Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

The Globalization of Clinical Trials

A Growing Challenge in Protecting Human Subjects

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SEPTEMBER 2001
OEI-01-00-00190

OFFICE OF INSPECTOR GENERAL

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EXECUTIVE SUMMARY

PURPOSE

To document the growth of non-U.S. clinical drug trials contributing data to New Drug Applications for Food and Drug Administration (FDA) approval, and to assess FDA's capacity to assure human subject protections in these trials.

BACKGROUND

In our June 2000 report, *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research* (OEI-01-97-00195), we drew attention to the fact that clinical drug trials conducted outside the U.S. can be an important source of data in FDA's determination of the safety and efficacy of new drugs. Pharmaceutical companies submit trial data to FDA as part of a New Drug Application, the application for FDA approval to market a drug in the U.S. Although the majority of foreign clinical drug research that is submitted in New Drug Applications is still conducted in countries with a history of clinical drug research, increasingly, countries with less experience are emerging as desirable locations for sponsors to conduct this research.

In conducting this inquiry, we analyzed two FDA databases: one of clinical investigators conducting drug research and one of clinical investigators conducting drug research who have been inspected by FDA. We interviewed FDA officials and industry representatives. We also reviewed pertinent FDA documents and related literature.

FINDINGS

FDA oversees significantly more foreign research than it did 10 years ago.

The number of foreign clinical investigators conducting drug research under Investigational New Drug Applications increased 16-fold in the past decade. In 1990, 271 of these foreign clinical investigators were in FDA's database. By 1999 the number grew to 4,458. FDA inspections of foreign clinical investigators conducting drug research have also increased dramatically, from just 22 in 1990 to 64 in 1999.

Sponsors have expanded research sites into many countries that appear to have limited experience in clinical trials.

The number of countries in which clinical investigators conduct drug research that is tracked by FDA increased from 28 in 1990 to 79 in 1999. Among the countries that have experienced the largest growth in clinical investigators are Russia and countries in Eastern Europe and Latin America. Sponsors explain this growth by pointing to readily

accessible human subjects, potential new markets for approved drugs, and recent international agreements that ease FDA acceptance of foreign research data. Contract research organizations are also moving into these areas. FDA is also beginning to inspect investigators in areas where FDA-regulated research has not previously been conducted.

FDA cannot assure the same level of human subject protections in foreign trials as domestic ones.

FDA receives minimal information on the performance of foreign institutional review boards. It does not inspect these boards, nor does it tend to receive much information from the host countries of these boards. It cannot necessarily depend on foreign investigators signing attestations that they will uphold human subject protections. It has an inadequate database on the people and entities involved in foreign research.

Key entities overseeing or studying foreign research have raised concerns about some foreign institutional review boards.

The pharmaceutical industry, national regulatory agencies, the National Bioethics Advisory Commission, and the World Health Organization have all raised concerns about some of the institutional review boards that review research at foreign sites. Their concerns tend to focus on the boards' lack of experience and insufficient monitoring practices.

RECOMMENDATIONS

The purpose of these recommendations is to help ensure that the protections provided for foreign clinical drug research are at least equivalent to U.S. regulations, not to discourage the submission of non-U.S. data. We direct most of our recommendations to FDA, since it has the jurisdiction for the commercially funded research that was the focus of our inquiry. We also make recommendations to the Office for Human Research Protections, which is in a prime position to foster integrated approaches to protecting human subjects across Federal agencies.

We recognize that FDA has taken many important steps in strengthening human subject protections despite the difficulties of limited resources and limited information about foreign research. In recommending an increase in human subject protection efforts, we also acknowledge that all efforts in this area must be respectful of the sovereignty of other countries and compatible with harmonization efforts. Furthermore, we recognize that some of our recommendations may require additional resources.

We recommend that FDA:

Obtain more information about the performance of foreign institutional review boards. By working with the regulatory authorities in foreign countries to

obtain information about the practices of local institutional review boards, or more directly by assisting in inspections, FDA can address its lack of information about the adequacy of foreign institutional review boards' review of human subject protection issues in clinical research submitted in New Drug Applications.

Help foreign boards build capacity. By working with the Office for Human Research Protections, the National Institutes of Health, and others, FDA can help newly established foreign review boards conduct effective human subject reviews.

Encourage sponsors to obtain attestations from foreign investigators. By encouraging attestations from non-U.S. investigators stating that they will adhere to ethically sound principles of research, FDA can promote adherence to ethical guidelines. Foreign investigators working under an Investigational New Drug Application should sign attestations, as Investigational New Drug Application regulations require. Similarly, foreign investigators working under other research guidelines could be encouraged to sign a statement of their intention to comply with the guidelines they follow.

Encourage greater sponsor monitoring. By encouraging more rigorous monitoring of foreign research sites by sponsors and their agents, FDA can reinforce their responsibility to ensure human subject protections. FDA can work with sponsors to achieve a clearer mutual understanding of the roles they can play in that regard.

Develop a database to track the growth and location of foreign research. Given the significant growth occurring in non-U.S. research submitted as part of New Drug Applications, it is important for purposes of oversight and resource allocation that FDA have more and better information about key elements of that growth.

Finally, we recommend that the Office for Human Research Protections:

Exert leadership. By developing strategies to ensure that adequate human subject protections are afforded for non-U.S. clinical trials that are funded by the Federal government and/or that contribute data in support of a New Drug Application, the Office for Human Research Protections can exert leadership. It is already moving in this direction. In its leadership role, it can foster integrated approaches that would apply across Federal agencies and to federally funded and New Drug Application research conducted at non-U.S. sites.

Encourage accreditation. Encouraging participation of institutional review boards in a voluntary accreditation system is one way to improve the capacity to conduct appropriate reviews of human subject protections in proposed research. The Office for Human Research Protections, working with FDA, NIH, and others, can help develop such a system internationally.

COMMENTS ON THE DRAFT REPORT

Within the Department of Health and Human Services, we received comments from the FDA and the Office for Human Research Protections (OHRP). The OHRP concurred with the two recommendations we directed to it and stressed its readiness to engage in the kind of leadership we called for. The FDA supported all of our recommendations except for the one calling for better data collection on foreign research. It indicated that the purpose and methods we presented concerning the recommendation were not sufficiently clear. In this final report, we modified the recommendation to more clearly define the goal for FDA to develop a database to track the location and growth of foreign research. Such a data base, we suggest, can be helpful in guiding FDA oversight and setting priorities. We also suggested one way to begin gathering such data as well as a broader strategy for the future.

