

Regulatory Issues for Clinical Trials in Humans

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Clinical trials in humans are research studies designed to evaluate two or more treatments in human participants. Major concerns in any clinical trial are the protection of study participants' safety and rights and ensuring the accuracy and validity of the data being collected. To ensure that these concerns are adequately addressed in a study, the funding institutions, the institutions where the research actually takes place, and federal and state regulatory agencies have developed regulations and guidelines for conducting human research.

In the United States, each of the granting federal departments and agencies has its own regulations and guidelines for conducting human research that must be followed. If a new drug/device is being tested or an approved drug/device is being tested for a new indication, then the study must be conducted under the rules and regulations of the US Food and Drug Administration (FDA). In cases where there is both a federal funding institution and a new drug/device being tested, the regulations of both the funding department or agency and the FDA must be followed. These regulations for the FDA (1) and the various federal departments and agencies can be found in the Code of Federal Regulations (CFR). A listing of the appropriate CFR for the various federal departments and agencies can be found in the instructions for federalwide assurance from the Office for Human Research Protections, Department of Health and Human Services (2).

Although many clinical trials in the United States are funded by federal departments and agencies, many are funded by the pharmaceutical industry. These industry studies will almost always comply with FDA regulations and the International Conference on Harmonisation guidelines that have been adopted by the FDA. In this article, some of the more pertinent regulatory issues that an investigator must address when conducting a clinical trial are described.

Received for publication July 12, 2001, and accepted for publication February 12, 2002.

Abbreviations: CFR, Code of Federal Regulations; FDA, Food and Drug Administration; IRB, institutional review board; VA, Department of Veterans Affairs.

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FEDERALLY SUPPORTED TRIALS

Protection of human subjects—The Common Rule

All federal departments and agencies supporting, conducting, or regulating research on humans have agreed to a set of ethical principles and regulations called the "Common Rule" (3). Although all departments and agencies adhere to the Common Rule, departments and agencies may add additional protections for research that they fund. Thus, an investigator should obtain the appropriate CFR (2) for the department or agency supporting his/her research.

The Common Rule is meant to ensure that all of an institution's human research activities are guided by the ethical principles found in the Belmont Report (4). In a broad sense, the Common Rule describes when the rule must be followed and how compliance with the rule will be ensured, provides guidelines for the establishment and functioning of independent institutional review committees called institutional review boards (IRBs), and gives general requirements for informed consent.

When rule must be followed (45 CFR §46.101). The Common Rule must be followed for all human research conducted, supported, or subject to regulation by any federal department or agency. It includes research conducted, supported, or subject to federal regulation outside the United States. For research in foreign countries, a department or agency head may approve the substitution of the country's regulations governing protection of human subjects if they are at least equivalent to those of the Common Rule. Exemptions from this policy are allowed, such as research conducted in established or commonly accepted educational settings involving normal educational practices; research involving the use of educational tests, survey procedures, interview procedures, or observations of public behavior; and certain taste and food evaluations. However, department or agency heads retain final judgment for exempting research from the Common Rule.

Ensuring compliance (45 CFR §46.103). The Common Rule states that each institution conducting research supported or regulated by the federal government will provide written assurance to the appropriate federal department or agency that the institution will comply with all requirements contained in the Rule. This written assurance must be executed by an individual authorized to act on behalf of (and who obligates) the institution. At a minimum the assurances must contain 1) a statement of the principles governing the institution for protecting the rights and welfare of participants in

research at the institution; 2) the designation of at least one properly constituted and functioning IRB to review research at the institution; 3) a list of IRB members; 4) written procedures for conducting and reporting initial and continuing reviews (at least annually) of research, for determining when more frequent reviews than annually are required, and for ensuring prompt reporting to the IRB of proposed changes in the trial; and 5) written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of any serious or unexpected risks or any continuing noncompliance with the Common Rule. A federalwide assurance program has been instituted that is discussed later.

