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CLINICAL TRIALS HANDBOOK
Americas

USA

United States of America

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Introduction

The Food and Drug Administration (FDA), among its other responsibilities, regulates drug[1] and medical device clinical trials under the Federal Food, Drug, and Cosmetic Act (FDCA), Section 1*et seq*, as amended, which is codified in 21 United States Code (U.S.C.) § 301*et seq* .[2]. The implementing regulations are in 21 Code of Federal Regulations (C.F.R.) Parts 50, 54, 56, 312, and 812.[3] Currently, the US represents 45% of the worldwide pharmaceutical market.

Many other laws and agencies may also be relevant to clinical trials. For example, patient privacy is regulated under the Health Insurance Portability and Accountability Act (HIPAA), codified in 42 U.S.C. § 201*et seq* .3. Laboratories themselves are required to be certified by the Department of Health and Human Services under 42 U.S.C. 263A, although the responsibility may be (and is) delegated to accreditation organizations under 42 U.S.C. § 263A-3. Medicare and Medicaid fraud and abuse laws are relevant to certain patient populations under 42 U.S.C. 1320a-7b(b)(1). Title 42 also requires reporting of payments to clinical investigators. Companies with other products that are compensated under the Medicare or Medicaid programs must also be attentive to the amounts and purpose of any payments to clinical investigators to avoid allegations of kickbacks. Further, the US Foreign Corrupt Practices Act (FCPA) may be relevant where the clinical trial is conducted outside the US, under 15 U.S.C. §§ 78dd-1,*et seq* . Additionally, the FDA enforces the requirements of the World Medical Association Declaration of Helsinki (Seoul) for ethical conduct of clinical trials, as codified in the Common Rule in Title 45 of the U.S. Code if the study data are submitted to the FDA. The US is also a major driver of standards set by the International Council on Harmonisation (ICH), which has established guidelines on the conduct, auditing, monitoring and reporting of clinical trails that have been adapted from US regulations. The ICH guidelines are applicable in many countries with clinical trial regulatory schemes. Thus, an understanding of clinical trial regulations in the US is beneficial to understanding how to conduct a clinical trial anywhere in the world. Industry groups may also have applicable codes of conduct that may apply.[4]

Regulatory framework

In this regard, the FDA's mission is to ensure that medical products are safe and effective for their intended use, as well as not adulterated, misbranded or otherwise violative under the FDCA. Certain new drugs, biological products, medical devices and combination products (or new uses of such products) must be authorized for marketing by the FDA before the product enters commercial distribution in the US market. There are a limited number of low-risk products for which the FDA's marketing authorization is not required, such as certain over-the-counter medicines, certain human tissue for transplantation, and certain low-risk medical devices. Proper assessment of the category of product should be undertaken if the Sponsor wishes to market without FDA authorization.

[1] FDA-regulated biological products are technically "drugs" and treated as such for clinical trial purposes.

[2] FDA has a wide range of statutory, regulatory, guidance and general information available at www.fda.gov. The text of the FDCA is available at http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/default.htm, while the U.S.C. is searchable at http://uscode.house.gov/search/criteria.shtml.

[3] The regulations of 21 C.F.R. are available on the FDA website at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm. The reader is advised to check the full text of the regulations before relying on this text.

[4] The Pharmaceutical Research and Manufacturers of America ("PhRMA"), and the Code of Interactions with Health Care Professionals (by Advanced Medical Technology Association or "AdvaMed") to name just a few. Additional codes or guidelines may be found at http://www.vadscorner.com/internet29.html.

Aside from the FDA, there are four other principal players in the FDA clinical trial process: (1) the Sponsor; (2) the Investigator; (3) the ethics committee or Institutional Review Board (**IRB**); and (4) the patient. Each has legal responsibilities. The Sponsor is the entity communicating with the FDA about the parameters of the clinical trial. The Sponsor can be an individual qualified as an Investigator. More typically, the Sponsor is the company or manufacturer that is developing the investigational product. The Sponsor also typically funds the clinical trials, except for Investigator Initiated Studies or those that might be government funded (e.g., by the National Institutes of Health). Regardless of funding, the Sponsor is legally responsible for the conduct of the study. The Investigator is the qualified individual who is responsible for evaluating and treating the patients in accordance with the protocol and regulations applicable to Investigators. There may also be several co-investigators working under a principal Investigator, or multiple Investigators at one or different sites. Investigators are required to demonstrate their qualifications to the FDA. On occasion, in the setting of an Investigator-sponsored study, the Investigator will also hold all responsibilities of a Sponsor, such as ensuring that the investigational product is manufactured under Good Manufacturing Practices where applicable. The IRB is the group responsible for evaluating the quality of the study in terms of compliance with the ethical principles governing the conduct of clinical trials, that is, autonomy and beneficence. The IRB is also responsible for approving (or disapproving) the clinical trial protocol (or changes thereto), deciding if a study has a reasonable risk-benefit profile, approving the informed consent form as assuring the autonomy of the patient, and conducting at least yearly reviews of ongoing clinical trials to ensure ongoing compliance with beneficence and autonomy. The patient's responsibilities are to provide assurance of compliance with the protocol, provide informed consent for enrollment, and permit access by regulatory authorities to the medical record. A Contract Research Organization (**CRO**) may perform certain clinical trial activities of the Sponsor if lawfully delegated by the Sponsor.

Drugs

Before a clinical investigation begins, an investigational new drug (**IND**) application must be filed with the FDA even in the setting of Emergency Use, although abbreviated conditions may sometimes apply.[5] The IND contains: administrative information; a statement that the Sponsor and Investigator will comply with all regulations signed, under penalty of perjury; animal pharmacology and toxicology studies; drug chemistry; synthetic and analytical, manufacturing and stability information; proposed clinical protocols, including information relating to informed consent and IRB oversight; as well as complete information on the proposed Investigator's qualifications, among other things.[6]

Once the IND is submitted, the Sponsor must wait for 30 calendar days before initiating any clinical trial.[7] During this time, among other things, the FDA has the opportunity to review the IND, discuss objections with the Sponsor, and issue a clinical hold should the FDA determine that the research subjects could be subjected to unreasonable risk. If the FDA has no objections within 30 days, and assuming IRB approval is obtained, the trial may commence.[8]

Drug development generally proceeds in three clinical trial phases. The protocol must be submitted to the IND before each new trial begins.[9]

Phase 1: Testing of tens of usually healthy subjects for pharmacology, pharmacodynamics, pharmacokinetics, toxicity, and to arrive at a safe metabolically active dose — if toxicity is expected, then patients with the target disease are exposed as with oncologic agents.