FDA emphasized its lack of resources and its limited authority in foreign countries as constraints in carrying out the remaining recommendations. While we agree that these are limiting factors, we believe the FDA can use its technical expertise, its influence as the approving authority for drugs marketed in the U.S., and its prestige and experience in international circles to promote reforms even in foreign countries.

External to the Department, we solicited comments from the Pharmaceutical Research and Manufacturers of America (PhRMA), Public Citizen Health Research Group, Public Responsibility in Medicine and Research (PRIM&R), and Applied Research Ethics National Association (ARENA). The following is a summary of the comments we received: PRIM&R and ARENA urged FDA "require" not as we suggested "encourage" investigator attestations for foreign research used in support of New Dug Applications. But in general the two organizations supported our recommendations. Public Citizen was more critical, indicating that our recommendations were not strong enough in light of the problems we identified. The comments of these organizations warrant consideration and reinforce our central concern: that FDA cannot assure the same level of protections in foreign trials as domestic ones.

TABLE OF CONTENTS

INTRODUCTION

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BACKGROUND

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In this report we seek to determine the extent to which this overseas research has been increasing and to assess FDA's oversight of such research as it relates to human subject protections. The importance of such oversight is underscored by a December 2000 *Washington Post* series focusing on the adequacy of protections afforded in international clinical drug trials.[2]

FDA Oversight of New Drug Research

This report refers often to two applications that FDA uses to oversee and evaluate new drug research. The first application is the Investigational New Drug Application (IND). Sponsors of drug research submit an IND to FDA prior to the start of research that will be conducted under FDA regulations. The second application is the New Drug Application (NDA). After research is complete, sponsors submit an NDA to obtain FDA approval to market a new drug.

FDA approves an NDA after determining that a drug is safe and effective for its intended use(s). The application contains the clinical and other data FDA needs to evaluate risks and benefits. The drug sponsor, usually a pharmaceutical company, demonstrates that a drug is safe and effective by conducting clinical trials on human subjects. A sponsor must test a drug on many subjects—often several thousand—to produce data that reliably predict the drug's effects. Sponsors generally contract with many clinical investigators,

who conduct this research simultaneously at multiple research sites. Although these research sites were based almost exclusively in the U.S. in the past, they are increasingly based in foreign countries.

NDAs can contain research conducted at U.S. and foreign sites. Although all U.S. clinical drug research must be conducted under an IND, foreign clinical drug research may be conducted either under an IND or other international guidelines. If foreign research is not conducted under an IND, then FDA requires it to have been conducted under the standards of the 1989 version of the Declaration of Helsinki or other guidelines, if they provide a higher level of human subject protections. (See Primer on p. 5 for application information, and appendix B for international guidelines.) FDA accepts NDAs containing three types of research data: (1) U.S. research, (2) foreign research conducted under an IND, and (3) foreign research conducted under other guidelines. A single NDA can contain any combination of these three types of data (see table 1 below).

Table 1
Possible Combinations of U.S. Research Data and Two Types of Foreign Research Data in a Single FDA New Drug Application

Possible combinations of data	U.S. research conducted under an IND	Foreign research conducted under an IND	Foreign research Not conducted under an IND
Combination 1	×		
Combination 2	×	×	
Combination 3	×		×
Combination 4	×	×	×
Combination 5		×	×
Combination 6		×	
Combination 7			×

Source: OIG analysis of FDA information.

Mechanisms for Assuring Human Subject Protections in Foreign Trials

FDA's investigational new drug regulations define institutional review boards as the oversight bodies "designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects."[3] Institutional review boards are intended to protect human subjects in clinical trials, in part, by independently reviewing proposed research before investigators can enroll subjects in trials.

According to FDA regulations, foreign boards must adhere to international ethical standards, whether the standards are set by FDA, the Declaration of Helsinki, or the International Conference on Harmonization, as well as any regulations of their respective countries' regulatory agencies.[4] Although these ethics boards go by several names, in this report we will refer to them all as institutional review boards.

In addition to foreign institutional review boards, other entities play roles in overseeing foreign drug trials that contribute data to NDAs. FDA oversees the protection of subjects in foreign clinical trials through its regulation of the clinical investigator (see Primer p. 5). The sponsor, under an IND, is also responsible for monitoring the investigator. Finally, the regulatory agency of the country hosting the research, analogous to FDA in the U.S., may play an oversight role.

Another entity that plays a role in the oversight of human subject protections is the Office for Human Research Protections, in the Office of the Secretary of the Department of Health and Human Services, previously known as the Office for Protection from Research Risks in the National Institutes of Health. This office is primarily responsible for overseeing research funded through the Department of Health and Human Services, but also serves an important leadership role within the Department, and in the Federal government as a whole.

International Harmonization of Research

FDA has played an important role in efforts to create international standards for clinical research that facilitate the acceptance of well conducted international research. The International Conference on Harmonization was established in 1990 to create international standards for ensuring and assessing the quality, safety, and efficacy of drugs, including Good Clinical Practice guidelines for investigators, institutional review boards, and sponsors. Its members include FDA, the regulatory agencies of the European Union and Japan, and the pharmaceutical industry trade groups from these three regions. In May 1997, FDA published the International Conference on Harmonization guidelines in the Federal Register, as official U.S. guidance. These guidelines are very similar to FDA regulations.[5] An increasing amount of international research is being conducted under these voluntary guidelines.

This Inquiry

In this report we seek to document the extent of the growth of non-U.S. research that is submitted to FDA as part of an NDA and to assess FDA's oversight of this research. We focus primarily on FDA's capacity to ensure human subject protections in this foreign research. Our aim is not to examine or judge the merits of the ethical decisions made by foreign institutional review boards. Rather, we intend to assess FDA's capacity, regulatory or otherwise, to adequately ensure human subject protections in this subset of foreign clinical research. In the past we have raised concerns about the oversight of

clinical research *within* the U.S.[6] We do not expect these foreign trials to meet a higher (or lower) standard than those conducted domestically.

This inquiry primarily focuses on FDA's oversight of clinical drug trials that sponsors monitor and submit in an NDA. Of all the foreign clinical trials that FDA oversees, including drugs, medical devices, and biologics, drug trials constitute the largest number of non-U.S. trials and have occurred over the longest period of time, making these trials the most informative area to examine. This report does not focus on international research that is funded by the U.S. government or by non-profit organizations. However, some of the same concerns raised here may apply to this sphere of research as well.