IRB requirements (45 CFR §46.107–.111). The Common Rule requires an IRB to have at least five members of varying backgrounds sufficiently qualified through expertise and experience to promote complete and adequate review of research activities commonly conducted by the institution. An IRB should not be composed entirely of men or entirely of women. It should have at least one scientist and one nonscientist member and have at least one non-institution-affiliated member. An investigator who is a member of an IRB may not participate in the IRB's initial or continuing review of any trial in which he/she has a conflict of interest except to provide information to the IRB. The IRB will develop and follow written procedures of conduct except in cases of an expedited review. All initial and continuing reviews of trials by an IRB will be conducted at convened meetings of a majority of its members including at least one nonscientist member. An IRB has the authority to approve, to require modifications of, or to disapprove a research project. An IRB also has the authority to suspend or terminate approval of research not being conducted in accordance with IRB requirements or that is associated with unexpected serious harm to subjects. Decisions of an IRB must be made in writing to the investigator and the institution. Although upon further review an institution may disapprove a project approved by an IRB, it may not approve research that has not been approved by an IRB. Table 1 lists the minimal criteria on which IRBs should be rating trials.

Informed consent (45 CFR §46.116). The Common Rule requires that all subjects in a clinical trial provide written, legally effective informed consent except as specifically provided for in the Rule. The Rule specifically states that an investigator should seek consent only from a prospective subject or the subject's legally authorized representative under circumstances that provide the subject or representative sufficient opportunity to consider participation in the trial and that minimize the possibility of coercion or undue influence. Table 2 lists the elements of informed consent specifically listed in the Common Rule. An IRB may approve a consent procedure that does not include or alters some of the elements of informed consent. However, the IRB must determine and document that the research involves no more than minimal risk, the waiver or alteration will not adversely affect the rights and welfare of the subjects, the research could not be practically carried out without the waiver or alteration, and, when appropriate, subjects will be provided with additional pertinent information after participation. The Common Rule

TABLE 1. Common Rule criteria for institutional review board approval of research

1. Risks to subjects are minimized.
2. Risks to subjects are reasonable in relation to anticipated benefits.
3. Selection of subjects is equitable.
4. Informed consent will be sought from each prospective subject or subject's legally authorized representative.
5. Informed consent is appropriately documented.
 - a. Informed consent is in accordance with general requirements set forth in Common Rule.
6. When appropriate, there is a data-monitoring plan to ensure subjects' safety.
7. There are adequate provisions to protect subjects' privacy and to maintain data confidentiality.
8. When appropriate, additional safeguards are included in the research plan to protect the rights and welfare of subjects from coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, and so on.

TABLE 2. Common Rule elements of informed consent

- A. Basic elements
 1. A statement that study involves research
 2. An explanation of the study's purpose and expected duration of subjects' participation
 3. Description of procedures and identification of procedures that are experimental
 4. Description of any foreseeable risks or discomforts
 5. Descriptions of benefits to subjects or to others
 6. Disclosure of other treatment options available
 7. Statement of the extent to which the confidentiality of subjects' records will be maintained
 8. An explanation of whether any compensation is available and whether any medical treatments will be provided if injury occurs and, if so, what is available and where information can be obtained
 9. An explanation of whom to contact concerning the research and research subjects' right
 10. An explanation of whom to contact concerning a research-related injury
 11. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of entitled benefits, and that the subject may discontinue participation at any time without penalty or loss of entitled benefits
- B. Additional elements (when appropriate)
 1. Statement that research procedures and/or treatments may involve risks that are currently unforeseeable
 2. Circumstances under which subjects' participation may be terminated without regard to subjects' consent
 3. Any additional costs to subject because of research participation
 4. Consequences of subject's decision to withdraw and procedures for early termination of participation
 5. Statement that subjects will be provided any new findings that may relate to their willingness to continue participation
 6. Approximate number of subjects involved in the study

also requires the subject or his/her legal representative to sign the informed consent but allows the IRB under certain circumstances to waive this requirement.

