DRUG RESEARCH & DEVELOPMENT

Before a drug can be studied in humans, research must be conducted in the laboratory to learn more about the product and how it works. This is referred to as pre-clinical, meaning prior to human testing. Clinical trials in human can only be conducted after this work is done.

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

Once adequate preclinical data have been obtained and there is reasonable justification to warrant studying the drug in humans, an IND must be obtained from the Food and Drug Administration (FDA) to formally investigate the safety and effectiveness of the product in humans.

PHASES OF CLINICAL INVESTIGATIONS

Phase I: The purpose of phase I studies is safety. This often involves healthy Volunteers. Sometimes seriously ill patients with no other options such as cancer patients who have exhausted all other treatment options are involved in phase I studies. These are most often open label, single center studies. These studies often involve real life time data with frequent blood draws and constant vitals. This is generally the first time the drug has been used in humans.

Phase II: The purpose of phase II studies is safety and effectiveness; dose ranging. The subjects in this phase are patients with the condition. The sample size is small with no more than several hundred subjects. This design is usually blinded. This study also looks at longer term effects and are looking at finding the maximum, yet safe, dose.

Phase III: The purpose of phase III studies is safety and effectiveness. These are often pivotal trials to prove claims. The participants in this phase have the condition being studied. The sample size for phase III studies can be up to several thousand participants. These studies are usually blinded.

Phase IV: The purpose of phase IV study is to add additional claims to a drug already marketed for some other condition. These studies are usually blinded and the study size is variable depending on what is being studied. An example of phase IV would be if a drug is approved for osteoporosis, but the company is looking to have it approved for reducing the incidence of breast cancer.

REGULATORY DOCUMENTS

Regulatory documents consist of all records, reports and pertinent correspondence related to the conduct of the study. The regulatory documents are the official study files and provide an audit trail detailing all the information and the course of events for the entire study.

Regulatory documents generally include the following:

- **Investigator's statement**
  Statement signed by the principal investigator that they approve this protocol and will adhere to the guidelines.
- **1572 form.**
  The 1572 form is a contract between the FDA and the principal investigator (PI). The form is a legal commitment by the PI to comply with federal regulations and will personally conduct or supervise the investigation. The 1572 form will state the name and address of any facility doing the research, any laboratory facilities to be used, the name and address of the responsible IRB, the names of sub investigators participating in the study, and the study name and number.
- **Financial disclosure** for each investigator listed on the 1572 form. The form discloses if any investigator involved in the study has a financial interest in the company sponsoring the study. Each investigator must complete this form prior to the study being initiated.
- **Curriculum vitae and medical license** for the principal investigator, sub investigators, and coordinators.
  Curriculum vitae are the statement of qualifications for the PI and sub investigators. This form must be updated and signed every 2 years. The medical license for each investigator is updated yearly.
- **Protocols and amendments.**
  The original protocol and any amendments must be filed in the regulatory binder. If there is a new version of the protocol, the older version must also be kept in the binder.
- **Investigator's brochure.**
  The investigator's brochure is a collection of all relevant information on the investigational product known prior to the start up of a particular drug including pre-clinical data such as chemical, pharmaceutical, toxicological, pharmacokinetic, and pharmacodynamic data. This information supports the justification for the proposed trial.
- **Safety Reports**
  Safety reports are updates from the company when a serious adverse event occurs with the drug. These are to be submitted promptly to your IRB.
- **Copy of IRB approval letter**
  Official receipt from the IRB that the protocol and consent form have been approved

INVESTIGATIONAL REVIEW BOARD (IRB)

The investigational review board is an independent body with no member having a vested interest in the trial. It is composed of both specialists and lay people with its primary function being to ensures the safety of all trial participants. I order to approve research, the IRV shall determine that all of the following requirements are satisfied:

- Risks to subjects are minimized,
- Risks to subjects are reasonable compared to the expected benefits,
- Selection of subject is equitable,
- Informed consent will be sought,
- Informed consent will be documented,
- Adequate data monitoring is provided to assure the safety of subjects,
- Provisions are in place to protect the subject's privacy and confidentiality of the data.

IRB MEMBERSHIP

- Each IRB shall have atleast 5 members with varying backgrounds.
- The IRB shall be sufficiently qualified through the experience of its members and the diversity of the members including considerations of race, gender, cultural backgrounds and such issues as community attitudes and knowledge of vulnerable subjects.
- The IRB should not consist entirely of men or entirely of women and should not consist of members of one profession.
- Each IRB will have atleast one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in a nonscientific area.
- At least one member should be not affiliated with the institution.
- Members of the IRB who have a conflicting interest in any proposal under review may not participate in the review except to give information. They may not vote on that proposal.
- An IRB may invite individuals with competence in special areas to assist in the review. These individuals may not vote. For example, if a pediatric study is being discussed, a pediatrician may be invited to review the study for scientific value.

INVESTIGATIONAL REVIEW BOARD

The IRB has the authority to approve, require modification in order to secure that approval, or disapproval research. Institutions may choose to use their local IRB or waive that right and use a central IRB. An **institutional IRB** is an IRB within a specific hospital. This IRB is made up of members specifically associated with that hospital and usually reviews protocols only for that hospital. An example of an institutional IRB that R-Research uses is the Medcenter One IRD located at Medcenter One Hospital in Bismarck, ND. That IRB reviews all research activity for Medcenter
One and will not allow a central IRB to approve research at their hospital. A **local IRB** is an IRB located in your city compromised of members of the community, hospital staff, and local physicians or scientists. A local IRB may be shared by several hospitals or clinics. A **central IRB** is a company who will provide IRB services for researchers. An example of a central IRB that R-Research uses in the Western IRB.

BEFORE THE STUDY:
Ensure that you know which documents you are expected to submit to the IRB. In general, the IRB will require the following:

1. A cover letter detailing the documents submitted,
2. Investigator's brochure
3. The full protocol,
4. Consent form
5. Advertisements
6. Up to date curriculum vitae on the principal investigator, sub investigators, and study coordinators involved with the study,

DURING THE STUDY:

1. Make sure you have IRB approval before you put a patient on the study.
2. Keep your regulatory blinder up to date with current IRB approval letters and copies of the protocol, amendments, and safety reports
3. Promptly report to the IRB any safety reports, amendments, or changes to the study which require IRB approval. Keep a copy of the submission letter which require IRB approval letter in your regulatory binder. Most changes to the consent form will require IRB approval.

AFTER THE STUDY:

1. Inform the IRB upon completion of the study.