Methodology

We analyzed FDA's database on foreign clinical investigators who are conducting drug research under INDs. Investigator information in this database is taken primarily from FDA Form 1572, which we will refer to as "attestations." We also analyzed the FDA's database of the results of both foreign and domestic inspections of clinical investigators conducting drug research. In addition, we interviewed key FDA officials involved in overseeing and harmonizing international drug research, including five who have inspected foreign sites. We also interviewed sponsor representatives. Finally, we reviewed pertinent FDA documents and related literature.

We conducted this inspection in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

Primer on FDA Oversight of U.S. and Foreign Drug Research

This Primer applies to FDA's regulation of clinical drug research. The distinction between U.S. and foreign research is based on the location where the research is conducted, not on characteristics of sponsors or investigators. After completing their research, sponsors submit research data in a New Drug Application (NDA). A single NDA can contain combinations of data from research conducted under an Investigational New Drug Application (IND) and data from research conducted under other research guidelines. All investigators whose research is submitted in an NDA are subject to inspection by FDA.[7]

Research conducted at U.S. Sites

Sponsors intending to conduct U.S. based clinical studies *must* submit an IND to FDA before beginning research.[8] FDA then has an opportunity to review the study design and procedures and suggest changes. Sponsors are also required to obtain a signed attestation (1572 form) from each of their clinical investigators, stating that they will conduct research in an ethical manner and according to FDA regulations. (See appendix C for specific commitments.) During the study, sponsors submit annual reports and other information to FDA.

Research conducted at foreign sites

In contrast to U.S. research, FDA does not require sponsors of foreign-based research to conduct research under an IND, although these sponsors can choose to do so.

Foreign research conducted under an Investigational New Drug Application. Sponsors of foreign-based research who choose to submit an IND to FDA must also conduct research according to FDA regulations. However, FDA has less information about this research than it does for U.S. based research because it does not track investigators through a comprehensive database of signed attestations.

Foreign research *not* conducted under an Investigational New Drug Application. If sponsors submit an NDA containing foreign research that was not conducted under an IND, that research must adhere to FDA regulations for foreign clinical studies not conducted under an IND.[9] This type of foreign clinical research must be conducted according to the ethical principles of the Declaration of Helsinki, or the countries' own regulations, whichever offers the greater protection to the human subject.[10] Many countries have adopted the Good Clinical Practice guidelines from the International Conference on Harmonization as their regulatory standard.[11] (See appendix B for a description of international guidelines.) Sponsors are not required to obtain attestations for investigators conducting research under these guidelines.

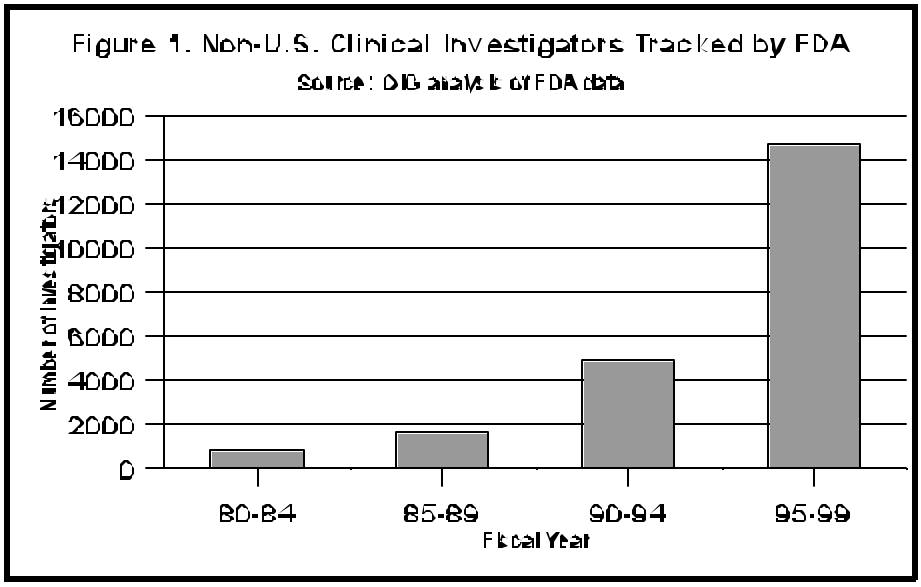
FINDINGS

FDA oversees significantly more foreign research than it did 10 years ago.

Until recently, almost all of the clinical drug research submitted in support of NDAs was conducted at sites within the U.S. Increasingly, sponsors are conducting this research at sites outside of the U.S. Determining the precise growth of this particular subset of foreign research is difficult, however, because FDA's current data system does not track NDA information by the location where research was conducted. As a result, FDA's existing databases cannot provide information on the growth of NDAs that contain data from foreign clinical trials. FDA's database for tracking clinical investigators who conduct drug research is based upon INDs, not NDAs. It therefore does not include foreign investigators whose research was not conducted under an IND, but was submitted in an NDA.[12] Thus, we use this database as just one source of information to support our finding of growth in foreign research that is submitted in NDAs.

