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Regulatory processes for sponsor-investigators

Gordon D. MacFarlane*

ICON Clinical Research, Marlborough, MA, USA

Abstract

Translational sciences have brought many investigators into the clinical space for which clinical research and regulatory affairs are not their primary expertise. Academic institutions tend to focus their regulatory compliance activities on IRB approval and informed consent. However, many other regulatory issues may apply. The participation and assistance of trained regulatory personnel may be beneficial in reducing delays and compliance risks.

Introduction

Translational science is the bridge between basic and applied science. In medicine, this has brought many investigators into the clinical space, whose expertise is not clinical research. The clinical research space is highly regulated, and regulatory affairs are also an area that is not these investigators' primary expertise. Academic institutions are usually well equipped to support investigators with regard to basic research regulations, such as animal welfare and waste disposal requirements. In the clinical space, academic institutions and investigators are usually well aware of the requirements for Institutional Review Board (IRB)/Ethics Committee (EC) review and Informed Consent. However, most institutions are not well prepared to support investigators in dealing with any other regulatory requirements. Table 1 shows the United States federal statutes and regulations that could apply to clinical research, depending on the circumstances of the individual clinical trial. In the United States, institutions which have been granted a Clinical and Translational Science Award (CTSA) through the National Center for Advancing Translational Sciences have access, either directly within their institution or indirectly through the CTSA consortium, to voluntary regulatory assistance. Use of these regulatory services is completely voluntary, and forcing investigators to utilize these services is often seen as a threat to the investigators' academic freedom. Indeed, the regulations themselves are often seen as a threat to the academic freedoms essential to the academic environment [1]. Furthermore, it relies on the investigator's understanding that s/he is in need of assistance. This is unfortunate, as the risks of non-compliance to both the individual investigator and the institution can be significant. As one can see from Table 1, the federal regulations are extensive and expecting investigators new to the clinical research field to be familiar with all of these as well as their clinical fields may be unrealistic. In addition to Table 1, there are State and institutional regulations to comply with as well.

This work will attempt to outline for the Sponsor-Investigator the common regulatory requirements and considerations for clinical trials, and provide an understanding of the regulatory agency expectations. While this work will focus on United States requirements, it should be noted that similar regulations exist for most jurisdictions. The types of activities discussed here are almost universally regulated. The details of those regulations vary by jurisdiction, underscoring the need for regulatory support for Sponsor-Investigators. Most important for the investigator is to know when assistance is needed.

Source materials

Sources of materials and/or investigational products may be regulated if they are biological, derived from, or contain biological components. For example, traditional Chinese medicines are often plant or animal derived products or extracts. Monoclonal antibodies are of animal origin. If these products are sourced outside of the United States, use of these products in research requires import permits from the United States Department of Agriculture [2]. Note that a separate permit is required for each importation, and separate permits are required for research activities, distribution, and/or transit shipments which become important during collaborations. The permit process can be initiated online [2,3]. Certain toxins and selected agents may be regulated by the Department of Agriculture, the Public Health Service, or both [4-6]. Note that if the investigator is involved in collaborations, the shipment of biological materials between research sites is also regulated [7,8]. If collaborating with investigators in another country, export permits may be required from the FDA to ship the product to the country in question, and import permits may be required for the destination country.

Clinical trials

If the investigational product has not been approved/cleared by the FDA for the intended use in this particular trial, authorization to conduct the trial will require either an Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) application [9,10]. Note that a legally marketed drug or device is investigational if it is being used "off-label", or not in accordance with the labeled intended use. In addition, whether or not the product is defined as a drug or device, and hence subject to regulation, may depend on how

Correspondence to: Gordon D. MacFarlane, ICON Clinical Research, 62 Forest St., Suite 300, Marlborough, MA, USA, Tel: 353 (1) 291 2000; **E-mail:** gordon.macfarlane@iconplc.com

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Table 1. United States Federal Statutes and Regulations.

