



Testing, Testing, (Phase) 1-2-3: Legal Considerations for Clinical Trials of Potential COVID-19 Vaccines

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In the race to develop a Coronavirus Disease 2019 (COVID-19) vaccine, several pharmaceutical companies, governments, and educational institutions around the world have [begun testing](#) their potential COVID-19 vaccines in clinical trials. Clinical trials are used to [assess](#) whether a new pharmaceutical product, such as a vaccine, is safe for humans and effective in achieving its intended purpose. Companies must generally test new pharmaceutical products on humans through clinical trials to obtain U.S. Food and Drug Administration (FDA) approval to market the product. But using human subjects to test these novel products exposes them to unknown health and safety risks, raising ethical considerations for FDA and for the sponsors and Institutional Review Boards (IRBs) overseeing the investigations. These stakeholders—sponsors, IRBs, and FDA—aim to balance the need to ensure that the product is safe and effective against the desire to bring the product to market quickly, tensions that are heightened during a worldwide pandemic. Existing law requires FDA and IRBs to weigh these considerations when evaluating proposed clinical trial designs for COVID-19 vaccines.

This Sidebar describes the legal and regulatory framework that governs clinical trials for pharmaceutical products, such as vaccines, and some avenues researchers and Congress may consider for accelerating that process during the COVID-19 pandemic. (For ease of reference, this Sidebar uses the term *drugs* includes both traditional drugs and biological products, including vaccines.)

Clinical Trials of Investigational New Drugs

Sponsors use clinical trials to generate the data needed to obtain FDA approval to market their products. Because clinical trials expose human subjects to unapproved pharmaceutical products, they risk causing unanticipated serious adverse side effects in the participants. To manage these risks, the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations have imposed procedural requirements on clinical trials, such as advance and ongoing scientific and ethical review, to help protect the participants by minimizing risks, requiring informed consent, and ensuring that the studies collect the data needed to determine whether to approve the product.

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Using Clinical Trials to Collect Substantial Evidence

Sponsors must submit “[substantial evidence](#)” to FDA that their products are safe and effective (or safe, potent, and pure) to obtain FDA approval. [Section 505\(d\)](#) of the FD&C Act defines substantial evidence to mean adequately and well-controlled investigations on the basis of which qualified scientific experts could fairly and responsibly conclude that the product has the purported effect. FDA assesses both the [quality and quantity](#) of the data provided when determining whether a product meets this standard.

[Quality](#) refers to the strength of the evidence and the amount of certainty it provides as to the product’s safety and effectiveness—i.e., whether the investigation is “adequate” and “well-controlled.” The [quality](#) of the evidence depends on how the clinical trial is designed and how the study is conducted. Under [FDA regulations](#), the design must allow for a valid comparison of the product to a control, such as a placebo, an existing therapy, or no treatment. FDA also evaluates whether the study’s method for selecting participants and assigning them to groups is adequate to ensure that meaningful data are collected. The methodology must also include a well-defined and reliable means of assessing the participants’ responses and explain the analytical and statistical methods used to assess the results. Finally, sponsors must provide a clear statement of the investigation’s objectives and take adequate measures to minimize bias in the study. FDA may, however, [waive](#) any of these criteria for a specific investigation if the sponsor can show that the criteria is not reasonably applicable to the study and an alternative approach yields substantial evidence of effectiveness. [FDA guidance](#) further clarifies how sponsors should select their clinical trial design, endpoints, and statistical methods.

As for quantity, FDA generally requires that sponsors complete [two “adequate and well-controlled clinical investigations”](#) to meet the substantial evidence standard. FDA notes in its [guidance](#) that two studies, particularly those that are designed and conducted differently, reduces the likelihood of a design flaw, bias, or other issue or anomaly that could result in erroneous conclusions. However, under the [Food and Drug Modernization Act of 1997](#), FDA may allow sponsors to rely on [one large multi-center adequate and well-controlled clinical investigation](#) supported by another form of additional data, such as data regarding the effectiveness of other drugs in the same pharmacological class. In deciding whether to allow a sponsor to rely on a single study, FDA [states](#) that it considers, among other factors, the seriousness of the disease, whether there is an unmet medical need, and whether additional trials would be ethical and practicable.

