

THE PHASES OF CLINICAL TRIALS OF VACCINES AND DRUGS

Vaccine development

Phase I *Refers to the first introduction of a candidate vaccine into a human population for initial determination of its safety and biological effects, including immunogenicity. This phase may include studies of dose and route of administration, and usually involves fewer than 100 volunteers.*

Phase II *Refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is immunogenicity.*

Phase III *Trials are intended for a more complete assessment of safety and effectiveness in the prevention of disease involving a larger number of volunteers in a multicentre adequately controlled study.*

Drug development

Phase I *Refers to the first introduction of a drug into humans. Normal volunteer subjects are usually studied to determine levels of drugs at which toxicity is observed. Such studies are followed by dose-ranging studies in patients for safety and, in some cases, early evidence of effectiveness.*

Phase II *Investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients.*

Phase III *Trials are performed after a reasonable probability of effectiveness of a drug has been established and are intended to gather additional evidence of effectiveness for specific indications and more precise definition of drug-related adverse effects. This phase includes both controlled and uncontrolled studies.*

Phase IV *Trials are conducted after the national drug registration authority has approved a drug for distribution or marketing. These trials may include research designed to explore a specific pharmacological effect to establish the incidence of adverse reactions or to determine the effects of long-term administration of a drug. Phase IV trials may also be designed to evaluate a drug in a population not studied adequately in the premarketing phases (such as children or the elderly) or to establish a new clinical indication for a drug. Such research is to be distinguished from marketing research, sales promotion studies, and routine postmarketing surveillance for adverse drug reactions in that these categories ordinarily need not be reviewed by ethical review committees (see Guideline 14).*

In general, Phase I drug trials and Phase I and Phase II vaccine trials should be conducted according to the articles of the Declaration of Helsinki that refer to

non-clinical research. However, some exceptions can be justified. For example, it is customary and ethically justifiable to conduct Phase I studies of highly toxic chemotherapies of cancer in patients with cancer, rather than in normal volunteers as prescribed in the Declaration of Helsinki, Article 11.2. Similarly, it may be ethically justifiable to involve HIV-seropositive individuals as subjects in Phase II trials of candidate vaccines.

Phase II and Phase III drug trials should be conducted according to the articles of the Declaration of Helsinki that refer to "medical research combined with professional care (clinical research)". However, the Declaration does not provide for controlled clinical trials. Rather, it assures the freedom of the physician "to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering" (Article II.1). Also in regard to Phase II and Phase III drug trials there are customary and ethically justified exceptions to the requirements of the Declaration of Helsinki. A placebo given to a control group, for example, cannot be justified by its "potential diagnostic or therapeutic value for the patient", as Article II.6 prescribes. Many other interventions and procedures characteristic of late-phase drug development have no possible diagnostic or therapeutic value for the patients and thus must be justified on other grounds; usually such justification consists of a reasonable expectation that they carry little or no risk and that they will contribute materially to the achievement of the goals of the research.

Phase III trials of vaccines do not use "a new diagnostic and therapeutic measure" that offers "hope of saving life, reestablishing health or alleviating suffering" (clinical research). Yet administration of the vaccine is intended to be a benefit to the subject rather than "the purely scientific application of medical research carried out on a human being" (nonclinical biomedical research). Thus, Phase III vaccine-trials do not conform to either of the categories defined in the Declaration of Helsinki.

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