

A Program to Provide Regulatory Support for Investigator-Initiated Clinical Research

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Abstract

Investigator-initiated clinical trials represent a small but extremely important portion of medical research. In the process of translating basic science discoveries to novel therapies, new drugs or devices may be developed and tested. In light of increased compliance scrutiny, the need to streamline research projects, and the growing complexity of the U.S. Food and Drug Administration's (FDA's) regulations, the research leadership at the University of Minnesota Academic Health Center (AHC) determined in 2002 that a service should be established to address these issues. The assumption was that providing a service to assist

researchers with regulatory obligations would result in additional clinical research that might not have been pursued due to perceived regulatory hurdles. The authors present an overview of the FDA regulatory process as it applies to investigator-initiated research involving investigational new drugs and investigational medical devices. The rationale for creating a program designed specifically to assist faculty with investigational new drug (IND) applications and investigational device exemption (IDE) applications is discussed. The services provided by the IND/IDE Assistance Program (IAP) at the University

of Minnesota Academic Health Center are described. The value of the IAP to the AHC is presented along with examples of successes attributable to the IAP and lessons learned so far.

Since the establishment of the IAP several issues that might have placed the university at risk have been identified. These issues have been addressed to help improve the ease in which investigator-initiated research is conducted and compliance is maintained.

Investigator-initiated clinical trials are an important aspect of medical research in an academic institution. In the process of translating basic science discoveries to novel therapies, new drugs or devices may be developed and tested. Clinical trials of new drugs and devices, off-label use of marketed drugs, or modified medical devices often require the submission of an *investigational new drug application* (IND) or an *investigational device exemption application* (IDE) to the U.S. Food and Drug Administration (FDA). Investigator-initiated INDs are also referred to as *research INDs*. These applications contain the information necessary for the FDA to provide oversight to protect the safety of the study participants. This information describes the rationale for the investigation, the design of the study, safety data, manufacturing processes, and investigator qualifications. When a study is conducted under an IND or IDE, the FDA's regulations must be followed so that the investigator and the university will not be placed at risk for legal and/or financial sanctions.

Complying with the FDA's regulations can be daunting and an overwhelming burden to faculty researchers who are

rarely familiar with their obligations as sponsors of an IND or IDE application. In order to assure that the regulations and obligations of IND and IDE *sponsor investigators* (SIs) are met, the University of Minnesota Academic Health Center (AHC) established the IND/IDE Assistance Program (IAP) in 2002 to assist faculty who conduct clinical research studies that require the submission of an IND or IDE application. The two most important services offered to faculty researchers are education of the research team about the regulatory process and ongoing regulatory support to assure that the SIs' obligations are met.

Knowing when an IND or IDE is required and complying with the obligations of an SI are both vital for the researcher and his or her institution. The IAP, as set up by the University of Minnesota, has helped both the researcher and the institution comply with their respective regulatory obligations. As shown by the experiences of several prominent academic institutions, the consequences of noncompliance can be catastrophic.

Background and the FDA Process

The FDA is a part of the United States Department of Health and Human

Services. It is a complex organization with a budget in fiscal year 2005 of \$1.8 billion with over 10,000 employees.¹ Reporting to the commissioner of the FDA are the five product review centers: the Center for Food Safety and Applied Nutrition, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine, Center for Devices and Radiological Health (CDRH), and Center for Biologics Evaluation and Research (CBER), as well as several administrative, scientific, and regulatory offices. Each center has its own organizational structure. The IAP interacts with all five product review centers, but primarily CDER, CBER, and CDRH. (Figure 1 presents a simplified organizational chart for these three centers.)

It is important to have a basic understanding of the IND and IDE processes in order to appreciate the complexity of the situation and the need for an IND/IDE assistance program. The Federal Food, Drug and Cosmetic Act (FFD&C Act) defines *drug*, *new drug*, and *device*.² *Drugs* are articles recognized in the official compendia; articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; and articles (other than food) intended to affect the structure or any function of the body. A *device* is an instrument,

