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

Sponsor-Investigator: An individual who both initiates and actually conducts, alone or with others, a clinical investigation. Corporations, agencies or other institutions do not qualify as sponsor-investigators. A sponsor-investigator is responsible for all regulations governing each of these roles.

OVERVIEW

Once a chemical (drug) is identified as having a potential effect on a disease state, it is subjected to testing in animals. Initial animal tests are designed to see whether the chemical has any desired drug effects, what dosage levels are poisonous, what the safe dosage range might be in humans, and whether there is a reason to test the chemical in humans. Additional animal tests may be required as human tests progress. If initial animal tests indicate that the drug can be safely tested in humans and that the chemical may be therapeutically useful, the drug sponsor will submit an Investigational New Drug Application (IND) to the FDA.

In the IND, the sponsor must describe the complete composition of the drug, its source, and how it is made. In addition, the sponsor must submit the results of all animal studies that support the drug's potential usefulness in humans and that define its toxicity in animals. The data should indicate that no human subject will be exposed to an unreasonable risk. The IND must also include a protocol describing the plan for testing in humans. To permit the FDA to review the materials and make sure subjects will not be exposed to unreasonable risks, the sponsor may not begin clinical tests for 30 days after submitting the IND. At the end of that period, the sponsor may begin the proposed clinical trial unless the FDA has asked for a delay because of a potential safety problem involving use of the drug.

Clinical trials are conducted by clinical investigators (usually physicians) who have entered into an agreement with a sponsor to conduct the study. All physicians administering an investigational drug agree to conditions regarding the conduct of the study outlined by FDA regulations. Clinical investigators agree to these conditions by signing an FDA form that certifies that the investigator has obtained IRB review and approval prior to conducting the study.

Investigational new drugs may be available outside of a clinical trial, through a treatment protocol, to patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapy exists. Established by the FDA in 1987, the Treatment Investigational New Drug exemption (Treatment IND) is a treatment protocol that is added to an existing IND. The Treatment IND allows physicians to treat qualifying patients according to the protocol.

IRB CONSIDERATIONS

In reviewing proposed drug research, IRBs must first consider whether the protocol is scientifically sound. Since this decision is not the IRB's primary concern, however, an IRB may rely on the FDA, institutions, scientific review committees, funding agencies (*e.g.*, NIH), or others for this determination. Evaluating the risks and benefits of drug trials requires IRBs to consider many aspects of the study design, paying special attention to the study population, the trial phase, and mechanisms for data analysis

and surveillance. Risk/benefit analysis and review of the procedure for obtaining informed consent must be performed in all IRB reviews. In addition, subjects participating in studies involving investigational drugs must be told that the FDA may have access to their medical records as they pertain to the study.

The obligation of IRBs and investigators to assure that subjects understand the purposes, methods, and possible hazards of the research is more difficult to fulfill when prospective subjects are seriously ill and in need of therapy. The consent process may require additional efforts and attention for research involving particularly vulnerable subjects such as the seriously ill.

Phase 1 trials are historically safest because they usually involve administering a single dose to healthy volunteers. However, Phase 1 trials may pose the highest level of unknown risk because they involve the drug's first administration to humans. (With highly toxic drugs such as cancer chemotherapies, Phase 1 trials are usually conducted with cancer patients as subjects.) Insofar as possible, risks should be identified from previous laboratory experiments and animal trials. The FDA, which reviews Phase 1 trials submitted in the initial IND application, may have valuable information and recommendations on particular protocols.

Subjects in Phase 2 trials are usually patients with the condition that the new drug is intended to detect or treat. IRBs should recognize that although Phase 2 testing is preceded by earlier clinical trials, the physiological responses of healthy volunteers to a therapeutic drug may not be reliable indicators of how safe the drug is for persons who are ill, taking other medication, or have immunodeficiencies. Since the primary purpose of a Phase 2 trial is to test the drug's effectiveness in achieving its purpose, the responses of subjects receiving the drug are usually compared with those of subjects who are not receiving the drug (control subjects). Whether control subjects receive some existing therapy or a placebo is a research design issue with serious ethical implications. Where an alternate safe and effective drug is available for a serious condition being studied, it should generally be given to the control subjects; however, existing therapies may be inadequate because they are of limited effectiveness against the disease, they have relatively high levels of toxicity, or because they are inconvenient to administer. When determining the acceptability of a proposed research design, IRBs must examine the risks and effectiveness of existing therapies, as well as the risks associated with providing no therapy (or a placebo).

While most drug trials involve agents that the FDA has not yet approved for marketing, some drugs may be the subject of further testing concurrent with or following FDA approval. Post-marketing investigations, also called Phase 4 trials, are conducted to develop further information about the article's safety or effectiveness. Such studies might, for example, seek to establish the safety or effectiveness of using the drug for a new indication, with a new dosage level or a new route of administration (21 CFR312.85; 45 CFR).).

Phase 4 studies should be distinguished from use of a marketed product by a physician for an indication not in the approved labeling as part of the "practice of medicine." Investigational use of a marketed product differs from such uses by physicians in that the principal intent of the investigational use of a test article is to develop information about its safety or efficacy; the submission of an IND or IDE may therefore be required.

Throughout drug trials, the distinction between therapy and research must be maintained. A physician who participates in research by administering a new drug to consenting patients must ensure that the patients understand and remember that the drug is experimental, and that its benefits for the condition under study are unproven. Furthermore, whereas the principal investigator's primary allegiance is to the protocol, the physician's allegiance is to the patient. Where an individual is both an investigator and the subject's treating physician, these two allegiances may conflict. The subject must recognize that the person with whom he or she is dealing may have such conflicting interests. The IRB should be aware of the need to inform the patient of the potential conflict.

If the trial is to collect accurate and timely data concerning the drug's safety and effectiveness, procedures for identifying positive and negative responses to the drug should be in place, and all participating physicians should be well integrated into a reporting system. The principal investigator is responsible for keeping all subjects informed of material changes in the design and conduct of the research, and must communicate new information that might affect their willingness to continue as subjects (45 CFR 46.116(b)(5);38 CFR 16.116). The IRB may assist the investigator in deciding when information from accumulating data should be disclosed to participating or prospective subjects. The disclosure of information gained during the conduct of the trial is especially important with patients entering a study when it is nearing completion.

As part of their determination of the appropriate methods for conducting continuing reviews of ongoing studies, IRBs should be aware of the arrangements made for monitoring the study results. In FDA-regulated clinical investigations, arrangements for data monitoring are the sponsor's responsibility. The sponsor may designate an independent person or group (often called a data and safety monitoring board) to assume this responsibility. An IRB may function in such a capacity; however, most IRBs do not have the necessary expertise. The IRB must approve monitoring plans of sponsor-investigator studies. Independent monitoring is most appropriate when the study is double-masked (*i.e.*, neither the subjects nor the investigators know which drug a subject is receiving) or if the trial is multicentered. Ongoing monitoring of drug trials includes review of data on therapeutic effects, side effects and the effects of any changes in the study design. Sponsors must notify the FDA and all participating investigators of any adverse experiences associated with the use of an investigational new drug that is both serious and unexpected (21 CFR 312.32).

Occasionally, hazards are discovered after a trial is concluded. If the drug has since been marketed, the FDA and the drug manufacturer are usually responsible for notifying users and physicians.