Additional protections. The Common Rule allows the head of a department or agency to impose additional conditions that he/she judges to be necessary to protect human subjects with respect to a specific research project or to any class of research projects. The policy for protection of human subjects for the Department of Health and Human Services (45 CFR §46) has three subparts in addition to subpart A, the Common Rule. Subpart B gives additional protections to research activities involving fetuses, pregnant women, and human in vitro fertilization; subpart C gives additional protections for research involving prisoners as subjects; and subpart D provides additional protections for children involved as subjects in research. The Department of Veterans Affairs (VA) has added a section to its policy that states that VA medical facilities will provide all necessary medical treatment to subjects injured as a result of participation in a VA-approved research project by a VA investigator at a VA institution (5).

Federalwide assurances of protection for human subjects

As previously stated, the Common Rule requires that an institution performing federally supported or regulated research in humans must provide written assurance that it will comply with the Common Rule. Prior to February 2001, the Department of Health and Human Services had a system of assurance statements that covered Department of Health and Human Services-supported research. After February 28, 2001, the Department of Health and Human Services no longer routinely accepted assurances limited to Department of Health and Human Services-supported research into special categories of research or to individual research projects (6). Instead the Department of Health and Human Services has developed a two-step assurance process that covers all of an institution's federally supported human subject research. Under this process, each legally separate institution needs its own federalwide assurance.

The first step in the process is for the institution to register its IRB with the Office for Human Research Protections. For institutions not having their own IRBs, the IRB that they intend to use must be registered. Registration is done by completing a three-page form and submitting it to the Office for Human Research Protections (7). It should be noted that currently the FDA does not require the registration of IRBs (8). Thus, only institutions having federally supported research are required to use registered IRBs at this time. The responsibilities of IRBs and independent ethics committees for FDA-regulated research and for federally supported research in both the United States and outside can be found in an Office for Human Research Protections Web site (9). These responsibilities are basically those given in the Common Rule. To maintain an active registration, the registration form must be updated every 36 months.

The second step in the process is the actual filing for federalwide assurance. Any institution is eligible to file for federalwide assurance, but those conducting federally supported research are required to do so. Filing for feder-

alwide assurance is done by completing a four-page form (10). The federalwide assurance form requires an assurance that the institution will be guided in its human research by a named appropriate document (e.g., the Belmont Report (4)), an assurance that the institution will comply with a specifically named procedural standard (e.g., 45 CFR §46 (3)), a listing of all institutional components that will be covered by the federalwide assurance, and a designation of a registered IRB(s) or independent ethics committee(s) for review of research on a regular basis. For VA facilities there is an additional form that ensures that these facilities will follow all VA policies and procedures (11). The terms of the federalwide assurance for institutions both in the United States and outside can be found in an Office for Human Research Protections Web site (2). Frequently asked questions on IRB registration and federalwide assurance are answered at another Office for Human Research Protections Web site (12).

Investigator training

Beginning on October 1, 2000, the National Institutes of Health required education on the protection of human research participants for all investigators submitting National Institutes of Health applications for grants, contracts, or new or noncompeting awards for research involving humans (13). This training is required for all human research including research exempt from IRB review. The requirement applies to all key personnel involved in the design or conduct of the human research even if they do not receive compensation from the award. The VA required similar training for human research begun after January 1, 2001.

Neither the National Institutes of Health nor the VA currently mandates or endorses a specific training program. The amount and type of training are left to the investigators and their institutions. Many institutions have developed their own training programs as have some professional organizations. The Office of Human Subjects Research at the National Institutes of Health offers two online computer-based training courses, one for researchers (14) and another for IRB members (15). A certificate of training is provided for each course.