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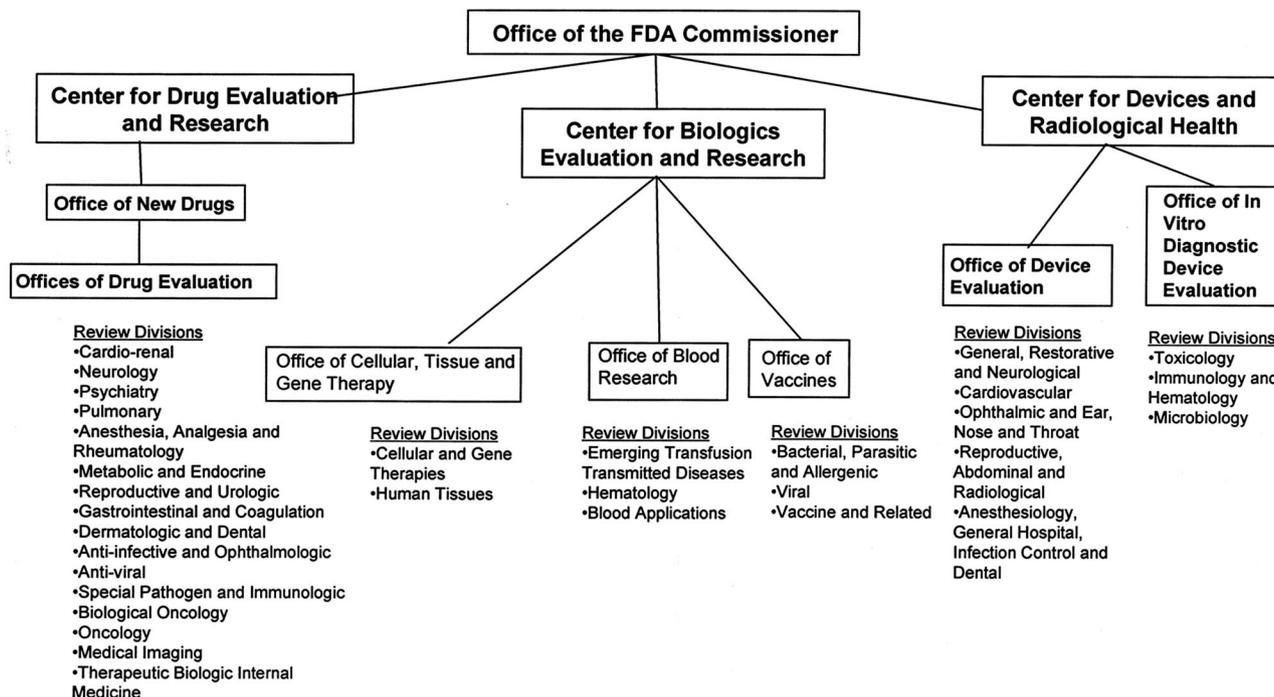


Figure 1 Simplified organizational chart of the Food and Drug Administration, 2005. Sources: (<http://www.fda.gov/cder/cderorg/ond.htm>), (<http://www.fda.gov/cdrh/organz.html>), and (<http://fda.gov/cber/inside/orgtchart.pdf>).

apparatus, implement, machine, contrivance, implant, or in vitro reagent that is recognized in an official compendium; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body, and which does not achieve its primary intended purposes through chemical action and is not dependent upon being metabolized to achieve its purpose.²

The FDA approves drugs, biologics, and medical devices for marketing in the United States. Whenever a researcher intends to administer a new drug or device, an IND or IDE application must be submitted to the FDA. The FFD&C Act defines a *new drug* as a drug that is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed.² The Code of Federal Regulations (CFR) states that a drug is a new drug if it is a new substance or a marketed drug used in new combination, new proportions, new use, new dosage form, new route of administration, or in a patient population that would be put at increased risk.³ An IND is always needed to perform clinical research employing a

new drug. The FFD&C Act does not define *new device*. However, the CFR defines *significant risk device*. This is a device that is intended as an implant, is used to support or sustain life, is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of health, and/or otherwise presents a potential for serious risk to the health, safety, or welfare of a research participant.⁴

Both medical knowledge and regulatory knowledge and an understanding of how the FDA makes its determinations are required to determine the need to file an IND/IDE application for a lawfully marketed product in the United States (see Figures 2 and 3). An IND is required to study a new drug unless the study meets several specific exemption criteria⁵: the data from the study will not be submitted to the FDA to support a new indication or change in advertising; institutional review board (IRB) approval is obtained as well as patient informed consent; the patient will not be charged for the investigational drug; and “the investigation does not involve a route of administration or dosage level or use in a patient population or other factor that *significantly increases the risks* (or decreases the acceptability of the risks) associated with the use of the drug

product.” A significant risk device to be used in a clinical research trial would require an IDE application to be submitted to the FDA. If the device is a nonsignificant risk device, although an IDE application does not need to be submitted, the study is subject to the requirements of the IDE regulations.⁶

The IND application contains the clinical study protocol; information about the investigator(s), facility, and IRB; chemistry, manufacturing, and control data; pharmacology and toxicology data; and a summary of any previous human experience. The IDE application consists of similar information but is specific to the medical device. These applications can be many inches to several feet thick. CDER and CBER are currently accepting regulatory submissions in electronic format.⁷