Federal Statutes
Best Pharmaceuticals for Children Act
Health Research Extension Act of 1985
Pediatric Research Equity Act
Clinical Laboratory Improvements Amendments of 1988 (CLIA)
Clinical Trials Registration (ClinicalTrials.gov) [Public Law 110-85]
Code of Federal Regulations
7 CFR Part 331 Possession Use and Transfer of Select Agents and Toxins
9 CFR Part 104 Permits for Biological Products
9 CFR Part 121 Possession Use and Transfer of Select Agents and Toxins
9 CFR Part 122 Importation and Transfer Across State Lines
10 CFR Part 20 Standards for Protection Against Radiation
10 CFR Part 35 Medical Use of Byproduct Material
15 CFR Part 774 The Commerce Control List
16 CFR Part 1500 Hazardous Substances
18 USC Part 175 Prohibitions with Respect to Biological Weapons
21 CFR Part 11 Electronic Records, Electronic Signatures
21 CFR Part 50 Protection of Human Subjects
21 CFR Part 54 Financial Disclosure
21 CFR Part 56 Institutional Review Boards
21 CFR Part 312 Investigational New Drug Applications
21 CFR Part 315 Diagnostic Radiopharmaceuticals
21 CFR Part 316 Orphan Drugs
21 CFR Part 361 Radioactive Drugs for Certain Research Uses
21 CFR Part 803 Medical Device Reporting
21 CFR Part 809 In vitro Diagnostic Products for Human Use
21 CFR Part 812 Investigational Device Exemption
21 CFR Part 814 Premarket Approval of Medical Devices
21 CFR Part 1271 Human Cells, Tissues, and Cellular and Tissue-based Products
21 CFR Part 1312 Importation and Exportation of Controlled Substances
29 CFR Part 1910 OSHA – Blood-borne Pathogens
32 CFR Part 219 Protection of Human Subjects (DOD)
37 CFR Part 401 Rights to Inventions Made by Non-profit Organizations and Small Business Firms Under Government Grants, Contracts, and Cooperative Agreements
38 CFR Part 17.33 Patient Rights (VA)
42 CFR Part 71 Foreign Quarantine
42 CFR Part 72 Interstate Shipment of Etiologic Agents
42 CFR Part 73 Select Agents and Toxins
42 USC Part 262 Regulation of Biological Products
42 CFR Part 1003 Civil Money Penalties, Assessments and Exclusions
45 CFR Part 46 Protection of Human Subjects
45 CFR Parts 160/164 HIPAA
49 CFR Parts 100-185 Hazardous Materials Transport
45 CFR Part 493 CLIA
50 CFR Part 23 Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)
Federal Guidelines
National Cancer Institute Guidelines
NIH Guidelines for Research Involving Recombinant DNA Molecules

it is utilized in the study. This distinction may not be obvious to the new investigator, particularly in the areas of nutraceuticals and food supplements, leading to significant delays [11].

The initial determination of the need for an IND or IDE is the responsibility of the Sponsor-Investigator. FDA provides guidance to assist the investigator in this initial determination [12,13]. For studies involving drugs and biological the investigator is directed to 21 CFR 312.2(a) to determine if the study requires an IND. If the investigator is uncertain if an IND is required, the investigator is referred to FDA for determination. It is the responsibility of the IRB to determine if the investigator has made a determination of the need for an IND. Unfortunately, most IRBs do not include a regulatory professional, and are poorly equipped to make an independent determination regarding the need for an IND. If an investigator believes the clinical study does not require an IND, s/he should prepare a written determination that is submitted to the IRB and becomes a part of the clinical trial record.

For studies involving medical devices, the investigator is responsible for determining if the study represents a significant risk or not. Note that the determination is for the study, not the device. A non-significant risk study in adults could be a significant risk if conducted in pediatrics. The investigator provides the IRB with a determination and justification of the risk which then determines if an IDE is needed. To be efficient, this determination should be made before the submission to IRB, again underscoring the need for the assistance of a regulatory professional. FDA is also available to assist in the determination of the need for an IDE and if FDA makes a determination, that determination is final [14].

The content of the IND or IDE application are similar. FDA does not have specific templates for the applications, and an online search will produce several versions in use at various academic institutions. The major sections include:

- Introduction/Background/Literature Review
- Investigational Product (Drug or Device Description and Manufacturing)
- Investigational Plan (Clinical Protocol/Informed Consent/ Investigator Qualifications
- Prior Investigations/Analytical Testing/Pre-Clinical Testing
- Risk Analysis
- Labeling
- Cited References

The introduction section should include background and a comprehensive literature review. The review need not be exhaustive, but should be comprehensive. All references cited in the application need to be provided in English. Therefore, one wants to choose references carefully.

