

# “General Considerations for the Clinical Evaluation of Drugs” (1977), by the United States Food and Drug Administration

The United States Food and Drug Administration, or FDA, published “General Considerations for the Clinical Evaluation of Drugs,” in September 1977. The document defined acceptable practices for investigators who studied new drugs. Specifically, the document outlined the common clinical trial methods. Clinical trials are studies to test whether a new drug is safe before doctors can prescribe it to patients. Prior to 1977, the Protection of Human Subjects Rule primarily regulated clinical drug trials, but it did not specify who could and could not be included in clinical trials. In the document the FDA recommended that anyone who could become pregnant be excluded from early-phase clinical trials to minimize risks to a potential fetus. After the FDA published the document, investigators excluded women from clinical trials. The document ultimately prevented women of reproductive capacity from participating in early phase clinical trials, which affected women’s health research.

In the US, the FDA regulates the safety and efficacy of drugs. To do that, the FDA establishes regulations that apply to drug manufacturers and publishes recommendations that apply to clinical studies. While those recommendations are not mandatory, the authors call them guidance documents as they indicate the FDA’s opinion on a particular practice. In 1977, the FDA published “General Considerations for the Clinical Evaluation of Drugs,” hereafter “General Considerations...”.

In 1974, before the FDA published “General Considerations...,” it had published the Protection of Human Subjects Rule. That rule was the first instance where the FDA regulated clinical drug trials in respect to a specific population. The Protection of Human Subjects Rule focused on children as participants of clinical trials and established requirements for ensuring the safety and welfare of research participants. The US Department of Health, Education, and Welfare, a part of the FDA, published the “General Considerations...” in 1977. At the time, the director of drug evaluation within the US Department of Health, Education, and Welfare was Marion Finkel. It was part of her job duties to ensure that drugs for sale in the US were safe. Finkel’s department collaborated with the Bureau of Drugs at the FDA to write the guidelines. At the time, Richard Crout directed the Bureau of Drugs.

The FDA separates “General Considerations...” into four general sections. In the introduction, the FDA discusses its goals for publishing the guidance. Then, they outline the phases of clinical drug trials and the process for conducting a clinical drug trial. In the final sections, they discuss ways to determine who should be included and excluded from clinical trials, guidance for designing them, and the different types of clinical trials that exist.

The first section is the abstract, in which the FDA asserts its intentions and goals for publishing a guidance document for clinical trials. The FDA states that their purpose is to assess a drug’s value relative to its risks and side effects. For example, the FDA might not approve a harmful drug, or a drug that has very severe side effects, unless that drug is very effective. To make educated decisions on benefits and risks of drugs, the FDA says that drug manufacturers need to conduct clinical trials to show whether drugs, treatments, and devices are safe for humans. The abstract also cites the Protection of Human Subjects Rule, which the FDA published in 1974 to ensure the ethical treatment of humans who participated in biomedical and behavioral research studies. Treating humans ethically in clinical trials means protecting their rights, not subjecting them to undue harm, and keeping their information confidential. The FDA states that the “General Considerations...” guidance is intended to discuss special situations in which the Protection of Human Subjects Rule

could be insufficient for safe clinical trials. The Protection of Human Subjects Rule provides general guidelines for conducting a safe and ethical clinical trial, but “General Considerations...” provides specific instructions for conducting clinical trials.

The following section of the article is the foreword. In that section, the FDA notes that drug manufacturers should not interpret the guidance document as a requirement, nor should they interpret compliance with the guidance as an automatic FDA approval for a drug. The FDA intended “General Considerations...” to be the guidance document for investigators conducting clinical trials. Advisory Committees write guidance documents. Advisory Committees include a leader, a consumer representative, an industry representative, and a patient representative. As of 2017, there were thirty-three total committees in the FDA.

Following the abstract and foreword, in the introduction, the FDA outlines the process of reviewing a drug. According to the guidance, the public must have a need for a particular treatment for the FDA to approve a drug for sale. The FDA also states that drug manufactures must test drugs without hurting patients and that the people who conduct the investigation are responsible for the wellbeing of all subjects. To ensure that the investigators abide by those requirements, Institutional Review Boards or IRBs review the studies. Most studies are associated with an institution, such as a hospital or a university. Five professionals who are not a part of the institution that funds the research make up the IRB. IRBs make sure that the investigators treat clinical trial participants ethically and abide by the FDA regulations. According to the guidance, without IRB approval, investigators cannot conduct a clinical trial at all.

The FDA also outlines the principles of informed consent in the introduction. They state that the investigator must explain to the patient how they will conduct the trial and the purpose of said trial. The investigator must also state any possible risks associated with the study, discuss other options for treatment, answer any questions a patient might have, and inform the patients that they can decide to stop participating in the trial at any time. Those practices comprise informed consent. The FDA states that anyone who conducts a clinical trial should follow those criteria to make sure that the patients are safe and informed. In the US, experimenting on people without their knowledge or consent is illegal.