The FDA regulations specify the order and general content of information to be included in an IND or IDE application.⁸ The FDA also publishes guidance documents for industry that help explain in greater detail what is acceptable to the agency in an IND or IDE application. It must be noted that even though guidance documents are titled “Guidance for Industry,” they apply to everyone who submits information to the FDA. This includes industry, academia, and

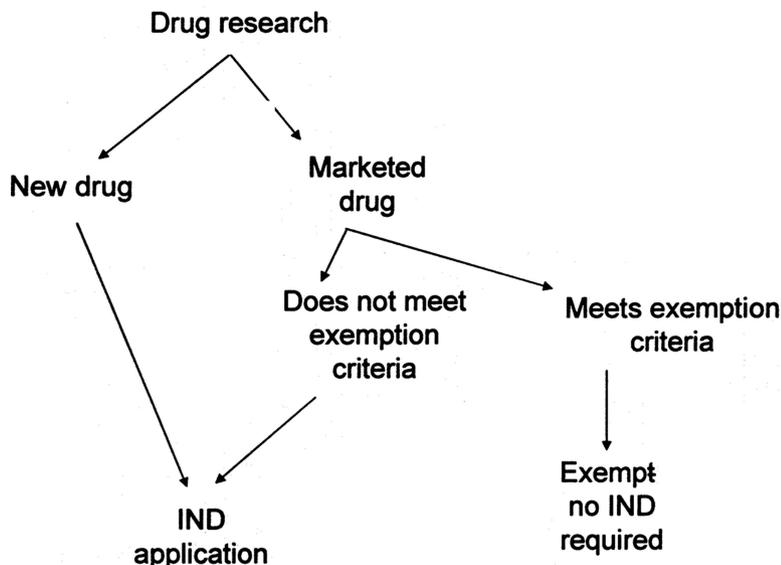


Figure 2 The process for deciding whether an investigational new drug (IND) application is required by the U.S. Food and Drug Administration.

individuals. The FDA also publishes guidance documents for FDA reviewers in which it lists what information the reviewer must find in the application in order for it to be accepted.^{9,10}

A study cannot begin, nor can study participants be recruited, until 30 days after the FDA has received the application unless the FDA notifies the applicant that the study may begin earlier or that the IND has been placed on clinical hold. There are other regulatory obligations that apply during the life of the study. The FDA must be notified of protocol amendments, the addition or change of investigators, any adverse events, and must receive periodic progress reports. The FDA may also perform unannounced inspections to evaluate study conduct and protocol adherence, collect data, and assess regulatory compliance. Under the FDA’s Bioresearch Monitoring (BiMo) program, field investigators conduct inspections of randomly chosen active IND clinical trials.

The BiMo program is implemented domestically and internationally through four multicenter compliance programs resulting in over 1,000 inspections annually. These compliance programs address inspections of nonclinical testing labs, clinical investigators, sponsors/monitors, and IRBs. Between FY 1998 and FY 2004, CDER conducted over 2,400 clinical investigator inspections, CBER conducted about 800

inspections, and CDRH has conducted over 1,500 inspections under the BiMo program. As a result of these inspections approximately 5% of the violations resulted in warning letters.¹¹ Examples of these violations include inadequate monitoring, failure to follow the protocol, inadequate case histories, discrepancies between source documents and case report forms (CRFs), inadequate drug/device accountability records, enrollment of ineligible subjects, lack of supporting data for CRF entries, inadequate informed consent, failure to retain records, failure to report adverse events and failure to obtain FDA and/or IRB approval. Timely and adequate corrective actions on the part of the sponsor-investigator may avert serious problems. At other times an inspection may lead to the issuance of a warning letter citing numerous and serious violations. These are published on the FDA’s Web site for all to read.¹² If warnings are ignored, the FDA can take further action such as filing injunctions and disqualifying investigators.

Rationale for the Program

The University of Minnesota AHC had been concerned that investigator-sponsored IND research was not being adequately supported. Unfamiliarity with the required regulations places the researcher and the university at risk of noncompliance. Research participants’ safety is, of course, the primary concern. Attempting to learn the regulations and

how to apply them took valuable time away from conducting clinical trials. This problem called for a program to assure that researchers are in compliance with the obligations of a sponsor investigator, to assist with the regulatory process to allow faculty members to be more productive and use their time to conduct research, and to support the faculty in all IND and IDE processes and documentation.