On December 7, 2000, the Public Health Service of the Department of Health and Human Services released a policy on instruction in the responsible conduct of research (16). This policy was suspended on February 21, 2001, to permit additional review (17). While currently suspended (January 2002), it can be expected that some kind of training on the responsible conduct of research will be required eventually for Department of Health and Human Services-supported studies. In the original policy (16), training was to include 1) data acquisition, management, sharing, and ownership; 2) mentor/trainee responsibilities; 3) publication practices and responsible authorship; 4) peer review; 5) collaborative science; 6) human subjects; 7) research involving animals; 8) research misconduct; and 9) conflict of interest and commitment. Exact

content, length, level, and format are to be determined by individual institutions.

Data and safety monitoring

It is the policy of the National Institutes of Health that each of its Institutes and Centers has a system for the appropriate oversight and monitoring of all National Institutes of Health-supported or -conducted clinical trials to ensure participant safety and the validity and integrity of the data (18). This policy states that monitoring should be commensurate with risks and with the size and complexity of the trials. For phase III clinical trials, Data and Safety Monitoring Boards are generally required. For phase I (e.g., physiologic, toxicity, and dose-finding studies) and phase II (efficacy studies) trials, the National Institutes of Health require that investigators submit a monitoring plan for these trials to the funding Institute and Center before the trial begins (19). The elements of the plan may vary depending on the potential risks, complexity, and nature of the trial. At a minimum, these monitoring plans must include the reporting mechanisms for adverse events to the IRB, FDA, and the National Institutes of Health. Institutions with a large number of clinical trials may develop standard monitoring plans for phase I and phase II trials, which individual investigators may include in their submissions to the National Institutes of Health. The VA's Cooperative Studies Program, which conducts multicenter clinical trials, also requires Data and Safety Monitoring Boards for its studies, and proposals submitted for review must include a monitoring plan (20).

Reporting of adverse events

The Common Rule requires that IRBs have written procedures for ensuring prompt reporting of any serious or unexpected risks or problems to the IRB, appropriate institutional officials, and the federal department or agency head (3). Investigators are responsible for knowing the policies of their local IRBs and adhering to the policies. They must retain a copy of the policies in the study files. An investigator is also responsible for the accurate documentation, investigation, and follow-up of all possible study-related adverse events (21).

For multicenter studies, the National Institutes of Health require that Data and Safety Monitoring Boards prepare summary reports of adverse events without specific disclosure by treatment groups, which are forwarded to the site investigators for distribution to their IRBs (21). Therefore, instead of receiving individual adverse event reports from each of the clinical sites, IRBs should be receiving from an investigator the adverse events from only his/her site and the written summary report from the Data and Safety Monitoring Board. Investigator responsibilities for multicenter trials, in addition to those listed above, include identifying the Data and Safety Monitoring Board involved, describing the adverse events monitoring plans when submitting the protocol for IRB review, and submitting the periodic Data and Safety Monitoring Board written sum-

maries to their IRBs. The VA's Cooperative Studies Program has a similar requirement (20).

Financial conflicts of interest

Since 1995, the US Public Health Service agencies have had regulations concerning financial conflict of interest (22). These regulations require institutions to maintain a written, enforced policy on financial conflict of interest; to inform research investigators of the policy and the federal regulations; to report to grant-awarding offices any conflicting interests; and to ensure that the interests have been managed, reduced, or eliminated in accordance with the regulations. Institutions are not required to provide the details of the conflict. Under these regulations, investigators are required to disclose to the appropriate institution official(s) a listing of any significant financial interests, including those of his/her spouse and dependent children, that would reasonably appear to be affected by the proposed research.

A draft interim guidance from the Department of Health and Human Services on this topic (23) states, among other things, that clinical investigators should consider the potential effect that having a financial relation of any kind with a commercial sponsor might have on the conduct of a clinical trial or interactions with research subjects, that any agreements between investigators and a sponsor should be reviewed by the appropriate institutional committee/official, and that investigators should participate in educational and training programs concerned with financial conflict of interest issues. This draft guidance also suggests including in the informed consent document the source of study funding and any financial conflict of interest on the part of the institution and/or investigator that has not or cannot be eliminated.