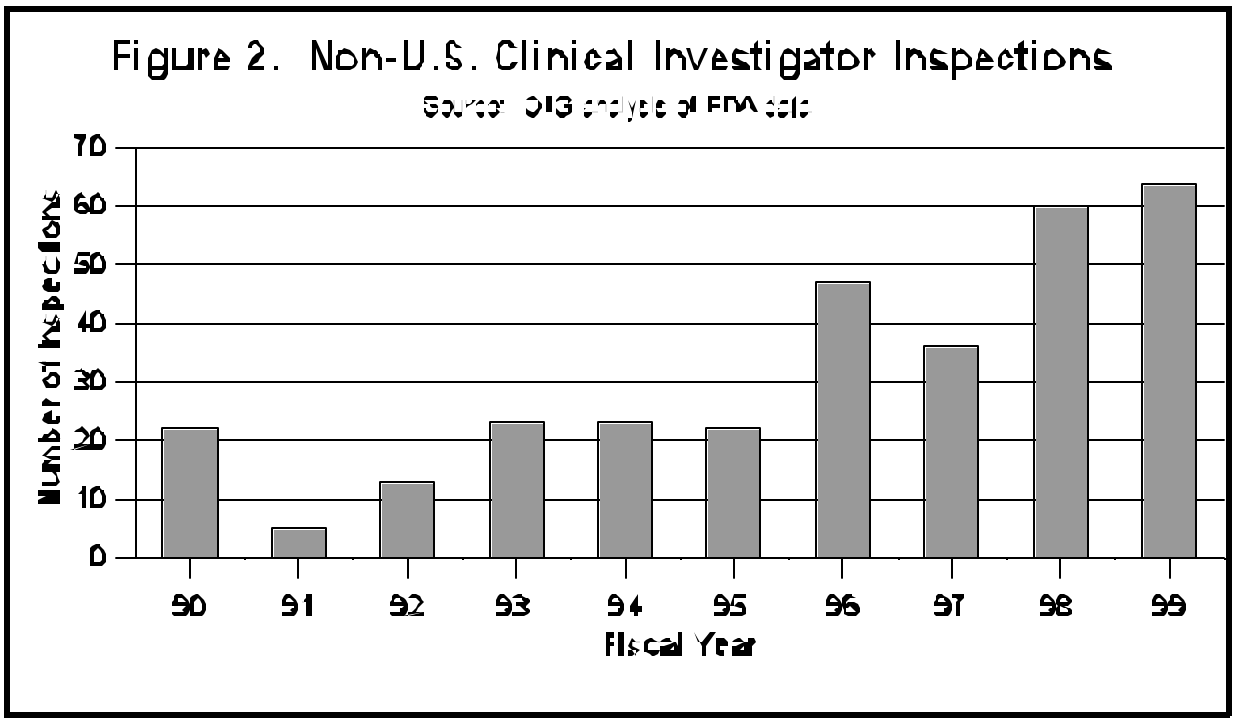
The number of foreign clinical investigators conducting drug research under Investigational New Drug Applications increased 16-fold in the past decade.

In 1980, just 41 foreign clinical investigators conducted drug research under an IND. By 1990, that number grew to 271, and by 1999, to 4,458. The growth of these foreign clinical investigators has been particularly sharp in recent years (see figure 1). As mentioned previously, although FDA's database does not capture the growth of foreign investigators who have submitted data in NDAs, the number of foreign clinical investigators FDA tracks under INDs has increased sharply.



The number of FDA investigator inspections at foreign sites increased dramatically.

After receiving an NDA, FDA inspects clinical investigators at some of the key—sometimes referred to as "pivotal"—sites contributing data to the application. Pivotal sites are generally those that have enrolled the most subjects, and therefore contribute the most data to an NDA. High enrollment is not FDA's only criterion for selecting investigators to inspect, but it is the main one.[13] The number of FDA clinical investigator inspections that occurred at sites outside the U.S. increased sharply over the past decade—from 22 in 1990 to 64 in 1999 (see figure 2). The rising number of investigator inspections occurring outside the U.S. does not fully reflect the growth of applications that contain some foreign data.[14] However, dramatic growth in the number of foreign investigator inspections indicates the increasing role of foreign clinical drug research under FDA oversight.



Sponsors have expanded research sites into many countries that appear to have limited experience in clinical trials.

Although the majority of foreign research contained in NDAs is still conducted in countries with a history of hosting this research, such as the United Kingdom, Germany, and Canada, countries in regions such as Eastern Europe, Latin America, and East Asia are emerging as desirable locations for sponsors to conduct research. For the purposes of this report, we will be referring to regions that are experiencing a vast growth in this research and that lack a history of hosting research as "emerging sites."

Once again, no definitive source of data exists on the amount of research occurring in each country that is intended for or is included in NDAs. Yet the pharmaceutical industry and FDA agree that this research is expanding into many new areas. Several sources of evidence demonstrate the regions and countries experiencing the most rapid growth.

Sponsors attest to this growth.

An industry source reports that, in 1992, 61 premarket clinical research protocols were approved in Hungary; by 1998, that number almost tripled to 178 approved protocols.[15] Another industry source reports that the number of multi-site trial protocols in Russia grew from 38 in 1996 to 99 in 1999.[16]

Access to subjects. Sponsors report using emerging sites for their research to gain access to large numbers of subjects with a particular disease, especially those that are "naive subjects" (i.e., have not been treated for the disease being studied), and to obtain data on different racial or ethnic groups.[17] Sponsors also report that these sites allow them to recruit subjects quickly and, therefore, bring their drugs to market faster. Sponsors report being able to recruit subjects more quickly in certain countries, particularly Russia and those in Eastern Europe, than in Western sites. For example, an organization specializing in managing clinical trials in Eastern Europe cited a study conducted in Poland where "the recruitment was so fast that 40 extra patients were enrolled at the sponsor's request before some of the Western countries, still awaiting Ethics Committee's approvals, had even started."[18] Another organization, specializing in Russian trials, states that, on average, any Russian site recruits twice as many subjects as any site in Western Europe, and some Russian sites have recruited up to 300 percent more than other sites.[19]

Market development. Another reason why sponsors are conducting drug research in these emerging sites is to develop a market for the study drug in the event that it is approved by the FDA.[20] Many of these emerging sites are in regions of the world that are gaining purchasing power.

Regulatory standardization. The recent growth in this research is also likely related to the international regulatory harmonization efforts of the past decade. During this period, the International Conference on Harmonization standardized procedures of trial design, institutional review board review, and research conduct. As a result, FDA has become increasingly willing to accept data from foreign research as part of an NDA. In fact, FDA has the authority to approve applications that contain data exclusively from foreign sites, although such approvals are rare.

Contract Research Organizations are beginning to expand into these countries.

Contract research organizations are entities with whom drug sponsors often contract to manage trials in foreign countries, particularly those in which sponsors have no offices.[21] An analysis of industry trends cited a "global presence" as one of the main qualities that will make these organizations competitive in the future.[22,23] The expansion of these organizations into more countries suggests that these countries are emerging as places where sponsors are currently conducting research or plan to in the future. In July 2000, the world's largest contract research organization, which is currently located in 38 countries, opened offices in 7 new countries: Chile, Czech Republic, Greece, Norway, the Philippines, Romania, and Thailand.[24] The second and third largest organizations, located in 29 and 17 different countries respectively, also recently opened offices in emerging sites.[25] In 2000, another large organization expanded its clinical monitoring services into Asia and the Pacific Rim, claiming "the opportunity for the conduct of clinical trials in Asia, let alone prosperous drug sales, provides potentially limitless pharmaceutical business possibilities—especially in China."[26]

In addition, contract research organizations and site management organizations that specialize in managing and conducting clinical trials in these emerging areas have recently been established. For example, a contract research organization specializing in organizing clinical trials in Eastern Europe was established in 1994 and, in 1999, began applying this experience to trials in Latin America.[27] A site management organization entirely focused on Russian clinical trials was established in 1999.[28] Another organization began specializing in Baltic countries in 1998.[29]

FDA tracked investigators working under Investigational New Drug Applications in 28 foreign countries in 1990 and 79 countries in 1999.