The IND/IDE Assistance Program (IAP) was created in 2002 to assist faculty researchers who needed to submit an IND or IDE application to the FDA. Many faculty researchers in our AHC are unfamiliar with the FDA’s regulatory requirements and their obligations as sponsor investigators and were wasting valuable time deciphering the regulations. Some applications were not in compliance, and a few researchers had even given up on a particular research initiative because they didn’t know what was required for an IND or IDE application. A review of IRB-approved studies since 1993 revealed that 35 investigator-initiated IND/IDE applications from our AHC were filed with the FDA. Since August 2002, after the creation of the IAP, 37 IND/IDE applications have been filed. Of these, 9 were filed without IAP assistance.

A second important reason for establishing the IAP was to determine whether an IND or IDE is even required for a given clinical protocol. The criteria that are used by the IAP to make this assessment are the same as those used by the FDA. A common misconception is that a clinical study involving a marketed drug does not need an IND. If the administration of the drug is for research, and not as standard medical practice, an IND application may be needed. And if the marketed drug will increase risk to the study participant, an IND is required.¹³ The parts of the protocol that concern dose, schedule, route of administration, and patient population are examined closely. For a medical device, an assessment is made to determine whether the study poses a significant risk.¹⁴ Assessment of IND or IDE applicability was previously determined by the principal investigator (PI) with input from the IRB. Both PIs and the IRB have been grateful for the advice provided by a knowledgeable regulatory affairs professional.

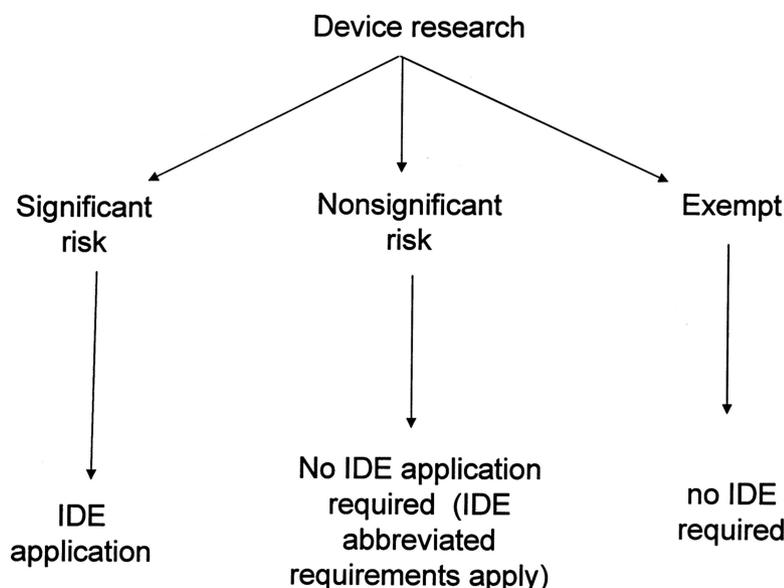


Figure 3 The process for deciding whether an investigational device exemption (IDE) application is required by the U.S. Food and Drug Administration.

Getting Started

The IAP at the University of Minnesota Academic Health Center is part of the office of the senior vice president for health sciences and reports to the assistant vice president for research. The IAP is a shared resource and is funded by the AHC. The service is offered at no charge to faculty. The staff consists of the program director and a part-time assistant. The cost of running the program (salaries, benefits, space, and other expenses) is approximately \$180,000 per year.

For the program director, an individual was sought with a minimum of a bachelor's degree and five years of experience with industry-sponsored clinical trials and the FDA. Additionally, the candidate would be familiar with the academic research processes, have regulatory affairs or clinical research certification, and the ability to work well with faculty investigators and the FDA. Understanding the IND/IDE regulatory process and hands-on experience writing, compiling, submitting, and following up on IND/IDE applications were the primary criteria for the position. A food and drug lawyer, although extremely knowledgeable regarding FDA and its laws and regulations, would not often have the desired hands-on application experience. The individual who was ultimately hired to establish and direct the IAP (Dr. Arbit) is a pharmacist with Pharm D and MBA degrees, regulatory

affairs certification, and over 30 years of experience in both the pharmaceutical and medical device industries. After the IAP was in operation for two years, a second-year PharmD student was hired part-time to assist with compliance reviews and the continuing development of the program.

Services Provided

The IAP provides services regarding all aspects of applying for and maintaining an IND or IDE application. In most instances, the assistance begins by determining whether an IND or IDE is needed. When an investigator-initiated study is submitted to the IRB for review, the IRB will usually request the investigator to consult the IAP for an assessment of IND/IDE applicability, if that has not already been done. This determination is documented and provided to the PI and the IRB. If it is determined that an application is required, instruction is given to the PI and members of the research staff regarding their obligations both as sponsor and as investigator. The IAP then drafts the application based on the scientific, preclinical, and clinical information provided by the researcher. The IAP also drafts the IND or IDE transmittal, or cover, letter. The IAP explains the application assembly process to the PI's clerical staff and reviews the completed application prior to its submission. Once the application is

submitted, the IAP monitors the communication between the SI and the FDA.