The FDA also requires anyone who submits a marketing application for any drug, biologic product, or device to provide certain information concerning the compensation to and financial interests of any clinical investigator conducting clinical studies submitted to the FDA in support of the application. The FDA requires disclosure of specified financial arrangements and any steps taken to minimize the potential for bias (24). The VA's Cooperative Studies Program also requires disclosure of any potential conflicts of interest (20).

FDA-REGULATED TRIALS

Trials conducted under an FDA investigational new drug application must adhere to all of the FDA regulations pertaining to conducting clinical trials that are outlined in the FDA CFR (1). Specifically, parts 50 (Protection of Human Subjects), 54 (Financial Disclosure by Clinical Investigators), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application) contain regulations that apply specifically to clinical investigators. Although there are some differences, such as the FDA's allowing exemptions from the informed consent procedures in emergency situations and providing sanctions for noncompliance with regulations (25), parts 50, 54, and 56 are similar to what was discussed under federally supported trials and will not be discussed here.

General responsibilities of investigators (23 CFR §312.60)

An investigator in a clinical trial is ultimately responsible 1) for seeing that the trial at his/her site is conducted in compliance with the statement that he/she signs (form FDA 1572 (26)) prior to starting the trial (see table 3 for commitments agreed to), the IRB-approved study protocol, and all applicable federal, state, and local regulations; 2) for protecting the rights, safety, and welfare of the study participants under his/her care; and 3) for controlling the use of the investigational drug. Except as specifically exempted in part 50 of the FDA's CFR, the investigator must obtain written, informed consent from patients volunteering to participate in the trial. The investigator is also responsible for compliance with the Guideline for Good Clinical Practice of the International Conference on Harmonisation as adopted by the FDA (27).

Control of the investigational drug (21 CFR §312.61)

The primary site investigator of a clinical trial must prescribe the study drug only to those patients under his/her supervision or under the supervision of a subinvestigator who is responsible to the primary site investigator.

Investigator record keeping and record retention (21 CFR §312.62)

Disposition of drug. The investigator must maintain adequate records of the use of the study drug, which includes the amounts prescribed to the patient, returned by the

patient, consumed by the patient, and destroyed locally or sent back to the sponsor of the investigation. The investigator is ultimately responsible for this drug accountability activity; however, this activity is, in most cases, performed by the pharmacy service available to the investigator.

Case histories. The investigator must prepare and maintain for analysis and audit adequate and accurate case histories that are evidence of the observations and other data pertinent to the trial. The case histories should include case report forms, any changes to the forms, signed and dated informed consent documents, and pertinent parts of the medical record (diagnosis, physician and nurse progress notes, and hospital or clinic charts (electronic or otherwise)).

Record retention. The investigator must retain study records including evidence of source documents for a period of 2 years following the date a marketing application is approved for the drug being studied. If a marketing application is not relevant to the clinical trial, the records must be retained until 2 years after the investigation is discontinued and the FDA is notified of its discontinuance.

Investigator reports (21 CFR §312.64)

Progress reports. The investigator must furnish all reports generated during the study to the sponsor of the drug or clinical trial.

Safety reports. The investigator must report to the sponsor of the clinical trial any adverse medical event that is reasonably thought to be caused by or probably caused by the

TABLE 3. Commitments that the investigator makes when signing the form FDA* 1572

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
I agree to personally conduct or supervise the described investigation(s).
I agree to inform any patients or any persons used as controls that the drugs are being used for investigational purposes, and I will ensure that the requirements relating to obtaining informed consent in 21 CFR* part 50 and institutional review board review and approval in 21 CFR part 56 are met.
I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR part 312.64.
I have read and understand the information in the investigator's brochure, including the potential risks and adverse effects of the drug.
I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
I agree to maintain adequate and accurate records in accordance with 21 CFR part 312.62 and to make those records available for inspection in accordance with 21 CFR part 312.68.
I will ensure that an institutional review board that complies with the requirements of 21 CFR part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the institutional review board all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without institutional review board approval, except where necessary to eliminate apparent immediate hazards to human subjects.
I agree to comply with all other requirements regarding the obligations of clinical investigations and all other pertinent requirements in 21 CFR part 312.

