A GUIDE TO CLINICAL DRUG RESEARCH

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What does the investigator need to know about the drug?

Introduction

An investigator may be asked to conduct a study with a new molecular entity which has never been administered to man before, or else has only been administered to a small number of subjects in Phase I studies. Alternatively, he may undertake a trial during Phase II or III, when there is already a considerable amount of clinical data available.

This chapter will concentrate predominantly on the information an investigator should know before embarking on a Phase I study, with some comment about extra data that should be available to conduct later phase trials.

When an investigator is approached by a sponsoring pharmaceutical company for the first time, it is worth trying to establish the overall plan or strategy for the drug's evaluation. The data may prove to be confidential, but even an outline of the sponsoring drug company's intentions will help to put the study which the investigator is being requested to undertake, in context. It is not unusual for the sponsoring physician or the Clinical Research Associate to bring a research scientist with him on an early visit if the drug to be tested is at an early stage of development. At a later stage, the investigator may be taking part in a multi-centre trial, in which case it is quite usual to have an investigator's meeting, when critical decisions about the drug – such as primary end points, interim analyses and the remit of data safety monitoring committees – are made.

Phases of drug development

Drug development is traditionally divided into four phases:

- **Phase I: Clinical pharmacology.**
  Studies in healthy volunteers or patients, according to the class of drug and its safety, to determine:
  Pharmacodynamics (biological effects) where practicable, tolerability, safety, and efficacy, if in patients
  Pharmacokinetics: absorption, distribution, metabolism and excretion

- **Phase II: Clinical investigation**
  Studies in patients with the target disease
  Pharmacodynamics and pharmacokinetics: dose-ranging in expanding, carefully controlled studies for efficacy and safety
- **Phase III: Formal therapeutic trials**
  Randomised and controlled for efficacy in large numbers, safety, placebo and active comparator trials
- **Phase IV: Post-registration**
  Marketing or user studies
  Expand clinical experience for safety and efficacy; further formal therapeutic trials; comparisons with other active comparators

This classification assumes a logical, sequential approach to drug development, which rarely occurs in practice. Phase I studies initiate the clinical development programme, but some clinical pharmacology trials, e.g. bioequivalence studies, studies in special risk groups, such as hepatic and renal disease, and drug-drug interaction studies, may occur at various stages in the execution of the clinical development plans. Phases II and III often overlap, as sponsoring drug companies attempt to save time by initiating long term parallel group therapeutic trials, before the dose-range is adequately defined.

The investigator's brochure

A responsible sponsoring drug company should provide the investigator with an Investigator's Brochure containing the essential information on the drug, independently of the protocol. It is a confidential document, which can serve as a check list for the investigator to be sure that he is informed of all relevant data relating to the efficacy and safety of the drug. Its content is listed in Box 3.1 and this may be supplemented by separate documents supplied on request from the sponsoring drug company – including publications.

Key elements from the Investigator's Brochure on which the investigator must be informed will now be discussed.

Pre-clinical evaluation

Pharmacology

This section should provide a scientific rationale for development of the drug and an hypothesis which is to be tested in man. An investigator reviewing this data for the first time may find this section rather daunting and unless he has a good grounding in pharmacology, many of the terms will be confusing. Readers are directed to some of the standard texts for further information.

Contents of Investigator's brochure **Box 3.1**

- **General description of drug**
  - Physical properties
  - Chemical properties including pH of solution
  - Solubility
  - Formula
- **Pre-clinical section**
  - **Pharmacology**
    - Specific pharmacology and biochemistry: in vitro / in vivo
    - General pharmacology
    - Safety pharmacology
    - Metabolism and pharmacokinetics
  - **Toxicology**
    - Single dose studies
    - Repeat dose studies, including maximal repeatable dose
    - Mutagenicity: in vitro / in vivo
    - Carcinogenicity or oncogenicity (if appropriate)
    - Reproductive studies (if appropriate)
- **Pharmaceutical section**
  - Purity
  - Percent and type of impurity
  - Formulation
  - Vehicle
  - In vitro dissolution
  - Stability
  - Shelf life
  - Light and heat stability
- **Clinical section**
  - **Clinical pharmacology (Phase 1)**
    - Safety
    - Tolerability
    - Pharmacokinetics
    - Bioavailability
    - Metabolism (including radio-labelled studies
    - Dynamics (biological effect)
    - Interactions (kinetic and dynamic)
    - Special groups
  - **Clinical research (Phases 2 & 3) – if available**
    - Dose-ranging studies
    - Placebo-controlled studies
    - Active comparator studies
    - Overall safety and tolerability

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