[5] 21 C.F.R. § 312.20.
[6] 21 C.F.R. § 312.23.
[7] 21 C.F.R. § 312.20. *See also* 21 C.F.R. § 812.30.
[8] 21 C.F.R. § 312.40.
[9] 21 C.F.R. § 312.21.

Phase 2: Testing of tens to hundreds of patients having the condition to be treated to obtain preliminary information about tolerability, safety and efficacy, and to determine sample size for a Phase 3 study

Phase 3: Testing of hundreds to thousands of patients or sufficient numbers in an adequate and well-controlled trial to establish the safety and efficacy with sufficient power on a clinically meaningful endpoint — Generally, patient-focused or patient-reported outcome (**PRO**) data are not acceptable as clinically meaningful endpoints unless specifically validated (e.g., walk distance for pulmonary disease). New legislation suggests that the FDA reconsider the importance of patient-focused data and involve patients in determining clinically meaningful endpoints for particular diseases.

There may also be Phase 0 studies, sometimes known as microdosing studies, which are exploratory trials designed to speed up the development of promising drugs by establishing very early on whether the drug or agent behaves in patients as predicted by preclinical studies. Phase 4 studies are post-marketing studies required by the FDA.

During the clinical trial, one of the more important requirements is reporting adverse events, which the Sponsor must send to the FDA within 15 days, or within 7 days for serious adverse events.[10] "Adverse event" has a specific statutory definition that has slight variations worldwide but generally refers to any treatment emergent events regardless of presumed cause.

Regulations require that the study be summarized in a complete Clinical Study Report (**CSR**) that has defined contents and scope. The CSR is submitted to support marketing authorization. A typical CSR may be hundreds of pages and include partially anonymized patient level data in appendices. De-anonymized data must be available to the FDA upon request if the study is used to support marketing authorization.

Clinical studies are intended to support marketing authorization. In general, all biological products must also comply with all clinical trial requirements applicable to small molecule drugs, although there may be additional requirements, such as assessment of antidrug antibodies or neutralizing antibodies.

Once a new drug is approved, certain clinical trials may be conducted without submission of an IND, so long as the trials are ethically compliant.[11] All clinical trials conducted by the Sponsor must be reported online at ClinicalTrials.gov.

There are mechanisms for expedited programs that shortens the duration of the FDA's review time. These include identification for Priority Review (six versus 12 months) and Breakthrough Therapy and Fast Track Designation, which include Priority Review but also assistance and support during development. Accelerated Approval may permit approval on less than full Phase 3 studies based on a commitment to complete such studies. Additional information on expedited programs is available in the FDA guidance. The processes available are undergoing expansion as well, such as policies on regenerative medicine.

Europe and the US collaborate on orphan drug designation.[12] In the US, a drug candidate may be designated as an orphan drug if the US patient population for the drug is less than 200,000. Such designation provides for access to expedited programs if the condition is serious or life-threatening, and the Sponsor will be rewarded for undertaking orphan drug development with seven years of market exclusivity.

Generic drugs may enter the market under an Abbreviated New Drug Application (**ANDA**), where the Sponsor need only show that the generic drug is "bioequivalent" to the already approved drug if there is no longer a viable patent listed by the FDA or drug exclusivity has expired.[13]

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[10] 21 C.F.R. § 312.32.

[11] 21 C.F.R. § 312.2.

[12] 21 C.F.R. § Part 316. Additional information is available at the following article on the FDA website: "Developing Products for Rare Diseases & Conditions" at http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.

[13] 21 U.S.C. § 355(j).

Similar to an ANDA, the Biologics Price Competition and Innovations Act (**BPCIA**) amends the FDCA and the Public Health Service (**PHS**) Act and other statutes to create a pathway for biosimilar licensure (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111-148)).[14] The biosimilar process is substantially different from the generic or ANDA approval process because the active ingredient is less well-defined. Biosimilar development should be done in stages. First, the product must be shown to be biologically and chemically biosimilar. Second, if so, the biosimilar must be shown to have comparable animal toxicology, immunogenicity, pharmacokinetics (as with generic) and also track the pharmacodynamics of the innovator compound. Finally, an exemplary clinical study (or studies) is required.[15] To that end, a biosimilar sponsor must demonstrate the biosimilar to be highly similar to the reference product in purity, potency, biological activity, chemical analysis, mechanism(s) of action, toxicology, pharmacodynamics and route of administration, with no clinically significant differences in efficacy or toxicity.[16]

As of this chapter, 19 biosimilars have been approved. As of 2017, five biosimilars have been approved in the US. The standards for biosimilar approval are substantially different as the tightness of fit of biological and chemical characterization and pharmacodynamics must adhere to more rigorous statistical standards in the US. Several biosimilars approved in the EU have not been approved in the US.

Sponsor

A Sponsor's legal obligations include: selecting qualified Investigators; providing them with the information they need to conduct an investigation properly; ensuring proper monitoring of the investigation; ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND; maintaining an effective IND with respect to the investigations; and ensuring that the FDA and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug.[17]

Additional Sponsor duties include selecting a trial monitor; controlling the drug by shipping investigational new drugs only to Investigators participating in the investigation[18]; reviewing ongoing trials; monitoring the progress of the ongoing trial; making safety reports to the FDA and discontinuing trials if needed to protect patient safety[19]; and retaining records and test samples for two years after New Drug Application (**NDA**) approval. If an application is not approved for the drug, the Sponsor must retain records until two years after shipment and delivery of the drug for trial.[20]

Moreover, there are numerous other obligations on Sponsors, including manufacturing quality, drug accountability, and assurance of compliance with stated regulations. Sponsors are required to adhere to the regulations in 21 CFR Parts 50, 54, 56, and 312, as well as to various interpretive guidance and guidelines from the ICH incorporated into the regulations. To the extent that the data will be used in Europe, there should also be compliance with Regulations (EC) 536-2014 and 726-2004. However, compliance with US regulations will assure compliance with most if not all European regulations with potentially some local or national requirements.