* FDA, Food and Drug Administration; CFR, Code of Federal Regulation.

study drug. If the adverse medical event is regarded as a serious adverse event, the investigator is responsible for reporting the event to the sponsor immediately. Serious adverse events are defined as any drug/device adverse experience that results in 1) death or is life threatening, 2) patient hospitalization or prolongation of existing hospitalization, 3) persistent or significant disability/incapacity, 4) congenital anomaly/birth defect, or 5) any other important medical event as determined by the investigator.

Final report. The investigator must provide the sponsor with a final report on the investigation after the investigator has completed participation in the clinical trial.

Financial disclosure reports. The investigator participating in a clinical trial must provide to the sponsor of the trial complete and accurate certification or disclosure statements. The information submitted by the investigator must be updated annually if financial changes have occurred.

Assurance of IRB review (21 CFR §312.66)

The investigator is responsible for 1) seeing that the IRB he/she is using for local approval of the clinical trial is duly constituted, 2) the initial IRB review and written approval of the proposed clinical trial, 3) continuing IRB review (in general, annually) and written approval of the clinical trial, 4) IRB review and written approval of any changes in the study protocol or informed consent document, and 5) submitting to the IRB descriptions of all unanticipated problems involving risks to the patient volunteers of the clinical trial. The investigator of a clinical trial is ultimately responsible for all aspects of the clinical trial he/she is conducting at his/her facility.

Inspection of investigator's records and reports (21 CFR §312.68)

The investigator must permit any authorized officer or employee of the FDA to have access to copy and verify records or reports generated by the investigator of a clinical trial. The names of volunteers for a clinical trial can be kept anonymous by the investigator under most circumstances, unless the records of particular individuals require more detailed study, there is reason to believe that the records do not represent actual case studies, or there is possible data fabrication.

Handling of controlled substances (21 CFR §312.69)

If a clinical trial involves a drug that is controlled by the Controlled Substances Act, the investigator is responsible for seeing that adequate precautions are taken for handling the study drugs. This includes locked storage of the study drug at his/her facility and limited personnel access to the storage area. All relevant laws promulgated by the Drug Enforcement Agency must be complied with. As with investigational drugs that are not controlled substances, the investigator's pharmacy service generally provides compliant receipt, storage, handling, and dispensing of these substances according to Drug Enforcement Agency regulations.

Disqualification of a clinical investigator (21 CFR §312.70)

If the FDA determines that a clinical investigator has failed to comply with the federal regulations governing his/her participation in a clinical trial of an investigational drug, it can, through a well-defined process, disqualify the investigator from receiving investigational drugs for any clinical trial for an indefinite period of time.

INTERNATIONAL CONFERENCE ON HARMONISATION

Good clinical practices guideline

The FDA has developed a guideline entitled, "Good Clinical Practice: A Consolidated Guideline," that was prepared under the review of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (27). The guideline defines the concept of "good clinical practice." In addition, the guideline provides an international ethical and scientific quality standard for the designing, conducting, data collecting, and reporting of clinical trials that involve the participation of human subjects. Moreover, the guideline outlines the essential documents that permit the evaluation of the completed clinical trial and the quality of the data generated by the trial. The objective of the guideline is to facilitate the acceptance of international clinical data by regulatory authorities in those countries recognizing and accepting the guideline.

Good clinical practice responsibilities of investigators

The International Conference on Harmonisation's good clinical practice guideline requires that the investigator be qualified to conduct the research and be able to demonstrate that he/she has adequate resources to conduct the trial. In addition, the investigator must provide for the medical care of the trial subjects, communicate with the IRB regularly with regard to the trial, comply with the study protocol, account for the use of the investigational drug used in the trial, follow the randomization and unblinding procedures, obtain informed consent from all trial subjects, and provide for the premature termination or suspension of a clinical trial. Moreover, the investigator is required to develop, submit, and retain the records and reports on the progress, safety, and final investigator reports for the trial. The documents that are required to be on file in the investigator's study office before the clinical trial formally starts, during the conduct of the clinical trial, and after completion or termination of the clinical trial are listed in tables 4–6, respectively.