Because the FDA only communicates with the IND or IDE sponsor or sponsor's authorized representative, the university had no way of knowing the status of the application, or if the SI was submitting reports and amendments as required by the regulations. Therefore, the University of Minnesota established a policy requiring that when a faculty member acts as an SI of a research project, all correspondence between the FDA and the SI must be submitted to a central documentation unit.¹⁵ The IAP serves as this central documentation unit. The program could then track the regulatory progress, inform the SI of regulatory obligations, and assist if requested. If these communications are not submitted to the IAP, the SI is not in compliance with university policy and can be disciplined accordingly.

SIs with preexisting IND or IDE applications were reviewed by the IAP for compliance to IND or IDE regulations and to the university policy. All SIs were informed in advance of the review. Many of these SIs were not compliant. The reviewer tagged those documents that needed to be submitted to the documentation unit and explained which documents must be submitted in the future. For existing IND and IDE applications there was reluctance by the SI to go back and make copies of the documentation required by the university policy. In contrast, those SIs who were starting an IND or IDE study had no problem complying with the policy.

The SI is sent reminders at appropriate times regarding the obligation to notify the FDA of protocol amendments, new co-investigators, serious adverse events, and annual progress reports. Should the FDA initiate an inspection, the IAP reviews the inspection process with the SI and provides support throughout the inspection process, including postinspection activities.

The IAP educates the faculty researchers and helps assure that their regulatory and university obligations are being met. Periodic reviews of all active SI IND/IDE projects are carried out by the IAP. During these reviews the requirements and obligations of an SI are reviewed. If issues of noncompliance are observed,

corrective actions are recommended and a follow-up review is scheduled to assure appropriate actions have been taken. These reviews are used to prevent minor issues from growing into significant regulatory issues that would necessitate FDA intervention.

Some assessments of IND/IDE applicability are easier to make than others. (*Applicability* is the term used by the FDA to indicate that a submitted IND or IDE application is required to legally conduct a particular clinical study.¹⁶) If there is uncertainty, especially if the IAP assessment is not to file, the FDA is contacted. Unfortunately, not all FDA reviewing divisions handle inquiries of IND applicability in the same manner. Some will provide a written opinion based upon a faxed or e-mailed protocol. Other divisions require that a full IND be submitted. The greatest uncertainty arises from studies involving marketed products. Two questions that need to be addressed in these instances are: “Is this protocol research or standard medical practice?” and “Will this research put this patient population at increased risk?”

When a researcher is an investigator under an IND or IDE held by a commercial entity, the company, as the sponsor of the IND or IDE, is responsible for complying with the regulations covering the obligations of a sponsor. The investigator needs only to comply with the regulations covering the obligations of an investigator. The

commercial sponsor’s regulatory affairs department, clinical research personnel, or a contract research organization usually assist the investigator to assure compliance. When the faculty researcher is the sponsor of the IND or IDE, that individual is obligated to comply with the regulations covering the responsibilities of both investigator and sponsor. Usually there is no one to assist that individual on regulatory compliance matters and the individual is left to wade through the maze of regulations and guidance documents available on the FDA’s Web site. The IAP provides one-on-one education and assistance to the SI to help assure regulatory compliance. The obligations of a SI¹⁷ are spelled out in an information sheet and explained to the individual. List 1 presents the SI’s obligations.

The IAP has developed educational pieces regarding the obligations of SIs, contents of IND and IDE applications, clinical monitoring procedures, and template documents for clinical protocols, annual reports, clinical trial monitoring activities, safety reports, case report forms, and a drug/device disposition log. Many of these documents can be obtained on the IAP’s Web site, www.ahc.umn.edu/research/ind-ide/. A list of the services provided by the IAP is shown in List 2.

The IAP conducts random reviews of SI research records to ensure that they are in compliance with the FDA’s regulations.

Although the IAP randomly reviews research records, it is not a clinical trial monitoring or compliance program. It does not act as a policeman or compliance officer. The IAP is an educational function that helps researchers understand their obligations and responsibilities as IND or IDE SIs and assists them throughout the investigational study. When a researcher is not following the regulations, the IAP provides the guidance, education, and “handholding” to get the researcher through the situation. If the researcher refuses to comply with the recommendations of the IAP, the IAP refers the issue to the university’s Office of Regulatory Affairs.