[14] Biologics Price Competition and Innovation Act of 2009, § 505 of 21 U.S.C. 355. *See also* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf.
[15] § 351(k) of the Public Health Services Act (42 U.S.C. 262(k))(added by the BPCI Act).
[16] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
[17] 21 C.F.R. § 312.50.
[18] 21 C.F.R. § 312.53.
[19] 21 C.F.R. § 312.56.
[20] 21 C.F.R. § 312.57.

Contract Research Organizations

Regulations require that a Sponsor use a qualified Investigator either directly or through a CRO to conduct any clinical trial. As noted in 21 CFR Part 312, the Sponsor does not actually conduct the clinical investigation. That must be done by a qualified Investigator either directly or through a CRO.

Either way, a contract that imparts legal obligations to the CRO and Investigator, including potential criminal liability, is required. Contracts with CROs typically use a Master Services Agreement (MSA) with an attached Statement of Work (SOW). The protocol and other study documents are referenced in the SOW. The MSA is an overarching agreement that details terms and conditions such as insurance requirements, various legal requirements, indemnification to deal with liability, etc. CROs must be legally delegated responsibility for regulatory requirements, so in a sense, CROs work for both the Sponsor and the FDA. Both the MSA and SOW are generally individually negotiated and may vary in terms, depending on the phase, scope of the study, Investigators being used, and relative bargaining power of the parties.

Historically, clinical Investigators could directly be a Sponsor. However, this is increasingly difficult after the application of Good Manufacturing Controls to drug products even in Phase 1 studies.

Sponsor responsibilities must be legally delegated to a CRO, and the CRO must accept those responsibilities. The responsibilities will be specific subsets of the regulations. The contract must be filed with the FDA. If the Sponsor transfers one or more obligations to a CRO, the Sponsor must provide the FDA with a statement containing the name and address of the CRO, identification of the clinical study, and a listing of obligations transferred. In this manner, the CRO assumes legal responsibility for the portion of the study conduct. That said, if the CRO fails on its obligations, the Sponsor is ultimately penalized because the clinical data cannot be used. Thus, there are legal requirements for CRO selection under the FDCA. The CRO must be qualified and be able to assume legal responsibilities and liability. A specific example is the prohibition against employing debarred companies or individuals, whether as an employee or within the institution of the Investigator.[21] Lists of debarred or restricted persons, warning letters and the like, are available on the FDA website.[22]

Investigator

The Investigator also has direct legal responsibilities to the FDA and must acknowledge and abide to those through the filing of documents with the FDA. The Investigator must conduct the study in accordance with the regulations, which include providing information to the Sponsor. To that end, there must also be a contract with the Investigator. Unless the Investigator is handling an over-the-counter drug investigation, the Investigator will typically be an employee of a medical institution. Thus, the contract or Clinical Trial Agreement (CTA) is in fact with the medical institution.

Other than specific compliance with regulations and demonstration of qualifications to conduct the study, the CTA will address the scope of work, drug supply and disposal requirements, recordkeeping and reporting obligations, cost and payment, confidential information, publication rights, intellectual property rights and site access; it may also include a synopsis or the entire clinical protocol as approved by the FDA. Generally, the CTA is negotiated before the protocol is finalized since the Investigator information, credentials, curriculum vitae and qualifications must be filed with FDA. CTAs are similarly bespoke, depending on the protocol, the Investigator, the relative negotiating power and the systems that are in place at the institution, such as whether the institution requires an IRB or can delegate to a commercial IRB as is increasingly common in multicenter trials. A critical component, required under European as well

[21] 21 U.S.C. 335a. *See also* 21 C.F.R. § 312.70.

[22] http://www.fda.gov/ICECI/EnforcementActions/default.htm.

as US law, is direct access to patient records by the Sponsor, a CRO if used, the monitoring organization (if other than the Sponsor's), and credentialed governmental regulators.

As noted, Sponsors must obtain information from the Institution, such as the Investigator(s), before commencing a trial. Such information include: the name and address of the Investigator; the name and address of any facility where the trial may take place; and any subinvestigators that will be used.[23] For example, under 21 C.F.R. § 312.57, the Sponsor must keep for two years records relating to drug shipment, use and disposition, financial interests of the Investigator, and test articles. However, the Sponsor cannot meet these duties unless the Investigator also complies. Similarly, the Sponsor cannot provide an adverse events report to the FDA unless promptly reported by the Investigator to the Sponsor. Therefore, Sponsors must also obtain the commitment of the Investigator that the Investigator will conduct the study/studies in accordance with relevant and current protocol(s), and that it will not make changes to a protocol except when necessary to protect the safety, rights or welfare of subjects. To ensure transfer of liability, the Investigators must personally supervise the protocol and all subinvestigators; obtain informed consent (21 CFR part 50); and report to the Sponsor adverse events that occur in the course of the investigation(s), in accordance with 312.64.[24]

Note that all duties of the Investigator are also duties of the Sponsor or CRO. The subset of duties specifically and directly assigned to an Investigator include obtaining informed consent from each human subject,[25] and the Investigator must maintain records relevant to the dates, amounts, and to which subjects the drug is dispensed. Further, unused portion of the drug candidate must be returned to the Sponsor or the destruction witnessed by the Investigator, or if delegated by the institution, the pharmacy. Specifically, the Investigator must witness and obtain a signed, contemporaneous, written, IRB-approved consent from any patient before enrollment. Records are to be retained by the Investigator for a period of two years following the date when marketing authorization is granted or when the study drug is abandoned. Some European countries may require a longer period of document maintenance.[26]

Investigator duties also include a duty to ensure IRB review,[27] permit FDA inspection,[28] ,[29] ensure proper handling and administration of the investigational drug,[30] and make prompt safety reports, as well as make annual reports and financial disclosures to the Sponsor.[31]