The investigational product needs to be described in detail. FDA recognizes that the available detail will vary with the status of the product's development. The basic intent of this section is to demonstrate that the investigational product can be prepared and characterized consistently over time. Stability over the time period to be used in the clinical trial needs to be demonstrated. Many larger academic institutions have facilities to prepare small quantities of drugs or devices under controlled Good Manufacturing Practices (GMP) that will meet FDA requirements. For clinical studies beyond feasibility/ pilot studies, a manufacturing facility that meets GMP requirements is highly recommended as studies with GMP manufactured product will be required for eventual commercialization.

The clinical investigation plan is a critical portion of the application. Many investigators are familiar with the short protocol summaries common in grant proposals; however for these applications those summaries are not adequate. The protocol should be compliant with Good Clinical Practice (GCP). Guidelines for the elemental content of a GCP compliant protocol are available for drugs or devices [15,16]. Taking the time to develop a complete GCP compliant protocol will reduce the number of questions from FDA in the review process and potentially reduce the need for protocol amendments. A recent study at Tufts University noted that the average number of amendments was 2.3 per protocol [17]. They found a large proportion (43%) of amendments occurred prior to the enrollment of the first subject suggesting the protocols were not executable at the time they were submitted for initial IRB approval. This results in significant delays and unplanned expenses. The median cycle time to resolve a protocol issue was found to be 61 days [17]. For a study conducted under an IND or IDE, this time may be longer, as both the IRB and the FDA must approve any amendments. The FDA review time is 30 days plus however long is required to resolve any questions or issues identified in that review. Included in the clinical investigation plan will be copies of the draft informed consent to be used, and for devices, copies of the draft case report forms. Creating the case report forms for drug trials prior to the IND submission may be beneficial in ensuring that all data elements are accounted for and that the logistics are feasible.

For Phase I drug studies or early feasibility device studies FDA provides guidance with respect to what they are expecting to see included in the trial designs. This often runs counter to the academic freedom expectations of many investigators unaccustomed to the regulated nature of clinical research. Regulatory agencies tend to be conservative, and innovative trial designs take time to gain acceptance [18-20]. Adaptive trial designs have expanded the trial options, making the most appropriate design more difficult to determine.FDA has recently released draft guidance for drugs and biologicals and for devices describing their expectations for adaptive clinical trial designs [21,22].

If the proposed investigation includes subjects that are defined by regulation as vulnerable, specific provisions to address those vulnerabilities may be required in the protocol [11,23]. The inclusion or exclusion of pregnant women, or women who may become pregnant, also introduces specific requirements into the protocol. The exclusion of some vulnerable groups, such as children, may require justification in the protocol. This is a result of the recognition of the lack of available pediatric data for drugs and devices and the attempt to address that deficiency with the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act [24,25].

The research setting may also present significant challenges. Community based care facilities may have the appropriate subject population, but lack the staff with the appropriate scope of practice or experience and training for the particular clinical trial [11]. The recruitment of additional investigators and/or the temporary granting of access or clinical privileges may be necessary to fill specific gaps [11].

Also included in the clinical investigation plan are the investigator qualifications. Under the regulations, an investigator must be qualified by training or experience to conduct the trial in the therapeutic area that is the subject of the investigation. This will normally entail the inclusion of a copy of the investigator's medical license, a signed and dated copy of the investigator's curriculum vitae (CV), and a listing of professional associations and memberships (if not included in the CV). For the investigator who is new to clinical studies, demonstration of the completion of human subjects' protections training will also be essential.

As noted above, both FDA and the IRB must approve the same clinical investigation plan. Alterations in the clinical investigation plan required by FDA must be approved by the IRB, and alterations by the IRB must be approved by FDA. This potentially becomes more difficult during collaborations and multi-center trials, as multiple IRBs may be involved. In this case, each IRB must approve the clinical plan. Institutions within the CTSA consortium have made efforts to reduce the number of reviewing IRBs, and cede review authority to each other's IRBs in some multicenter trials, but results are not universal. The situation becomes even more complex with multi-national studies. In the area of stem-cell research, the European Union is attempting to

address the issue with revisions in the clinical trial application process [26].