What the IAP Changed

Several highly publicized instances of violations of federal research requirements have taken place at academic health centers. Most recently in 2001 at Johns Hopkins University, a healthy 24-year-old woman who was part of an asthma study died.¹⁸ During the FDA’s inspection, the following observations were made: an IND had not been filed; the adverse event had not been reported to the IRB; the study protocol was not followed; changes were made to the protocol and IRB approval was not obtained; and the study participants were not informed that the inhalation of the drug was experimental.¹⁹ As a result of multiple violations of federal research requirements, the investigator at Johns Hopkins received a warning letter from the FDA. Johns Hopkins agreed to suspend all studies not federally funded but regulated by the FDA, and the institution took full responsibility for the death. Johns Hopkins had more than 2,000 experiments underway at that time.²⁰ Could these events have been avoided if an IND/IDE assistance program were in place? Very possibly. At the University of Minnesota the IRB would have requested an assessment of IND applicability. After a thorough evaluation of the drug and the protocol, and possibly consultation with the FDA, the determination would have been made that an IND application was needed. (Of course, this unfortunate event has sensitized all of us to proceed more carefully in interpreting FDA regulations than previously may have been the case.) The researcher would have been instructed about the obligations of an

List 1

Obligations of an Investigational New Drug (IND) Sponsor Investigator, Required by the Food and Drug Administration in 2005

As an IND sponsor-investigator you are obligated to

- conduct the study according to the approved protocol,
 - personally conduct or supervise the study,
 - assure that all associates are informed of their obligations,
 - obtain informed consent of each subject,
 - select a qualified clinical monitor,
 - monitor the progress of the clinical study and document the monitoring activities,
 - prepare and maintain adequate and accurate case records on each subject in the study,
 - maintain written records showing receipt and disposition of the drug,
 - inform the FDA of significant adverse events,
 - review and evaluate the evidence relating to the safety and effectiveness of the drug and submit reports to the FDA,
 - secure compliance by all investigators or terminate their involvement,
 - retain the records and reports for two years after the FDA has been notified the study has been completed or discontinued,
 - assure no conflict of interest,
 - assure initial and continuing approval of the study by the IRB,
 - submit annual reports of the progress of the study to the FDA,
 - submit, upon completion of the study, a final report to the FDA, and
 - permit inspection of the study records and reports by the FDA.
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List 2

Services Offered by the IND/IDE Assistance Program of the University of Minnesota Academic Health Center, 2005

The IND/IDE Assistance Program provides the following services:

- Overview of investigational new drug (IND) and investigational device exemption (IDE) regulations
- Explanation of obligations and responsibilities as an IND/IDE sponsor and investigator
- Determination and documentation regarding the need to file an IND/IDE application
- Information regarding the contents of the IND/IDE application and assistance in its preparation
- Templates for the initial IND/IDE application, clinical monitoring activities, adverse event reporting, annual report submissions, product disposition log, study protocol, and case report forms
- Assistance drafting the clinical protocol to comply with Good Clinical Practices guidelines
- Written procedure for clinical trial monitoring
- Assistance preparing forms and communications to the FDA regarding protocol amendments, additional co-investigators, process changes, and adverse event reports
- Reminders when annual progress reports and other obligations are due
- Review of IND/IDE documentation to assure compliance with FDA regulations and university policy
- Assistance during FDA inspections
- Registration of study with ClinicalTrials.gov
- News items relevant to investigator-initiated research

IND SI and would have had the ongoing support of the IAP.

Prior to establishing the IAP, the FDA's Minneapolis district office was contacted for feedback regarding our plans for the program. The request was forwarded to the FDA's Center for Biologic Evaluation and Research (CBER). The response was quite positive and supportive. At that time in 2002, to the best of our knowledge, there were no other academic institutions with such a program. In 2005, the IAP remains unique. We carried out a survey of all U.S. medical schools in August 2005 using the private listserv of the AAMC's Group on Research and Development (GRAND). GRAND members (the associate deans for research and other medical school administrative equivalents) were given brief background information about the IAP and then asked "At your institution is there an individual or office that assists faculty with the preparation and/or maintenance of investigational new drug applications?" Additional information was requested from affirmative respondents. Twenty responses were received, including answers from five of the top 20 National Institutes of Health grant recipient institutions. Only one other institution provides any sort of comprehensive IND assistance. The University of Oklahoma Health Sciences Center does so from within its Human Research Protection Program. Several respondents commented that they were very interested in learning more about the University of Minnesota's program.

Under normal circumstances the IAP does not provide IND or IDE assistance to commercial entities. Pharmaceutical and medical device companies should sponsor the IND for research using their products. There have been instances where a researcher is working with a start-up biotech company that has no regulatory resources. In the case where the faculty member cannot get the research done without the IND or IDE, and the product cannot be produced anywhere but at the start-up biotech company, the IAP has provided the necessary services. This exception is made providing the faculty member is the PI and the start-up company has no income from any marketed products.