Given the flexibility afforded sponsors in designing and conducting their clinical trials, FDA uses [written guidance](#) and individual meetings to help sponsors ensure that their investigations will generate the substantial evidence needed for approval. Sponsors that obtain fast track product or breakthrough therapy designation for their products are entitled to additional assistance from and communication with FDA staff to craft efficient and effective clinical trial designs.

Submitting an Investigational New Drug Application to FDA

New drugs and biological products that are being tested in clinical trials are referred to as investigational new drugs. [Section 505\(i\)](#) of the FD&C Act, [Section 351\(a\)\(3\)](#) of the Public Health Service Act, and their implementing regulations allow investigational new drugs to be used for research before they are approved. To conduct clinical trials of investigational new drugs, the company developing the product (i.e., sponsor) must generally receive FDA approval for the investigation and comply with regulatory requirements for human subjects research.

Sponsors obtain FDA approval to test an investigational new drug on human subjects through an [investigational new drug application](#) (IND). The IND gives FDA an opportunity to ensure that the study will [protect](#) the safety and rights of its human subjects and gather scientific data that adequately shows the product’s safety and effectiveness. The sponsor may begin its clinical trials [30 days](#) after submitting an IND unless FDA notifies the sponsor that it is either (1) authorizing the IND and the study can begin

immediately or (2) imposing a [clinical hold](#) due to concerns about the study. If FDA imposes a clinical hold, the study cannot begin (or resume, for ongoing investigations) pending further notification.

FDA regulations prescribe the information that sponsors must include in an IND. The IND [must contain](#) information about the product, such as the substance and formulation; existing data on use in animals or humans if available; and anticipated risks and side effects. The IND also contains a general investigational plan, which explains why the sponsor is undertaking the study and includes, among other things, the indications being studied, the sponsor's approach to evaluating the product, the kinds of clinical trials being conducted, the anticipated number of participants, and any anticipated risks. Along with the general investigational plan, the IND must include specific protocols for each clinical trial phase. The sponsor must also generally certify that an [institutional review board](#) (IRB) will provide initial and continuing review of each study, including the proposed protocols and any subsequent changes to the study. FDA may, however, [waive](#) any IRB requirements, including the requirement of IRB review itself.

Institutional Review Board Review and Approval

An [IRB](#) is a group convened by an institution to review and approve biomedical research involving humans. IRBs evaluate the initial clinical study design and protocols, along with any changes implemented during the investigation, in an effort to ensure that the rights and well-being of the human subjects are protected. [To that end](#), IRBs assess whether risks to the participants are minimized and reasonable in relation to the anticipated benefits, both to the participants directly and from the knowledge expected to be gained through the study. IRBs also aim to ensure that the researchers will obtain adequate informed consent from all participants (unless an exemption applies) and that selection of the participants will be equitable. IRBs may also require (as appropriate) that the research plan provide for monitoring of the collected data to protect the participants' safety and privacy. To the extent the study may include participants from populations that may be vulnerable to coercion or undue influence (e.g., children, prisoners), IRBs must ensure that sufficient safeguards are in place to protect these populations in participant selection and during the clinical trials.

IRBs review clinical trial plans and protocols from various standpoints, including ensuring that the study complies with legal, ethical, and professional standards; is scientifically sound; and is free from illicit discrimination. Accordingly, to ensure adequate and independent review, IRBs must have at least [five members](#) from multiple backgrounds, including at least one member with a scientific background and at least one with a nonscientific background. At least one member must be independent from the institution running the clinical trials, and the IRB members cannot have any financial or other conflicting interests in the project. IRB review must comply with any other requirements relating to IRBs and human subject research found in Parts [50](#) and [56](#) of Chapter 21 of the Code of Federal Regulation.