Study drugs

As discussed above, an open IND is required prior to administering any investigational drug to a patient.[32] There are no exceptions to FDA authorization. Even in the emergency use of an investigational drug, the FDA must be informed and provide authorization, even if only verbal and later documented electronically.[33]

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[23] 21 C.F.R. § 312.53.
[24] 21 C.F.R. § 312.53.
[25] 21 C.F.R. § 312.60
[26] 21 C.F.R. § 312.62
[27] 21 C.F.R. § 312.66.
[28] 21 C.F.R. § 312.68.
[29] 21 C.F.R. § 312.68.
[30] 21 C.F.R. § 312.61.
[31] 21 C.F.R. § 312.64.
[32] *See* 21 U.S.C. § 355(a) and (j). *See also* 21 C.F.R. § Part 312. Under certain conditions, a drug may be approved in the US based on foreign clinical trials not conducted under an IND. (21 C.F.R. § 312.120)
[33] *See* 21 C.F.R. § 312.310. There are some exceptions for medical devices as well. For example, a waiver of the IDE and other requirements for medical devices is possible if that requirement is not needed to protect the rights, safety or welfare of patients. (21 C.F.R. § 812.10)

21 C.F.R. § 312.(8) – Clinical trials under an IND

Generally, charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of the FDA. In requesting such approval, the Sponsor shall provide an accounting of the rationale for the charge, as well as a justification for the amount charged. There are settings where ancillary requirements of the protocol, such as radiological investigations, may be subject to usual healthcare charges.

Under this section, the Sponsor may not market or promote an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development and handling of the investigational drug.

FDA has also issued guidance documents relating to charging for investigational drugs. These may be found on the page titled "Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs."[34]

The FDCA does not mandate who must pay for any medical tests that are required by the clinical trial protocol. However, in practice, the Sponsor often pays for these in order to facilitate enrollment in the trial.

A health plan may reimburse for ancillary studies or costs associated with the clinical trial and cover some or all of the costs. Many states have passed legislation or developed policies requiring health plans to cover the costs of certain clinical trials, and there are some federal programs to help pay costs. Further, the federal healthcare reform law — the Patient Protection and Affordable Care Act (ACA) — includes the requirement that private insurers cover routine patient costs associated with participation in approved clinical trials starting January 2014. The Act also prohibits health plans or insurance issuers from denying participation in clinical trials; denying or limiting coverage of routine patient costs, subject to the plan's out-of-network coverage policy; and/or discriminating against the individual on the basis of participation in a trial.[35] For more information on alternate payment options, visit http://www.cancer.gov/about-nci/organization/clinical-center-fact-sheet#q7.

As discussed above, responsibility for the clinical trial belongs to the Sponsor, except for those specific responsibilities delegated to a CRO.[36]

Private or tort liability is imposed on any party that was negligent or reckless or that acted with intentional disregard for patient safety under general state tort law principles or that failed to provide adequate informed consent, which can be interpreted, as well, to be assault.[37] [38]The road to compensation, however, can be difficult if the informed consent ensures that the patients were well aware of the experimental nature of the drug and the likelihood of serious side effects and the overall risk/benefit of participation. All Sponsors should maintain clinical trials insurance. Frequently, a clinical trials rider is available as part of Corporate General Liability insurance. The CTAs and CRO contract should require such insurance for all parties in specific clauses and provide for appropriate indemnification.[39] The indemnification language may be specific to the institution. For instance, some large institutions are self-insured or, if a state institution, may be covered by state laws.

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[34] *See* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm

[35] *See* http://www.asco.org/sites/www.asco.org/files/asco_information_for_providers_on_aca_clinical_trials_coverage_provision.pdf.

[36] 21 C.F.R. § 312.52.

[37] A full discussion of state law liability principles lies outside the scope of this publication.

[38] *See* Mello, M.M, et al., The rise of litigation in human subjects research, Ann Intern Med. 139(1):40-5 (2003); Shaul, R.Z., Legal liabilities in research: Early lessons from North America, BMC Med Ethics 6: 4 (2005) (available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1182131/#B6).

[39] Fiscus, P.W., Insuring global clinical trials, PharmExec.com (2009), available at http://www.pharmexec.com/insuring-global-clinical-trials.

Sec. 312.59 – Disposition of unused supply of investigational drug

The Sponsor shall assure the return or destruction of all unused supplies of the investigational drug from each individual Investigator whose participation in the investigation is discontinued or terminated or on study completion. The concept is that an investigational drug is considered inherently harmful and should not be administered to any subject without the controls in place. The Sponsor or CRO must inspect for written records of any disposition of the drug in accordance with 312.57. Failure to maintain drug disposition is a frequent citation when the FDA investigates the clinical site.

Public reporting

On study start, the study details must be published pursuant to Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA).[40] The FDAAA has expanded clinical trial registration to include all clinical trials, including those that are discontinued, and requires reporting of numerous features, including study sites, study design, study drug, final results, as well as other information.[41] The database for reporting clinical trials is available at www.ClinicalTrials.gov.

Clinical trials must be registered at Clinical.Trials.gov within 21 days of enrolling the first patient.[42] Updated information must be posted within one year of the estimated completion date or the actual completion date, whichever is *earlier, unless* an NDA or a new use application will be submitted.[43]

"Completion date" is defined as the date the "final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome" and thus does not include analysis time or patient care relating to secondary outcomes. Further, since the completion date relates to the last patient care date rather than completion of the analysis, the FDAAA applies even to drug trials that have been *discontinued*.

If the Sponsor intends to file an NDA or new use application and files a certification to that effect, the posting of results may be delayed. Under these circumstances, the results must be posted within 30 days of approval or rejection, within 120 days of withdrawal without resubmission, or within two years of the certification date if none of these actions has occurred.[44]

The type of information to be reported includes descriptive information regarding study design, recruitment, and contact and administrative information. Basic results are to include demographic and baseline data, as well as primary and secondary outcome measures. A results registry is available and includes both technical and non-technical summaries of the clinical trial, the full protocol and such other categories as may be deemed appropriate.[45] Updates

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[40] The FDAAA is codified in part in 42 U.S.C. § 282(j)(2)(C). The full text of the FDAAA may be found at http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm. Additional information may be found at https://clinicaltrials.gov/ct2/manage-recs/fdaaa.