DISCUSSION AND CONCLUSIONS

An investigator undertaking a clinical trial that is being funded, supported, or regulated by a department or agency of the US federal government needs to be aware of and to adhere to all of the appropriate regulations. Although all departments and agencies adhere to the Common Rule, there may be additional regulations for some departments and

TABLE 4. Documents that must be on file in the investigator's study office before the clinical trial formally starts

1. Investigator's brochure
2. Signed protocol and amendments
3. Informed consent document
4. Advertising for subject recruitment
5. Financial aspects of the trial
6. Insurance statement if required
7. Signed agreement with the sponsor
8. Written institutional review board approval
9. Institutional review board composition
10. Regulatory authority approval (investigational new drug no.)
11. Food and Drug Administration form 1572 and curriculum vitae
12. Normal values/ranges for medical/laboratory/technical procedures and/or tests
13. Sample of labels used on the investigational products
14. Written instructions for handling the investigational products
15. Shipping records for investigational products
16. Decoding procedures for blinded trials
17. Trial initiation monitoring report

TABLE 5. Documents that must be on file in the investigator's study office during the conduct of the clinical trial

1. Investigator's brochure updates
2. Any revisions to the protocol, informed consent document, or advertisement for subject recruitment
3. Additional reviews and approvals of the institutional review board
4. Food and Drug Administration form 1572 and curriculum vitae of subinvestigators
5. Updates to normal values/ranges for medical, laboratory, or technical procedures and/or tests
6. Updates on medical/laboratory certification
7. Documentation of investigational product shipments
8. Relevant communications with the sponsor
9. Signed informed consent documents
10. Data source documents
11. Signed, dated, and completed case report forms
12. Documentation of case report form corrections
13. Reports of serious adverse events to sponsor
14. Documentation of submission of serious adverse events to the institutional review board
15. Notification by sponsor to investigator of safety information
16. Interim or annual reports to the institutional review board
17. Subjects' screening log
18. Subjects' identification code list
19. Subjects' enrollment log
20. Investigational product accountability at site

TABLE 6. Documents that must be on file in the investigator's study office after completion or termination of the clinical trial

1. Investigational product accountability at site
2. Documentation of investigational product destruction
3. Completed subjects' identification code list
4. Final report by the investigator to the institutional review board
5. Clinical study report

agencies. Thus, an investigator is advised to contact the department or agency that he/she is involved with to determine the exact requirements of the department or agency.

Specific responsibilities of an investigator in a clinical trial include obtaining proper initial and continuing IRB approval of the trial; ensuring that all study participants are fully informed about the trial that they are being asked to enter and that they sign a valid informed consent; obtaining appropriate training for all key trial personnel; providing appropriate data and safety monitoring; reporting of adverse events, especially serious or unexpected ones, to appropriate officials; maintaining proper control of all trial materials such as drugs and devices; maintaining proper records and preparing appropriate reports; and collecting study data. These tasks can be expensive and time consuming. Therefore, prior to undertaking a clinical trial, a potential investigator should ensure that he/she has the appropriate resources available or that the trial will provide the appropriate resources, remembering to include sufficient resources to provide for the regulatory requirements of the trial.

Although this article has addressed mainly US federal regulations, investigators should be aware that individual states in the United States may also have regulations that must be adhered to. For example, Maryland has an IRB review requirement for release of patient information for research, while Virginia allows for release of such information as long as identifiers are removed (28). Individual institutions will also have regulations that an investigator must follow. Many IRBs have their own rules for submission with specific formats for presentation to the IRB and for informed consents. Thus, before embarking on a clinical trial, an investigator would be well served to discuss the regulatory requirements for conducting his/her research with the trial's sponsor as well as his/her institution's research office and/or IRB.

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