Clinical Trial Phases

Clinical trials for a new pharmaceutical product generally proceed in [three phases](#), transitioning from smaller trials focused on initial safety early on to larger trials assessing safety and effectiveness to inform approval and labeling. The size, duration, and specific purpose of each clinical trial phase varies from product to product depending on such factors as the type of product (e.g., a vaccine, treatment, or preventative medication), how the product works, and the relevant underlying patient population. However, as defined by FDA regulations, a clinical investigation generally proceeds as follows:

- **Phase 1 Trials.** Phase 1 trials are the first time the product is introduced in human subjects. These carefully controlled trials typically involve 20 to 80 patients or volunteer subjects, though the exact numbers may vary depending on the product. Phase 1 trials generally assess how the product acts in the body and evaluate initial safety (i.e., side effects). They may also be used to determine the dosing levels to use in phase 2 (e.g., the

maximum safe dose or what dose is required to have an effect). Depending on the product, phase 1 trials may also provide some initial indication as to whether the product may be effective. In the case of vaccines specifically, phase 1 trials also assess their ability to provoke an immune response in the body (i.e., immunogenicity).

- **Phase 2 Trials.** Phase 2 trials continue to assess safety but also evaluate the product's effectiveness and common short-term side effects or other risks associated with the product. Phase 2 trials are also used to determine the optimal dose of the product. For vaccines, phase 2 assesses how much of the vaccine to administer and on what dosing schedule (e.g., whether a boost is needed to maximize its effectiveness or whether the vaccine must be administered on a regular schedule to maintain immunity). As with phase 1 studies, phase 2 studies are carefully controlled. However, phase 2 involves a larger (though still relatively limited) number of volunteer subjects—generally no more than a few hundred participants.
- **Phase 3 Trials.** Phase 3 trials involve an expanded number of participants—from several hundred to thousands—and are used to assess the product's safety and effectiveness across a wide range of patient categories through controlled and uncontrolled studies. These trials are intended to present a clearer picture of expected risks and benefits under real-world conditions. The information obtained from phase 3 trials also forms the basis for the product's labeling.

Sponsors must generally complete all three phases to obtain FDA approval unless they obtain [accelerated approval](#), in which case FDA requires [post-approval trials](#) to confirm the expected clinical benefit. FDA may also require, at its discretion, additional clinical trials after approval (i.e., [phase 4 trials](#)) for any approved product to continue assessing the product's safety and effectiveness once on the market.

Considerations for Congress

The current legal framework seeks to balance various competing interests, which may be amplified in the current crisis. The FD&C Act and implementing regulations provide standards and factors to consider but otherwise give FDA and IRBs discretion to evaluate investigational plans and clinical trial protocols for investigational new drugs. FDA may also waive requirements relating to IRB review and clinical trial design. To the extent Congress may seek to direct how FDA and IRBs exercise that discretion with respect to any potential COVID-19 vaccine, Congress could consider implementing legislation that provides more specific direction on how to approach clinical trials either specifically for the current COVID-19 pandemic or in epidemic, pandemic, or other emergency situations more generally. For example, [courts](#) have determined that Congress can cabin FDA's discretion by imposing mandatory (e.g., "shall") rather than permissive (e.g., "may") language in a statute.

In light of the multiple companies involved in developing potential COVID-19 vaccines, Congress could also consider facilitating the coordination of any clinical trials or appointing a neutral scientific body to consider the ethical and scientific considerations and generate guidelines or a master protocol. The World Health Organization (WHO) [employed](#) this approach to facilitate development of an Ebola vaccine following the 2014 to 2016 Ebola epidemic. Congress could also direct or fund increased [global collaboration](#) between regulators to promote information sharing, which could potentially result in more streamlined clinical investigations with fewer participants being exposed to investigational vaccines. Congress could also consider providing additional funding or other resources to facilitate the clinical trials themselves or any research directed toward understanding the SARS-CoV-2 virus or COVID-19 disease to allow for improved risk minimization in future clinical trials.

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