[41] Massachusetts has imposed the publication requirement on Phase I trials; some journals and industry groups have done the same under their ethical guidelines. For example, the International Committee of Medical Journal Editors (ICMJE) also has a registry requirement applying to all clinical trials, including Phase I, but does not (yet) require reporting of results. See http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. Note that many journals have followed the ICMJE's lead in this regard. Moreover, the Pharmaceutical Research & Manufacturers of America (PhRMA) Principles on Conduct of Clinical Trials Communication of Clinical Trial Results provides for timely registration and posting of summary results of "all clinical trials," including discontinued trials. *See* http://phrma.org/sites/default/files/pdf/042009_clinical_trial_principles_final_0.pdf.

[42] 42 U.S.C. § 282(j)(2)(C).

[43] The Secretary may increase this to 18 months. 42 U.S.C. § 282(j)(3)(D) (iv)(I).

[44] FDAAA § 801(a)(j)(3)(E)(iii-iv), codified in 42 U.S.C. § 282 (j)(3)(E)(V)(iii).

[45] FDAAA § 801(d), codified in 42 U.S.C. § 282 (J)(3)(D)(iii)

are required not less than once every 12 months,[46] and recruitment status updates and completion updates are required within 30 days of such status change. Sponsors also need to submit tables of adverse events, including frequent (>5%) adverse events.

This results database also includes additional elements, such as information on adverse events, including the seriousness, frequency, organ system targeted, and stage of event.[47]

Intellectual property (IP) and data

The Patent Act[48] governs the substance of US patent law, including the requirements for patent eligibility of an invention, inventorship, patent application and prosecution, patent issuance, and patent enforcement. However, the question of *ownership* of an invention and of the resulting patent application and patent is a matter of *state law*,[49] and is thus governed by contract terms.[50]

The CRO contract and CTA provide for ownership of all data and all intellectual property by the Sponsor of the trial if a CRO undertakes the trial and includes a definition of confidential information relevant to the study. Since most trials are conducted in academic settings, and there may also be government funding involved, the ownership of new intellectual property is always a source of negotiation. Alternatives to ownership by the Sponsor may be an exclusive license, a nonexclusive license, a limitation of academic rights to the educational purpose, or at least a right of first refusal together with a favored nation clause, whereby even if the right of first refusal is not exercised by the Sponsor, the institution must first offer the Sponsor a license on such terms as the institution would otherwise have offered to a third party.

Example alternative terms follow, although the specific terms and clauses should be individualized.

All data, knowhow and inventions resulting from the Study or relating to the Drug or Confidential Information are the property of the Sponsor, and the Investigator hereby assigns all rights, title and interest therein to the Sponsor.

The Investigator agrees to promptly disclose in writing to the Sponsor any data, knowhow and inventions resulting from the Study or relating to the Drug or Confidential Information, whether patentable or not.

The Investigator agrees to assist the Sponsor in connection with any application for patent rights and other forms of intellectual property rights, and execute any documents needed to apply for or perfect the Sponsor's ownerships interests therein, without further consideration. The application for patents or other intellectual property rights and the exploitation thereof shall be under the sole authority of the Sponsor and shall thus be filed by the Sponsor in its name and at its costs.

In these examples, the terms "Confidential Information," "Drug," "Investigator," "Sponsor" and Study are capitalized because each typically would be a defined term with the definition appearing elsewhere in the agreement.

[46] FDAAA § 801(a)(j)(4)(C)(i)(I), codified in 42 U.S.C. § 282(j)(4)(C)(i)(I).
[47] Codified in 42 U.S.C. § 282 (j)(3)(I).
[48] Title 35 of the United States Code (U.S.C.).
[49] *See Larson v. Correct Craft, Inc.*, 569 F.3d 1319, 1326 (Fed. Cir. 2009) ("questions of patent ownership are determined by state law").
[50] There may be exceptions for inventions conceived using federal money. *See, e.g.,* The Bayh-Sole Act, codified in Bayh-Dole Act as codified in 35 U.S.C. §§ 202-212. There are many other acts affecting technology transfer from government to the private sector, but these are not addressed herein, as most Sponsors are private entities that do not use federal funding for clinical trials.

Publication rights

In many instances, especially in academic institutions, Investigators have a right to publish study results. The CTA may still impose limitations on this right, such as restrictions on disclosure of confidential information, or provide the Sponsor with a period to review any publication prior to submission in order to obtain any needed patent protection, to protect confidential information or to ensure integrity and adherence to standards of authorship, disclosure, etc., as may be required. For instance, a clause to be considered is whether separated subsets of data can be published such as from one institution for a multi-site study.

21 C.F.R. § 312.315 or § 312.320 (b) – Treatment IND submitted by licensed practitioner

(1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the Sponsor of the controlled trial under a treatment protocol. If the Sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (1) of this section, the licensed medical practitioner may seek to obtain the drug from the Sponsor and submit a treatment IND to the FDA, requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after the FDA receives the IND or an earlier notification by the FDA that the treatment use under the IND may begin. Treatment INDs must meet certain criteria. For instance, the Investigator must still be qualified and the patient cannot be eligible for an ongoing enrolling clinical study.

MEDICAL DEVICES

Introduction

FDA-regulated clinical investigations of medical devices are principally governed by Section 520(g) of the Federal Food, Drug, and Cosmetic (FDC) Act, 21 U.S.C. § 360j(g), and implementing regulations in 21 C.F.R. Part 812, although additional regulations found at 21 C.F.R. Parts 50 (informed consent), 54 (financial disclosure of clinical Investigators) and 56 (institutional review boards) play important roles as well. There are also a myriad FDA guidance documents in which the agency interprets and expands on the statutory provision and implementing regulations.

The opening subsection of Section 520(g) articulates the guiding principle behind governmental oversight of medical device clinical trials as established by the US Congress.