We have noted the limitations of FDA's database of investigators conducting research under an IND for quantifying the growth of non-U.S. clinical research that is submitted in NDAs. Yet the fact that these investigators are conducting research in so many new countries over the past 10 years seems to indicate that sponsors are conducting their research in support of NDAs in areas not used extensively for this type of research in the past. The largest growth appears to be occurring in Eastern Europe, Latin America, and Russia (see table 2).

Table 2
Clinical Investigators Working Under IND Regulations in Selected Countries.
Fiscal Year 1991 to 1999

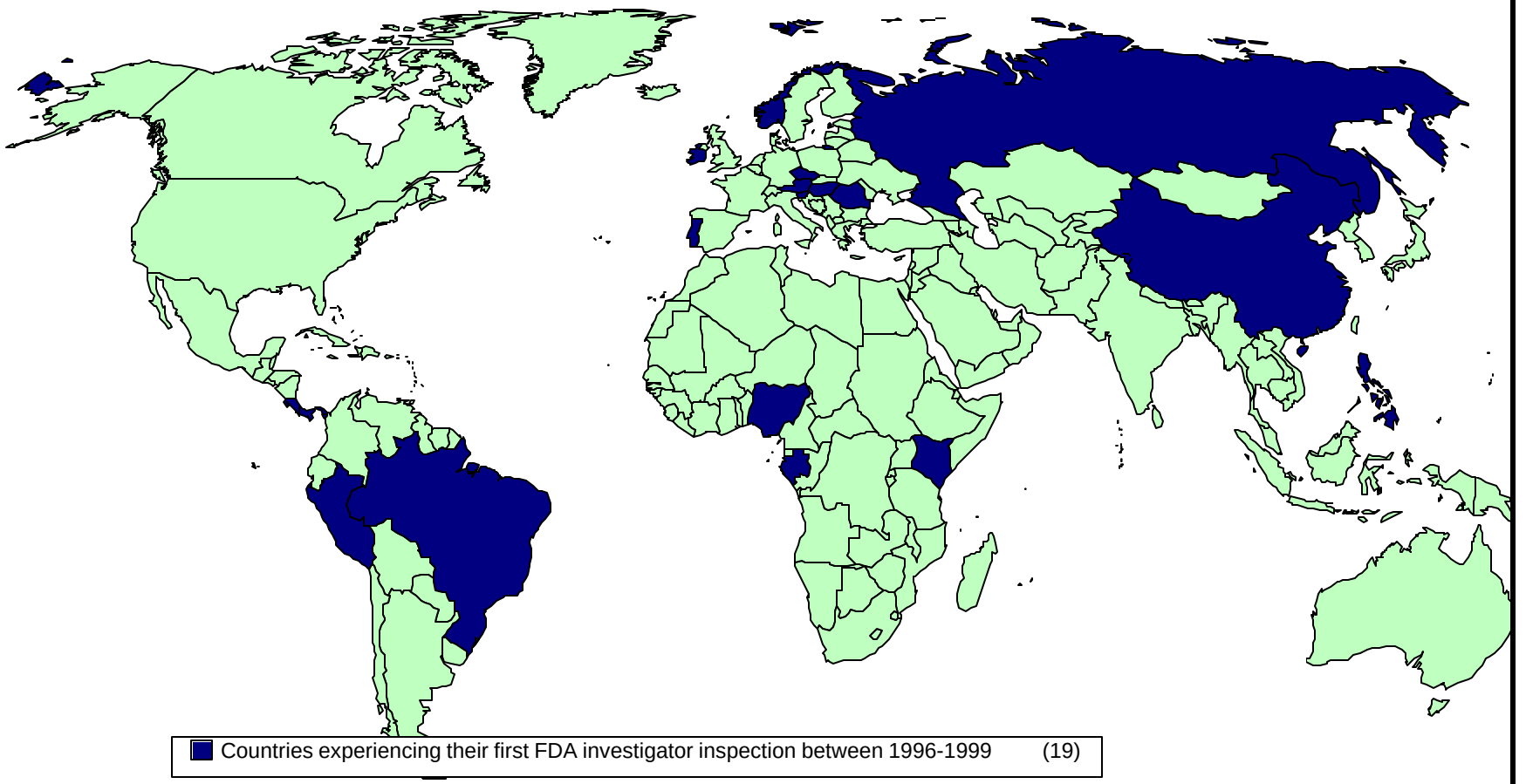
Country	91-93	94-96	97-99
Argentina	6	122	271
Brazil	16	52	187
Hungary	9	35	161
Mexico	29	48	187
Poland	4	100	190
Russia	0	5	170
Thailand	1	2	24

Source: OIG analysis of FDA data

FDA is beginning to inspect investigators in emerging regions.

FDA inspections of investigators can provide evidence of the growth of clinical research conducted outside of the U.S. as well as the areas where the research is taking place (see figure 3). Although FDA databases can not provide precise aggregate or specific information on the location of research contributing data to NDAs, the increasing number of countries experiencing their first investigator inspection demonstrates the growth of this research in emerging countries. FDA may choose to inspect investigators in certain countries, even if the site has not enrolled a large number of subjects, because these countries have not hosted research for NDAs before. In this case, FDA may use the investigator inspection as an opportunity to learn about the research conducted at a particular site and the conduct of clinical research in that country generally.

Figure 3. Emerging Sites



Brazil (1996), Costa Rica (1996), Peru (1996), Russia (1996), Austria (1997), Nigeria (1997), Panama (1997), Philippines (1997), Czechoslovakia (1998), Slovenia (1998), Hungary (1998), Romania (1998), Norway (1998), Hong Kong (1998), China (1998), Gabon (1998), Ireland (1998), Kenya (1998), Portugal (1998).

Source: OEI analysis of FDA data.

FDA cannot assure the same level of human subject protections in foreign trials as domestic ones.

FDA has minimal information on the performance of foreign institutional review boards.

Institutional review boards play a critical role in ensuring that proper protections are afforded to human subjects. They are responsible for carrying out this role at the outset, before the research is initiated, and on a continuing basis thereafter. These institutional review board reviews provide a valuable complement to FDA's own reviews of IND applications.