Next, in “General Considerations...” the FDA outlines the process of designing a clinical trial. According to the guidance document, the goal of a clinical trial is to obtain accurate results that tell the FDA whether a drug is safe and effective. The article states that it is important to plan a clinical investigation so that the conclusions of the study are accurate, reliable, and empirically valid. The FDA also suggests that investigators specify how they will select participants for the trial, outline the desired length of the study, and document all their findings to ensure that the research is proper. The FDA notes that researchers should test drugs on the same age group that will eventually take them. The paper also specifies that investigators should use placebos in early drug trials, but if the scientific community has already studied another similar treatment well, placebos may not always be necessary. A placebo is an inactive drug and its purpose is to make sure that a drug is more effective than not participating in treatment at all.

In the following section, the FDA discusses the process of conducting a clinical trial. The FDA suggests that the investigators have a plan for monitoring how patients are using the drug during and after the trial because subject noncompliance had been a problem for investigators in clinical drug trials. The FDA suggests documenting whether patients are taking the drug. If they are not taking the drug properly, then they would need to explain their reasons, as that information will contribute to the credibility of the trial. Finally, the FDA states that the investigator should have a plan for obtaining lab tests to evaluate whether the drug is effective or not.

Next, the FDA defines the different phases of clinical trials. There are three main phases. A Phase I Clinical Pharmacology Trial is the first trial where an investigator gives a particular drug to humans. In Phase I, investigators give the drug to healthy people to see if the drug makes them sick or kills them. If it does not harm healthy people, then investigators move on to the next trial to see how the drug affects sick people. At that point, the FDA states that investigators should conduct a Phase II Clinical Investigation in which researchers perform a study using a placebo on 100 to 200 patients. Phase II is for physicians to monitor effectiveness and safety of the drug in a large group

of participants. Drugs that are effective might decrease patient's symptoms or illnesses. Efficacy might be measured through blood tests, urine tests, or physical exams. If people take the drug and they get sicker than they were, the drug will not go on to Phase III.

There are two more advanced stages of clinical trials that only select drugs can participate in. The FDA states that a Phase III Clinical Trial is similar to an expanded version of Phase II. Investigators may have established that a drug is both safe and effective in Phase II but Phase III is meant for gathering information about more specific indications for use and monitoring adverse effects. After Phase III, if the drug works and proves safe, it goes to market, where doctors can prescribe it and people can buy it. After Phase III, drug manufacturers may choose to do a Phase IV Trial. According to the guidance document, Phase IV Postmarketing Clinical Trials occur after a drug has been approved and released and are meant to study the long-term effects of the drug.

After the FDA defines studies generally, they discuss how to plan and perform a Phase I study more specifically. First, the FDA recommends where to perform a study and whom to include in it. The authors recommend that the study occur in a hospital to ensure close monitoring. They also specify that a Phase I trial may be performed outside the hospital if the drug has already been studied outside the US or the drug is a combination of compounds that are already well-studied. The FDA recommends performing Phase I trials in a hospital on healthy volunteers and specifies that investigators should exclude fertile women either pregnant or at risk of becoming pregnant, elderly people, and children from participating in those studies.

Next, the FDA also describes Phase II and III trials more specifically. They note that subjects in Phase II do not need to be healthy, but subjects should be affected by only the sickness the drug is intended to treat. For example, if the drug is intended to treat a skin infection, subjects should have only the skin infection, not any other illnesses, to ensure purity of the results. Phase III is slightly more representative of the intended consumer. For Phase III studies, the FDA recommends including subjects with other illnesses as long as those illnesses are representative of the people who will eventually take the drug. For example, if the drug's intended user is overweight and overweight people commonly have high blood pressure, investigators can test the drug on people with high blood pressure, as they can follow the effect of the drug more accurately in the target population. The FDA also recommends that researchers use blood and urine tests to monitor excretion of the drug. The investigators should also make sure that the trial lasts at least six months for the study to be thorough and well-documented.

In the last section, the FDA discusses whom specifically should be excluded from clinical trials. They state that women of childbearing potential should be excluded from all Phase I trials and early Phase II trials to protect a potential fetus from drug exposure. Medications might negatively affect fetuses more commonly than adults. The FDA defines a woman of childbearing potential as any woman capable of becoming pregnant. They go on to specify that it does not matter if she is single or using birth control, and that investigators should still exclude any woman that falls into that category from early phase research. They do note that a woman in prison is an appropriate participant because she will not become pregnant while she is in prison. The FDA states that women of childbearing potential may be allowed to participate in late-phase trials, such as Phase II and III trials, as long as the earlier phase trials have established that the drug is safe and the participant is not and will not become pregnant during the trial. For women who are pregnant, the FDA states that investigators should assume that the drug will affect the fetus negatively and that any pregnant woman should not receive an experimental drug unless she has a life-threatening disease. Unless a drug has a potential use in children, the FDA states that experimental drugs should not be given to children. Overall, children should not participate in any studies unless the drug has already been proven safe in adults.

According to professor Karin Scheneck-Gustafsson's Handbook of Clinical Gender Medicine, investigators interpreted the FDA guidance as excluding all women from all drug trials. According to the US Public Health Task Force, women were largely excluded from clinical trials based on the guidance in "General Considerations..." The quality of health-related information available to women suffered as a result. In 1985, the Public Health Task Force on Women's Health Issues recommended that investigators include women in their studies. In 1993, the Clinton Administration passed the National Institute of Health Revitalization Act, which mandated that any study the NIH conducts

must include both women and minorities. As of 2018, the FDA has not officially amended the guidance but investigators include women more widely in early phase research.

## Sources

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