It is the purpose of this subsection to encourage, to the extent consistent with the protection of public health and safety, and with ethical standards, the discovery and development of useful devices intended for human use and to that end, to maintain optimum freedom for scientific investigators in their pursuit of that purpose.

21 U.S.C. § 360j(g)(1)

As such, as mandated by Congress, the FDA regulation on medical device clinical investigations is a balance between protecting study subjects and supporting scientific/medical innovation through research on humans.

Investigational Device Exemptions

An Investigational Device Exemption (IDE) is an application to the FDA seeking approval to conduct a clinical investigation of a medical device (or device use) that is not legally available in the US for commercial distribution. Once approved, an IDE permits a device that would otherwise be required to comply with a performance standard or other special controls, or to have premarket approval or clearance, to be shipped lawfully for the purpose of conducting clinical investigations of that device. *21 C.F.R. § 812.1(a).*

Medical device Sponsors and their products, once in possession of an approved IDE, are exempt from many statutory provisions and regulations that would normally apply for the products to be legally shipped for commercial use in the US. The provisions and regulations from which the Sponsors and products are exempt are as follows:

- Misbranding provisions under FDC Act Section 501 (21 U.S.C. § 352)
- Establishment registration, medical device listing and premarket notification under FDC Act Section 510 (21 U.S.C. § 360) and 21 C.F.R. Part 807
- Performance standards and other special controls under FDC Act Section 514 (21 U.S.C. § 360d)
- Premarket approval under FDC Act Section 515 (21 U.S.C. § 360e) and 21 C.F.R. 814
- Banned device provisions under FDC Act Section 516 (21 U.S.C. § 360f)
- Records and reports under FDC Act Section 519 (21 U.S.C. § 360i), 21 C.F.R. Part 803 and other related FDA regulations
- Restricted device requirements under FDC Act Section 520(e) (21 U.S.C. § 360j(e))
- Good manufacturing practice requirements under FDC Act Section 520(f) (21 U.S.C. § 360j(f)) and 21 C.F.R. Part 820 (except for the design controls requirements, 21 C.F.R. § 820.30, where applicable)
- Color additive requirements under FDC Act Section 721 (21 U.S.C. § 379(e))

IDE-exempt studies

Certain investigations and research are not subject to Part 812 and do not need to comply with its requirements. These investigations and research activities include the following:

- Studies of commercial devices used in accordance with their labeling
- Studies of many types of diagnostic devices
- Consumer preference testing
- Testing of a device modification or a combination of devices when the purpose is not determining safety or effectiveness of the device and study subjects are not put at risk
- Studies of veterinary devices
- Research on or with laboratory animals
- Studies of custom devices (See 21 C.F.R. § 812.3(b) for the definition of "custom device.")

See 21 C.F.R. § 812.2(c) for more information on investigations and research activities not subject to Part 812.

The "practice of medicine" is also outside the purview of Part 812. As enacted by Congress, Section 1006 of the FDC Act (21 U.S.C. § 396) states in relevant part:

"Nothing in this Act shall limit or interfere with authority of health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."

In short, a physician or other appropriately licensed practitioner, based on his or her medical experience and judgment, can decide that the use of an approved or cleared device for an unapproved use is desired for his or her patient,

without triggering the requirements of Part 812, among other requirements. This right of the practitioner presupposes that he or she is not studying the safety and effectiveness of the desired unapproved device use.

Basic physiological research to answer a pure research question is also not subject to Part 812 if certain criteria are met. The research must not be part of developing the device for commercial use, and device safety and effectiveness must not be evaluated.

Significant risk and nonsignificant risk device studies

Some medical device clinical investigations are only subject to abbreviated, as opposed to full, IDE requirements under Part 812. There are two types of studies subject to IDE regulations under Part 812: significant risk (SR) device studies and nonsignificant risk (NSR) device studies. What constitutes "significant risk" is defined in 21 C.F.R. § 812.3(m):

- A study device is intended as an implant and presents a potential serious risk to the health, safety and welfare of a study subject.
- A device is purported or represented for use in supporting or sustaining human life and presents a potentially serious risk to the health, safety and welfare of a study subject.
- A device is of substantial importance in diagnosing, curing, mitigating or treating disease or preventing impairment of human health and presents a potentially serious risk to the health, safety and welfare of a study subject.
- A device that otherwise presents a potentially serious risk to the health, safety and welfare of a study subject.

While the study Sponsor, with the IRB review, makes the determination as to whether a device study is SR or NSR, the FDA has the authority to disagree, impacting the scope of applicable Part 812 requirements for the clinical investigation (see below).

NSR device studies do not require the submission of an IDE application to the FDA for approval. They are considered to have an approved IDE if they are in compliance with certain abbreviated IDE requirements. These abbreviated requirements include the following:

- The devices used in the study comply with investigational device labeling requirements (21 C.F.R. § 812.5).
- The study has IRB approval (21 C.F.R. Part 56).
- Informed consent requirements are met for study subjects (21 C.F.R. Part 50).
- Required study monitoring controls are in place (21 C.F.R. § 812.46).
- Certain Sponsor and Investigator recordkeeping and reporting requirements are observed; (21 C.F.R. §§ 812.140(b)(4) and (5) and 812.150(b)(1)-(3) and (5)-(10) (sponsor) and 21 C.F.R. §§ 812.140(a)(3)(i) and 812.150(a)(1), (2), (5) and (7) (investigator).
- Prohibitions against investigational device promotion, commercialization, test marketing and certain other related activities are honored (21 C.F.R. § 812.7).

An NSR device study can commence upon IRB approval of the study. For SR device studies, they cannot start until an IDE application is approved by the FDA.

IDE applications

The required information for an IDE application is governed by 21 C.F.R. § 812.20 and includes the following:

- The name and address of the Sponsor
- A report of prior investigations and the investigational plan (*see* 21 C.F.R. § 812.25 for more information)
- Data on device manufacture, processing, packaging and storage
- A copy of the investigator agreement
- A list of the name, address and chairperson of each IRB, as well as participating institutions
- Any device charge to show that the study device is not being commercialized
- An environmental assessment of the study
- Investigational device labeling
- Study subject materials, including the informed consent form
- Any additional information requested by the FDA

Once an IDE application is filed, a decision on its approval is provided within 30 days (21 C.F.R. § 812.30). Technically, the study can start if the FDA does not respond in 30 days, but this is usually not advisable. The FDA will send a letter to the study Sponsor, either approving the study, approving it with conditions, or disapproving it. Id. In 2012, Congress amended the FDC Act with the following provision.