To help ensure that domestic institutional review boards perform their responsibilities in accord with FDA regulations, FDA conducts on-site inspections; in 2000, it carried out nearly 250 such inspections. In contrast, FDA does not inspect foreign institutional review boards. Given the emphasis on international agreements, the sensitivities associated with national sovereignty, and the resource implications of international inspections, it is understandable why FDA may be reluctant to inspect foreign institutional review boards. But as the amount of foreign research contained in NDAs continues to grow, particularly in areas where boards may have little experience, FDA's lack of information about the review of human subject protections in this subset of international research becomes increasingly problematic.

FDA draws on more indirect means of assessing the performance of foreign institutional review boards, but these are quite limited in scope. When conducting investigations of foreign clinical investigators FDA can get some indication of how thoroughly the institutional review board is carrying out its review responsibilities by examining the investigator's records of correspondence with the board.[30] Also, when reviewing NDAs, it gets some basic information on the institutional review board reviews conducted.[31] But neither of these processes provides the degree of information that can emerge from an on-site review of the board itself. FDA cannot depend on the regulatory bodies of the host countries to provide this information either.[32]

Not all foreign investigators who conduct research that is submitted in New Drug Applications sign an attestation that they will uphold human subject protections.

An attestation is a means of holding an individual investigator clearly and directly accountable for conducting research ethically. For foreign research conducted outside of an IND and subsequently used in support of an NDA, FDA does not require the sponsor to obtain a signed attestation from the foreign investigator; nor do the Declaration of Helsinki or the International Conference on Harmonization have any similar guidelines directed to the individual investigator.

For research conducted under an IND, whether foreign or domestic, FDA does require sponsors to obtain a signed attestation from an investigator before the investigator begins

research. The great majority of research submitted to FDA in support of NDAs is carried out by investigators working under INDs. FDA does not have data on how many of these investigators actually sign attestations. But through our inquiries in FDA, we learned that sponsors of foreign research conducted under INDs may not always be obtaining written attestations from foreign investigators, even though, as we have indicated, they are required to by FDA.[33]

Thus, for research submitted to FDA in support of an NDA, there is reason to believe that the potential of an investigator attestation as a means of fostering human subject protections is not being fully realized.

The Attestation

FDA requires that clinical investigators working under an IND sign an attestation. Following are some of the commitments they make in signing that document:

- To adhere to the study protocol.
- To personally conduct the research.
- To inform subjects that the drugs are being used for investigational purposes.
- To ensure that FDA regulations of informed consent and IRB review are met.
- To report adverse events.
- To report to the IRB any changes in the study protocol or any unexpected problems.

Source: FDA Form 1572

FDA experiences challenges inspecting investigators at foreign sites.

FDA's main mechanism for overseeing clinical research outside of the U.S. is its inspections of clinical investigators. It inspects investigators after research has been conducted, after an NDA has been submitted but before an approval decision. When FDA inspects clinical investigators, it focuses primarily on ensuring the integrity of the data submitted as part of the NDA. It also examines the adequacy of human subject protections by collecting from the investigator documentation of institutional review board approvals and modifications, subjects' records, and informed consent documents.[34] These inspections are a particularly useful oversight tool for FDA when inspecting clinical investigators who did not conduct research under an IND, since FDA is generally uninformed of these investigators' activities throughout the entire research process, in contrast to investigators conducting research under an IND (see Primer on p. 5). FDA has faced some challenges in inspecting foreign sites:

Logistics. FDA inspectors must give advance notice to the State department and obtain visas for the host countries. FDA schedules multiple foreign inspections in order to maximize resources. Domestic inspections, in contrast, are generally within driving distance of the district office. Another problem mentioned by one FDA official is that sometimes just before an FDA inspector is scheduled to inspect a foreign site, the site will contact them and inform them that they are missing source documents or other relevant documents at the site.[35]

Diplomacy. FDA officials must ensure the safety and integrity of clinical trials without offending the host country. This can require making arrangements through diplomatic

channels, such as parliaments or departments of health, commerce, or trade, which further complicates arranging foreign inspections. In addition, FDA inspectors must undergo additional training regarding cultural differences before conducting foreign inspections.

Expense. Foreign inspections are more expensive than domestic inspections. Airfare alone to some countries exceeds the entire FDA estimate of $2500 per investigator per inspection.[36] Foreign inspections are also more expensive than domestic ones because FDA must pay food and lodging expenses of its employees.[37]

FDA has limited information on the people and entities involved in foreign research.

During the course of research, FDA has little or no information about the sites, investigators, institutional review boards, and human subjects involved in research that is not conducted under an IND. It only obtains this information when a sponsor submits the NDA after completing all research. FDA's only database that aggregates data across projects is restricted to data from IND submissions. Presently, FDA is unable to generate data from a database, or set of relational databases, that could answer the following questions about institutional review boards, investigators, sites, and human research subjects:

Institutional review boards. How many are there? Where are they? How many protocols have they reviewed that ultimately led to NDAs?

Investigators. How many are there outside of the U.S.? In which countries are they conducting their research? Is this changing? How many are working under an IND?

Sites. How many are there? In which countries? How many research subjects are enrolled at each site?

Human research subjects. How many have participated in NDA research? Which countries contribute the most subjects? Is this changing over time?

Lacking this information, FDA is unable to systematically target its limited resources either for inspections or for educational purposes. It is also hard pressed to provide guidance or plan educational programs in regions experiencing rapid growth in clinical trials.

FDA typically does not review or discuss with sponsors the study designs and monitoring plans of New Drug Application research that was not conducted under an Investigational New Drug Application.

Sponsors are required by both FDA regulation and International Conference on Harmonization guidelines to monitor the progress of clinical trials.[38] But only under IND regulations is the sponsor required to submit its study design and monitoring plan prior to

conducting research. FDA is at liberty to reject the trial data when the NDA is submitted if it believes that the study was improperly designed or unethical. But, by the time a sponsor submits a New Drug Application, the trial is already completed. Thus, the study subjects would have already been placed at risk, or possibly harmed.

The critical time for FDA to provide advice to sponsors on trial design and oversight is when the sponsor submits an IND, *before* any research subjects are enrolled in the trial. FDA engages in dialogue with sponsors during IND submissions. FDA evaluates the study design to determine whether the study is designed in such a way that it can achieve its intended objectives. At the time of an IND submission, FDA may also recommend to sponsors what would be an appropriate level and type of monitoring for that particular study. In order to determine the proper extent and nature of the monitoring, FDA conducts a clinical review of data from the study's animal trials or earlier human trials to assess the potential risk of the trial.