When the IAP was first established, information was collected about which faculty members were IND or IDE sponsors. There were a few surprises. IRB records identified that an IND or IDE pertained to a clinical trial, but not whether the sponsor was the individual researcher or a commercial entity, such as a pharmaceutical or medical device company. In some cases, the sponsor was obvious. In others, the faculty members had to be contacted. In a few instances the researchers themselves were not sure. Obviously these investigators did not have a sufficient knowledge of relevant regulations. Today, the IAP and IRB work together sharing information to assure each other that all investigator-initiated research is identified as such. The IRB informs the IAP when an SI amends a protocol, reports a serious or

unanticipated adverse event, and reports when the study is completed. The IAP reminds the SI of the regulatory obligations for these events and works with the SI to submit the appropriate documentation.

Successes and Lessons Learned

At the University of Minnesota AHC there are more than 500 full-time faculty members eligible to carry out SI-initiated clinical trials. The exact number of those actually interested in taking on this responsibility is not known, but it is certainly a small fraction of those eligible. There are more than 300 active clinical trials in progress at any point in time.²¹ Approximately 200 of them are being conducted under an IND or IDE, either commercially or noncommercially held. Since August 2002, when the IAP was established, there have been 168 requests for IND or IDE assistance or consultation. One hundred and twenty assessments have been made as to IND or IDE applicability. Of these 120 assessments, it was determined that 59 projects required an IND or IDE application and 61 did not. Of the 59 assessments (by the IAP) that an IND was necessary, there were 27 cases when we received written confirmation by the FDA accepting the IND or notification that an IND is required. There were five instances where the FDA indicated that an IND was not required. In those cases where the FDA indicated that an IND was not needed, various reasons were cited. For example, the protocol did not present increased risk to the study participants, the use of a nutritional substance was not a drug, or the proposed experimental use was not considered different from the approved indication. In 21 cases, the IND has not yet been submitted or a reply has not yet been received from the FDA. Currently, there are 44 known active IND or IDE investigator-sponsored studies, and 23 in various stages of development.

In August 2002 when the IAP was established, there were 24 preexisting active IND/IDE studies. Some of these studies had been in progress for several years (one over ten years with close to 100 participants). The initial review of these studies showed that five were compliant with the obligations of an SI and 19 were not. Of the 19 that were not compliant, 15 were deficient because they had no plans for study monitoring. Some

SIs had difficulty understanding the difference between clinical trial monitoring (data integrity) and data safety monitoring (study participant safety). A monitoring plan was then prepared by the IAP and templates were provided to document the monitoring activities. The SI also received oral instructions. The remaining 4 had delinquent annual reports. The IAP created an electronic database that identifies when annual reports are due. The IAP sends reminders as well as an annual report template to the SI 30 days prior to the report's due date.

Since August 2002, 20 new investigator-initiated IND/IDE applications have been filed and are active. SIs' understanding of appropriate clinical trial monitoring performance and documentation is still problematic, and seven studies required assistance in developing a plan. However, all trials were being monitored early in their conduct. One study neglected to use a dispensing log, an error promptly discovered. Currently, all 44 active studies remain compliant.

Examples of successes

The IAP has had several successes in its early development in addition to determining IND/IDE applicability. There have been cases where one faculty member holds the IND, while another faculty member is responsible for the execution of the study. In one such example, a junior faculty researcher conceived a protocol and submitted it to the IRB. The original IND application had been submitted to the FDA by a senior faculty member for a previous study. The senior faculty member submitted the protocol to the FDA. The junior faculty researcher became the investigator of record with the IRB. An issue of noncompliance arose when the junior faculty member did not contribute his study data for the annual report, which remained the obligation of the IND holder, in this case, the senior faculty member. Once the regulatory obligation and relationship was explained to both faculty members, the report was written and submitted to the FDA.

In another instance, the IAP was contacted by a faculty researcher and asked to verify a mailing address because a report that had been sent to the FDA was not received. (Researchers are reminded to send all communications to

FDA such that receipt can be verified.) The FDA regulatory project manager told the IAP that the IND had been terminated by the FDA due to lack of response by the sponsor to a request for an annual report. The IND sponsor had left the university and had not transferred sponsorship to the subinvestigator. Therefore, no one was paying attention to sponsor responsibilities. When the FDA did not receive the annual report, the FDA sent a letter to the SI indicating that the IND was terminated. That information was never relayed to the researchers at the University of Minnesota, who continued their research. When the IAP learned of the IND termination, the departed researcher was immediately notified by the subinvestigator. The sponsorship was transferred, annual reports were submitted, and the IND was reinstated by the FDA. During this process the current researcher notified the IRB and stopped entering study participants until the FDA had transferred the sponsorship and reinstated the IND.