FDA shall not disapprove an IDE because the investigation may not support the substantial equivalence or de novo classification determination, or approval of a device, or the investigation may not meet a requirement, including a data requirement relating to the approval or clearance of device, or an additional or different investigation may be necessary to support clearance or approval of the device. (21 U.S.C. § 360j(g)(4)(C))

This provision prohibits the FDA from disapproving a device study because the agency believes the study design is not adequate to generate data to support a future device marketing application.

After an IDE is approved, the sponsor will continue to file IDE application supplements and amendments as needed, until the IDE is closed, for changes in the study or the device itself (21 C.F.R. § 812.35). Various reports also need to be submitted to the FDA, such as annual progress reports, unanticipated adverse device effective reports, and a current list of Investigators. *See* 21 C.F.R. § 812.150(b) for more details on Sponsor reports. See 21 C.F.R. § 812.140(b) for more information on Sponsor recordkeeping obligations.

Both pivotal and feasibility device studies can require approved IDE applications, although early feasibility device studies can be subject to lesser requirements to obtain IDE approval. Early feasibility studies are studies that are typically conducted on a small number of subjects, and where the device is typically early in the development, before its final design. See FDA guidance entitled, "Investigational Device Exemptions for Early Feasibility Medical Device Clinical Studies, including Certain First in Human Studies." The guidance in general provides that IDE application approval might be achieved on less non-clinical data than normally required to support approval of a larger clinical study on a more finalized device design.

Sponsors, Investigators and IRBs

In the context of medical device clinical investigations, Sponsors, Investigators and IRBs all have legal obligations. The Sponsor (unless a Sponsor-Investigator) initiates, but does not actually conduct, the medical device clinical investigation. The Investigator actually conducts the clinical investigation. It is under the Investigator's immediate direction that the test article is administered or dispensed to, or used on, a subject. Finally, the IRB is the reviewing body that approves clinical investigations at a medical facility or institution (although some commercial IRBs that are not tied to a particular medical facility or institution exist). The IRB carries out initial review and then continuing review of the clinical investigation over the study's life.

The Sponsor's responsibilities include many tasks and obligations. They include, but are not limited to: selecting qualified Investigators; providing the Investigators with the information and materials they require for a successful study; obtaining signed agreements from the Investigators; ensuring proper study monitoring, including selection of competent monitors; overseeing compliance with the study protocol; evaluating and handling any unanticipated adverse device effects during the study; and obtaining IRB approval (and FDA approval where relevant) of the clinical investigation. Sponsors are also responsible for maintaining adequate records and making certain reports. See 21 C.F.R. §§ 820.140(b) and 820.150(b) for more details on specific Sponsor recordkeeping and reporting obligations.

The Sponsor's responsibilities are detailed in 21 C.F.R. Part 812, Subpart C.

The Investigator is responsible for conducting the investigation in accordance with the investigator agreement, the investigational plan, applicable FDA regulations and any IDE conditions of approval. They also must protect the rights, safety and welfare of subjects under their care, control the investigational devices (including overseeing device use and disposing of devices in an appropriate manner), and obtaining appropriate informed consent from study subjects. The recordkeeping and reporting responsibilities of Investigators are somewhat similar to those for the Sponsor. See 21 C.F.R. §§ 820.140(a) and 820.150(a) for more details on specific investigator recordkeeping and reporting obligations.

The Investigator's responsibilities are detailed in 21 C.F.R. Part 812, Subpart E.

For FDA regulatory purposes, the mandate of an IRB is to protect the rights and welfare of human subjects involved in FDA-regulated clinical investigations. IRBs are responsible for: SR/NSR device study determinations for clinical investigations; review of study protocols and informed consent forms; review of any changes to a study protocol; and continuing review of those protocols, among other things.

The responsibilities of IRBs are found in 21 C.F.R. Part 56, and to a lesser extent in 21 C.F.R. Part 812, Subpart D.

Device studies and ClinicalTrials.gov

Like drug clinical trials, many device clinical trials must be registered with, and have study results submitted to, ClinicalTrials.gov. 42 U.S.C. § 282. In the vast majority of cases, these tasks are completed by the Sponsor of the clinical trial or PI of such clinical trial (if so designated by a Sponsor). *Id.*

With certain exceptions, the Sponsor or designated PI must submit the required clinical trial information for registration purposes no later than 21 days after enrollment of the first participant, just like in drug clinical trials.

In general, clinical trial results must be submitted no later than 12 months after the study's completion, although there are means by which to delay submission if certain criteria are met, just like in drug clinical trials.

The FDA has additional certification and informed consent requirements. In relevant part, device marketing applications to the FDA, such as PMAs and 510(k)s, must be accompanied by a certification indicating that the ClinicalTrials.gov requirements have been met as applicable. See FDA Form 3674. In addition, informed consent

pursuant to 21 C.F.R. Part 50 must include a specific statement about CliniccalTrials.gov registration. (21 C.F.R. § 50.25(c))

See FDAAA § 801, and the above discussion of drug clinical trials and ClinicalTrials.gov for more details on this topic.

Expedited development and review

Like drugs and biologics, there are mechanisms available to facilitate expediting the process of device marketing clearance or approval. The FDA is authorized to provide priority review for certain types of devices.

In 2015, the FDA established an expedited access pathway for devices for unmet medical needs for life-threatening or irreversibly debilitating diseases or conditions and that are subject to PMA applications or "de novo" classification requests ("**EAP Program**"). In the EAP Program, the FDA was required to assign a team with appropriate subject matter expertise and experience for the device and request senior agency personnel to oversee the team, to adopt an efficient process for timely dispute resolution, and to expedite the review of applicable manufacturing and quality compliance matters. Moreover, the FDA closely worked with the device Sponsor to coordinate an early agreement on a data development plan, to ensure an efficient and practicable design of clinical trials, to agree to binding clinical protocols on the Sponsor and the FDA, and to utilize postmarket data collection in the development and review process.