Key entities overseeing or studying foreign research raise concerns about some foreign institutional review boards.

FDA has no direct regular contact with foreign institutional review boards, but other entities that have worked with or studied foreign institutional review boards have raised concerns about those boards that are inexperienced in conducting ethical reviews.

The pharmaceutical industry. Sponsors have raised concerns regarding the capacity of the institutional review boards in some of the emerging sites to adequately review research according to Good Clinical Practice guidelines, under the International Conference on Harmonization or FDA standards. In one article, a pharmaceutical company representative stated, "...investing in Latin America, as in other emerging markets, presents some challenges not necessarily encountered in countries traditionally included in global clinical development programs," including verifying the adequacy of institutional review boards used.[39] A medical director of a U.S. pharmaceutical company based in China stated that it is difficult to obtain memberships, meeting schedules, and minutes of Chinese institutional review boards.[40] One representative of a contract research organization noted that the protocol-approval process of Malaysian institutional review boards is poorly defined.[41] An employee of a Russian-based contract research organization reported that she had frequently encountered problems with lack of full disclosure to potential subjects about the side effects of the study drug.[42] In fact, one large pharmaceutical company was concerned enough about the adequacy of ethics boards in some of these regions to contract a U.S. institutional review board to train members of the foreign institutional review boards reviewing its research.

Regulatory agencies in the countries hosting research. When the Korean regulatory agency for clinical research inspected its sites, it found such deficiencies as: institutional review boards unaware of departures from protocol, institutional review boards not being informed of protocol changes, inappropriate review board operations, inadequate

composition of review boards, inadequate informed consent, and lack of continuous trial review by review boards.[43] In another recent case, South Africa's health ministry forced companies to withdraw profitable clinical trials, stating that half the protocols seeking approval were substandard, both scientifically and ethically, including inadequate handling of informed consent of human subjects.[44]

National Bioethics Advisory Commission. A recently commissioned report, *Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations*, found that institutional review board shortcomings may be particularly common in the developing world.[45] It contained a survey of clinical investigators conducting research, mostly in Africa, Asia, and Latin America. The surveyed investigators raised concerns that some institutional review boards were improperly trained, were conducting primarily a scientific and budgetary review rather than an ethical one, and were not properly monitoring research.[46] The Nuffield Council on Bioethics, a British council with a similar mission to the National Bioethics Advisory Commission in the U.S., also expressed concerns about some institutional review boards.[47]

World Health Organization. In 1999, The World Health Organization's Tropical Disease Research group conducted two seminars analyzing the status of ethical review in Asia, Africa, and the Western Pacific. These seminars revealed several weaknesses in the ethical review systems of these countries (see box at right).[48] As a result of the seminars, the World Health Organization developed *Operational Guidelines for Ethics Committees that Review Biomedical Research*, a document which provides guidance to countries and institutions for creating and operating their own research ethics committees.[49] It also established the Forum on Ethics Committees in Asia and the Western Pacific, a network for mobilizing resources, exchanging information and coordinating activities relating to institutional review boards. Among other activities, this forum facilitates training and education of members of ethics committees.[50]

Some Weaknesses in Ethical Review Systems in Asia, Western Pacific, and Africa

1. Lack of procedures for reviewing the protocol and informed consent forms
2. Lack of trained institutional review board members
3. Insufficient resources
4. Lack of monitoring systems
5. Lack of quorum requirements for institutional review board meetings
6. Lack of independence

Source: World Health Organization

RECOMMENDATIONS

The evidence we have gathered indicates that the current situation is a serious one warranting further attention by the FDA and by the U.S. Department of Health and Human Services as a whole. The significant growth in foreign research that is submitted in New Drug Applications presents challenges to the Department's ability to assure human subject protections.[51]

We recognize that FDA has taken many important steps in strengthening human subject protections in foreign research, despite the difficulties associated with limited resources and limited information. We also recognize that all efforts in this area must respect the sovereignty of other countries and occur within the collaborative system governing international research. The National Bioethics Advisory Commission recently indicated the importance of achieving human subject protections, regardless of trial location.[52]

In many countries hosting drug trials that generate data for NDAs, a well-established set of rules and enforcement mechanisms exist to protect human subjects. But in some emerging sites, where a significant growth in NDA research is occurring—and is likely to continue to expand—current conditions may not allow for a level of protection comparable to that in U.S. sites.[53]

Some of our recommendations may require additional regulations or additional resources on the part of FDA, the Office for Human Research Protections, regulatory agencies in foreign countries, and sponsors.

We lead with five recommendations to FDA, which has the explicit jurisdiction for the commercially funded research that has been the focus of our inquiry, and close with two recommendations to the Office for Human Research Protections.

We recommend that FDA:

Examine ways in which it can obtain more information about the performance of non-U.S. institutional review boards reviewing clinical trials that provide data in support of New Drug Applications.

We recognize that this is a complex matter that raises difficult questions about international relationships and the use of scarce resources. But our review provides an early warning signal that FDA does not have adequate assurance of human subject protections in a growing proportion of the research submitted in support of NDAs. In foreign, no less than in U.S. sites, institutional review boards must play a key role in ensuring such protections.

FDA's informational void concerning the performance of foreign institutional review boards is of particular concern for emerging sites with little experience in conducting clinical research for NDAs and in providing human subject protections. One way in which FDA could help fill this void is to work with the host countries, encouraging them to oversee their institutional review boards and to share with FDA any information they have about the performance of those boards, particularly in cases where they review a substantial amount of research to be used in support of an NDA.

Another more direct approach is to selectively conduct some reviews of institutional review boards at sites where such research is occurring and where FDA has minimal information about board review. With the participation of the host countries, FDA could conduct reviews with a focus on providing assistance to enhance review board performance. To conserve resources, it could also consider conducting these reviews in tandem with non-U.S. clinical investigator inspections.

Help inexperienced non-U.S. institutional review boards build their capacity.