A review of prior investigations also forms a large and important portion of the application. The amount of analytical or bench testing may vary significantly with the developmental status of the investigational product, and FDA understand this. Sufficient analytical testing should be completed to provide a basic comfort level with the safety of the drug or device. It is assumed that all known testing will be included, whether favorable or unfavorable. Unfavorable data needs to be addressed in terms of either why it does not apply to the situation of the proposed clinical trial, or how the risks identified by the unfavorable data will be mitigated in the proposed clinical trial.

Pre-clinical data needs to be summarized as well. Again both favorable and unfavorable data needs to be included. Particular attention should be paid to explaining how the chosen animal models are relevant to the clinical situation in humans. For many clinical conditions, a truly appropriate animal model does not exist. Therefore the compromises accepted in choosing a specific model, and the consequences and limitations imposed by those choices needs to be explained.

For most academic investigators, the type and extent of the risk analysis needed will be unfamiliar. A risk analysis may be performed in a number of potential formats. What the investigator wants to convey to the FDA reviewer is that they have considered all of the known and potentially foreseeable risks, and applied an appropriate mitigation to reduce those risks to a minimum. For device studies in particular, the investigator needs to consider risks in addition to risks to the subject. Are there risks to the researchers associated with improper usage? Are there exposure or disposal issues? This may be particularly true for chemotherapy drugs and/or radiopharmaceuticals or devices containing isotopes.

Investigational products have very specific labeling requirements. How those labeling requirements will be satisfied is part of the labeling section of the IND or IDE. Labeling includes not only labels on the product itself, but instruction manuals and accompanying product literature. For studies of existing devices which represent an expansion of the intended use, dedicated investigational devices are recommended as their movement between approved and investigational uses may cause significant labeling issues and confusion.

Cited references are often a large section of the application. Any reference cited anywhere in the text of the application needs to be provided in English. The tendency of academic investigators is to be exhaustive rather than comprehensive. A typical sponsor-investigator application may have 30 to 50 references, more than 100 is likely excessive.

Once submitted, FDA has 30 days to provide a decision to the sponsor-investigator. That decision may be either approval to conduct the study, conditional approval requiring additional information, a clinical hold also requiring additional information, or denial. During the review process, negotiations and discussions with the FDA reviewer may occur.

Upon approval, there are specific regulatory requirements with regard to the execution of the study. Clinical monitoring is required for all IND and IDE studies. For many academic institutions, non-significant risk device trials, which are conducted under an abbreviated IDE do not get appropriate clinical monitoring. An abbreviated IDE does not require a submission to the FDA, nor does it require reporting to the FDA. The IRB is responsible for ensuring that the study is appropriately monitored. Unfortunately many IRBs are poorly equipped to perform clinical trial monitoring or audit functions, and the audit and/or monitoring of non-significant risk trials is not a high priority.

IND and IDE approvals also create reporting requirements. In addition to the annual progress reports, a six month report is due for IDE studies and serious adverse events need to be reported both to the IRB and FDA. Specific time windows are established for these safety reports, depending on the nature of the adverse event.

Subject data privacy regulations may be very unfamiliar to investigators new to clinical research [27]. These regulations are often counter to the open data sharing practices the investigator may be accustomed to in pre-clinical work. The inappropriate sharing of protected health information, even with the statistician analyzing the data and/or collaborating centers may create significant risks to the investigator and the institutions. The trained regulatory professional can assist in designing case report forms that minimize the collection of protected health information, and/or establish procedures to appropriately deidentify data that will need to be shared.

For most Sponsor-Investigators and academic institutions, commercialization of a product is licensed to a company for a royalty stream and further regulatory interactions in the form of marketing authorization applications are not encountered. If the investigator is involved in these applications it is usually as a contracted clinician conducting an industry defined protocol. However, some institutions will assist in commercialization start up activities and spin-off companies involving institutionally derived technologies. Regulatory assistance for these activities is generally not available through the institution, and need to be sought outside. The complexity of regulatory marketing submissions and commercialization strategies may make professional regulatory assistance both desirable and cost effective.

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