

Section 10: Research Methods for Drug Studies

Research involving human participants at the DFCI and conducted through the auspices of the DF/HCC is governed by federal regulations found at [45 CFR Part 46](#) and 21 CFR Parts [50](#) and [56](#). The latter set of regulations governs FDA regulated research involving drugs, devices and biologics.

The HHS regulations codified in 45 CFR Part 46 define research as follows:

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities meeting this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Under the federal regulations, human subjects are defined as living individual(s) about whom an investigator conducting research obtains data through intervention or interaction with the individual; or identifiable private information

The FDA regulations use the term “clinical investigation” and define it as follows:

Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory trials.

10.1 The Drug Development Process

The drug development and approval process relies heavily on clinical trials. When reviewing new drugs/devices/biologics for approval, the FDA is required by law to determine that such agents are safe and effective for specific uses.

Before an investigational agent can be introduced to humans, it must first show promising results in laboratory and/or animal experiments. After completing such experiments, a sponsor submits an Investigational New Drug (IND) application to the FDA. Technically, if the FDA requests no additional information within 30 days after submission, the sponsor may initiate clinical trials with human participants. Although technically correct, the DF/HCC does not recommend doing so. It is in your best interest to establish that the FDA has in fact received and reviewed your materials.

If the trials and data illustrate safety and effectiveness, the sponsor (or sponsor and PI) will then submit a new drug application (NDA) or biologics license application (BLA) to the FDA. Marketing of the new agent may begin once approval by the FDA is granted.

Types of Trials

This section provides descriptions of the different phases and types of research trials.

10.2 Pre-clinical

In pre-clinical trials, a drug's toxic and pharmacological effects are evaluated through *in vitro* and *in vivo* experiments. Through such trials researchers gather information about drug absorption, metabolism, and rate of excretion from the body.

10.3 Phase I

These trials represent the first or early use of the drug in humans. The major objective of a Phase I trial is to determine the maximum tolerated dose (MTD) of the trial agent given in this schedule for humans while identifying the dose-limiting toxicity (DLT). In a single Phase I trial, eligible subjects may have a variety of cancer types. The Phase I design may also be used to evaluate new treatment schedules or combinations of established drugs and/or radiation.

10.4 Phase II

Phase II trials are done after the MTD has been determined by the Phase I trial. The major objective is to determine the efficacy of an agent for a given disease or group of diseases. Typically, all subjects receive the same dose of drug (e.g., the MTD defined by the Phase I trial) or undergo the same intervention. A number of phase II trials are often done utilizing different dosing schedules of the same agent. Alternatively, randomized phase II studies may compare different dosing schedules or regimens to try to determine which is most promising for further evaluation. The most promising regimen, if shown to be sufficiently active, is then used in the subsequent Phase III trial. Phase II trials also collect additional toxicity information.

10.5 Phase III

The major objective of Phase III trials is to compare the efficacy of at least two treatments. This is typically the current standard therapy versus one or more experimental treatment groups. The usual primary purpose of a phase III study is to attempt to determine whether a treatment approach provides a survival advantage as compared with the other(s). Alternatively, if they produce equivalent survival, one might be preferred because it is associated with less toxicity.

10.6 Phase IV

Called *post-market approval trials*, these trials take place after a new agent has been approved for use and marketing by the FDA. Phase IV trials are designed to further evaluate the long-term safety and effectiveness of a treatment. These trials are less common than Phase I, Phase II, and Phase III trials and sometimes are required by the FDA.

10.7 Multi-Modality Trials

Combination trials are done when two or more modes of therapy, such as surgery, chemotherapy, and immunotherapy, are used in combination in an attempt to evaluate potential benefits of combined modality treatment of disease.