On 13 December 2016, the Federal Food, Drug, and Cosmetic Act was amended, through Section 3051 of the 21st Century Cures Act, to add the Breakthrough Device Program ("**BD Program**") provisions. The BD Program is intended to help patients have more timely access to devices and breakthrough technologies that provide for more effective treatment or diagnosis for life-threatening or irreversibly debilitating diseases, for which no approved or cleared treatment exists or that offer significant advantages over existing approved or cleared alternatives. The BD Program expands upon the EAP Program by making devices with 510(k) submissions eligible, as well as those with PMA applications and "de novo" classification requests. FDA has issued a draft guidance concerning the BD Program.

Other considerations

In compensating a health care professional for services provided relating to clinical trials, care must be taken to avoid violating the Anti-kickback Statute, the FCPA, and other similar laws and regulations.[51] All payments to Investigators or teaching hospitals must also be reported annually and are published on the OpenPayments website.

The Anti-kickback Statute makes it a criminal offense to, among other things, knowingly and willfully offer, pay, solicit or receive any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, in return for or to induce the purchase or recommendation to purchase items or services that may be reimbursable in whole or in part by a federal health care program (e.g., Medicare or Medicaid).[52]

Parties on both sides of an impermissible transaction are subject to criminal liability. Violation of the statute constitutes a felony. Punishment may be in the form of a fine of up to USD 25,000, imprisonment of up to five years, or both. Conviction also leads to automatic exclusion from federal health care programs. Additionally, under certain

[51] Interactions such as payment arrangements between a pharmaceutical or medical device company on the one hand, and a health care professional on the other, may also be influenced by voluntary industry guidelines. Such guidelines include the Code on Interactions with Healthcare Professionals and the Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results issued by PhRMA, and the Code of Interactions with Health Care Professionals issued by AdvaMed. These codes are available at http://www.phrma.org/code_on_interactions_with_healthcare_professionals, http://www.phrma.org/files/attachments/042009_Clinical%20Trial%20Principles_FINAL.pdf, and

[52] 42 U.S.C § 1320a-7b(b)(1) (2006).

circumstances, the Office of the Inspector General for the US Department of Health and Human Services (OIG) may impose civil monetary penalties.

The term "remuneration" is broadly interpreted and includes the transfer of anything of value. There are numerous specific examples of transfers of value that provide an idea of the scope, such as meals or reprints. The statute has also been interpreted to cover an arrangement in which one purpose of the remuneration is for past referrals or to induce future referrals. Because of the breadth of the Anti-kickback Statute, the OIG has promulgated the "Safe Harbor Regulations."[53] To fit within any safe harbor, the arrangement must meet all of the criteria for that safe harbor. However, the failure of an arrangement to fit within a safe harbor does not necessarily mean the arrangement violates the statute. Rather, a traditional analysis of the facts and circumstances will be necessary to determine whether any activity that does not fit precisely within the prescribed safe harbors is defensible.

Of particular importance to clinical trials are the personal services and management contracts safe harbor and the bona fide employee safe harbor:

- Personal Services and Management Contracts[54] – Arrangements with health care professionals for consulting, research or other services are permissible under the Anti-kickback Statute, as long as all of the following seven standards are met: (1) the agreement is set out in writing and signed by the parties; (2) the agreement covers all of the services of the health care professional, provides the term of the agreement, and specifies the services to be provided by the health care professional; (3) for periodic, sporadic or part-time arrangements, the agreement specifies exactly the schedule of such intervals, their precise length, and the exact charge for such intervals; (4) the term of the agreement is for not less than one year; (5) the aggregate compensation paid to the health care professional over the term of the agreement is set in advance, is consistent with fair market value in arm's-length transactions, and is not determined in a manner that takes into account the volume or value of any referrals or business otherwise generated between the parties for which payment may be made in whole or in part under Medicare, Medicaid or other federal health care programs; (6) the services performed under the agreement do not involve counseling or promotion of a business arrangement or other activity that violates any state or federal law; and (7) the aggregate services contracted for do not exceed those that are reasonably necessary to accomplish the commercially reasonable business purpose of the services.
- Bona Fide Employees[55] – Amounts paid by an employer to its bona fide employees are not considered "remuneration" under the Anti-kickback Statute.

Clinical trials that involve payments to health care professionals working for a foreign government or a foreign state-owned hospital or clinic may raise issues under the FCPA. Such health care professionals would be deemed "foreign officials" for purposes of the FCPA. Among other things, the FCPA makes it a crime to: (1) pay, or offer, or promise to pay, or authorize payment of, money or anything of value, directly or indirectly; (2) to any foreign official, politician, party official, candidate for office, or an intermediary who knows the payment will go to any of the foregoing persons (actual knowledge is not required); (3) with a corrupt motive; (4) for the purpose of influencing the person's official acts or decisions in violation of his or her lawful duty; (5) to assist in obtaining or retaining business.[56] The FCPA applies to "issuers" of securities traded on a US stock exchange, US persons or entities, and in some cases non-US persons or entities. In addition, under certain circumstances, a US entity may be deemed in violation of the FCPA as a result of the activities or conduct of its foreign subsidiaries. Care should be taken, therefore, to ensure that payments made are intended to further legitimate purposes only, and not corrupt motive.

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[53] *See* 42 C.F.R. § 1001.952 (2009).
[54] 42 C.F.R. § 1001.952(d) (2009).
[55] 42 C.F.R. § 1001.952(i) (2009).
[56] 15 U.S.C. § 78dd-2 (2007).

This article has provided a brief overview of the clinical trial requirements imposed under the FDCA, together with some resources for further reading. It also addresses certain other laws related to or which can have an impact on clinical trials. However, it has been simplified to accommodate space requirements. Moreover, as statutes, regulations and guidance documents are subject to change, the reader is encouraged to check the status, regulations and guidance documents or consult competent counsel before relying on this text.

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