Another researcher had been trying unsuccessfully for months to get an answer from the FDA whether an IND would be needed for a metabolism study using a stable isotope. When the researcher asked the IAP for assistance, a protocol was e-mailed to the appropriate review division at the FDA. Within two days a written response was received. Not only did the FDA indicate the study was exempt from IND requirements, but it also sent a detailed explanation regarding when a stable isotope may be IND exempt.

For those faculty members unfamiliar with IDE regulations the prospect of compiling an IDE application can be daunting. One researcher delayed progress on a study of a new surgical device for more than 12 months because he had no idea where to begin or where to turn. He found the FDA's Web site unhelpful in this regard. Within a week of contacting the IAP, a draft of the IDE application was completed. Within one month, the IDE application was submitted.

Other examples of assistance that made a difference in the conduct of IND studies involved assisting in the development of case report forms (seven times), reinforcing that monitoring clinical trials and documenting monitoring activities are required obligations (21 times),

assisting in the development of a log to document the disposition of investigational products (one time), helping secure investigational drug from outside the United States (three times), providing guidance in the development of dosage forms of botanical substances (two times), and providing information for the SI to specifically use for IRB review (two times). The IAP has also participated in clinical research coordinator training (seven times), and teaching about the IND process to graduate students in the School of Public Health (two times).

Lessons learned

As with many new programs, there are learning curves and challenges. The initial roll-out of the program met with resistance from a small number of investigators who had been submitting their own IND and IDE applications with little adverse feedback from the FDA. These individuals were reluctant to change and to accept the regulatory assistance and guidance. By not forcing the assistance on them and unobtrusively providing support for their regulatory needs, they eventually were won over. Two investigators who have been vocal opponents of the use of funds to support more "administrative oversight" nevertheless have indicated their intent to use the assistance that is available to them. The IRB was supportive of the program from the start. Initially, there was some reluctance by the IRB to share records. However, the recognition of the value of synergistic activities of the IAP and IRB has now made the identification of IND/IDE regulatory requirements and their impact on human participants' protection a more important item in IRB reviews.

On one occasion an FDA review division refused to provide information regarding an investigator-sponsored IND because the IAP director was not the IND sponsor. This was overcome by having the IND sponsor submit a letter to the FDA granting permission to communicate with the IAP director. Some review divisions at the FDA will provide an unofficial opinion regarding IND/IDE applicability, others will provide official opinions, while others will insist that the IND be submitted for any opinion regarding a clinical protocol. In instances where the need for an IND/IDE application is uncertain, the decision is made to file if an opinion cannot be

obtained from the FDA. Sometimes the investigator believes that an IND is not necessary and is reluctant to do the additional work required to submit the documentation to get a ruling from the FDA. But if an IND is indeed required, the work has already been done.

In addition to the activities specific to IND and IDE assistance, the director of the program serves on several AHC committees. His expertise and experience in FDA regulations and regulatory affairs has made him a valuable asset to the Molecular and Cellular Therapeutics (MCT) Quality Steering Committee, MCT Scientific Advisory Board, and the General Clinical Research Center Data Safety and Monitoring Committee.

Interest in the IAP from other academic institutions and the FDA has been substantial. The director of the IAP has been invited to speak at several national professional association meetings sponsored by the Drug Information Association, Association of Clinical Research Professionals, and Society of Research Administrators International. The FDA has also indicated their satisfaction with our program and expressed a desire that other academic institutions establish similar programs.

Thoughts on Future Developments

The IAP has reviewed documentation and record keeping of all the sponsor-investigators for compliance with FDA regulations, as well as with the university policy. Clinical trial monitoring and documentation of monitoring activities are areas that appear to be neglected most frequently. The FDA regulations are very clear on the sponsor's obligations of monitoring.²² Since the FDA has jurisdiction over all products it approves, it is prudent that all investigator-initiated research meet the same Good Clinical Practices (GCP) standards, regardless of whether an IND or

IDE is required to conduct the clinical study. The GCP guidelines, which are issued by the International Conference on Harmonization globally and the FDA domestically, provide details on clinical trial monitoring.²³ Having clinical trial monitoring services available to the SIs would greatly improve compliance in this area and enhance the validity of the data. We are currently developing such a program.

We have communicated with other academic institutions that have or are considering a similar program. There appears to be an interest in collaborating. The FDA has expressed a willingness to assist in this collaboration. Perhaps the outcome would be a program or guidance document acceptable to the greater academic community. The need for such support is definitely there. The desire to assist academic researchers has been expressed and the acceptance of the support has been appreciated.

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