As we have noted, various parties involved in clinical research have raised concerns about inexperienced institutional review boards, particularly when these boards are reviewing research not conducted under an IND. In recommending this capacity-building, we echo a similar recommendation made by the National Bioethics Advisory Commission in its recent report, *Ethical and Policy Issues in International Research.* The Commission found that "although ethics review committees are widely used throughout the international research community to ensure the protection of human participants, differences still remain in the level and quality of review."[54] It found that, in general, "ethics review committees in developing countries were less likely to raise either procedural or substantive issues for a given study, compared to U.S. boards."[55]

Many possible mechanisms exist for building the capacity of foreign boards. For example, FDA staff currently use travel outside of the U.S. for conferences or other reasons as an opportunity to conduct outreach to institutional review boards. It should continue these educational efforts but should expand them to provide technical assistance to these boards. It could also provide technical assistance to foreign ministries of health, which in turn could assist FDA in ensuring that boards are operating according to FDA or other research guidelines.

Other entities that are currently helping FDA in these capacity-building efforts should continue to do so. The National Institute of Health's Fogarty International Center recently awarded grants to U.S. and foreign academic institutions to extend existing U.S. bioethics curricula to the international arena and to assist developing nations in creating their own ethics education.[56] In addition, international bodies, such as the World Health Organization, have played key roles in this area.

Finally, sponsors should take steps to educate the non-U.S. boards that they use, particularly those that lack experience reviewing FDA-regulated research. One way that they could do this is by contracting with experienced U.S. boards to help train the foreign boards.

Encourage sponsors to ensure that all non-U.S. investigators participating in research for New Drug Applications sign attestations indicating that they will uphold human subject protections.

FDA can take two steps toward this end. The first is to make certain that the attestations that are required of foreign investigators working under an IND are, in fact, signed. We received some indications that this has sometimes not been the case. We suggest that FDA reinforce to sponsors their obligations to obtain attestations from all investigators (foreign and domestic) conducting research as part of INDs.

The second step concerns those foreign investigators who are not working under an IND, but are conducting research to be included in an NDA. In these instances, where there is no FDA requirement for an attestation, FDA could encourage sponsors to obtain an attestation from all participating investigators. The attestation could indicate readiness to comply with FDA requirements, the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice standards, or with other local standards. Securing commitments from all investigators prior to the start of research, that they will follow an established set of clinical and ethical practices, can promote greater accountability among investigators and sponsors for protecting human subjects.

Encourage more rigorous monitoring of foreign research sites by sponsors.

Sponsor monitors can play an important role in overseeing all clinical trials because monitors are present at the research site with some regularity. Sponsor monitoring of research is required under FDA regulations and under International Conference on Harmonization guidelines. This is particularly important in non-U.S. sites because of the gaps in monitoring by other oversight entities.

FDA could review all sponsor monitoring plans for research conducted at foreign sites to verify that those plans include provisions for ensuring that human subject protections are upheld. For example, in regions that are new to conducting research under FDA standards, FDA could encourage sponsors to occasionally observe the informed consent process or an institutional review board meeting. In doing this, FDA would be encouraging sponsors to shoulder additional review board oversight responsibilities. Currently, FDA often engages in an informal dialogue with sponsors about their monitoring plans. However, we suggest that FDA formalize this dialogue, as it has done recently for certain types of clinical trials. For example, FDA requires sponsors of gene transfer research to submit their monitoring plans for review prior to conducting research.[57]

Develop a database to track the growth and location of foreign research.

Currently, FDA databases lack important information on the extent of foreign research. They do not track the number of sites where NDA research is being conducted or the number of investigators or subjects involved in this research. Nor do they distinguish between sites that are operating under an IND and sites that are not.

FDA should explore ways to track information about NDAs, including the investigators involved in NDA research, not just those who are working under INDs, who are currently tracked. It could enter this information into the investigator database retrospectively after NDA submissions, which contain this information. Although retrospective data would not improve oversight during these trials, it would allow FDA to analyze trends in the growth and location of research.

FDA is now in the process of designing two other databases that relate to clinical trials. One will include a registry of all U.S. IRBs; the other will track demographic information on clinical trial subjects. As FDA designs these databases, it should consider ways in which it could develop them to facilitate the tracking of information on foreign research.

Such data would enable FDA to improve its planning of oversight activities. For example, FDA could analyze this data to determine which regions of the world are hosting FDA-regulated clinical research for the first time or which regions are experiencing rapid growth in clinical research and then could target educational programs accordingly. FDA could use investigators' and review boards' names and contact information to disseminate relevant guidance and training materials.

Finally, we recommend that the Office for Human Research Protections:

Exert leadership in developing strategies to ensure that adequate human subject protections are afforded for non-U.S. clinical trials that are funded by the Federal government and/or that contribute data to New Drug Applications.

The Office for Human Research Protections has already started moving in this direction through its stated intention to establish an office that will focus on international affairs. Because of its location in the Office of the Secretary, its recently established National Human Research Protection Advisory Committee, and its role (through the office director) as chair of Human Subjects Research Subcommittee of the White House Office of Science Technology and Policy, it is in a prime position to provide leadership on how to foster protections in non-U.S. sites where research is submitted in NDAs and/or is funded by the U.S. government.

As part of its leadership, we suggest that it work with FDA and the National Institutes of Health to determine specific steps that could be taken to assure proper protections for subjects participating in overseas trials. To the maximum extent possible, the Department of Health and Human Services should pursue developing an integrated approach that ensures proper protections regardless of whether the research is government funded or commercially funded as part of an NDA.

In this context, it could be particularly helpful for the Office for Human Research Protections to address how the Department can better assess whether other nations' laws and practices afford equivalent protections to those that apply to human subjects participating in clinical trials in the U.S. We recognize the sensitivities and complexities associated with such guidance, but the matter appears to warrant serious consideration.

We also suggest that the Office for Human Research Protections use its position on the White House Human Subjects Research Committee, composed of 17 Federal agencies that have adopted the Common Rule for human subject protections, to stimulate integrated approaches across Federal agencies.[58] The Common Rule has served such an integrating function for domestic research funded by the member agencies. Perhaps a new section of the rule could be added spelling out a similar integrated strategy directed specifically to government funded and NDA research at non-U.S. sites.

Encourage the development of a voluntary accreditation system for human subject research programs.

One way of helping inexperienced institutional review boards and research sites to improve their capacity to provide human subject protection is to encourage their participation in a voluntary accreditation system. While voluntary accreditation should not preclude additional FDA oversight, it can serve as a vital means of enhancing performance through collegial interaction and minimized reliance on the use of regulatory mechanisms. The Office for Human Research Protection has already contracted with the Institute of Medicine to develop a program and the Department of Veterans Affairs' Office of Research Compliance and Assurance has contracted with the National Committee for Quality Assurance to develop and conduct a program. The Office for Human Research Protections should work with FDA, the National Institutes of Health, and international partners to foster effective accreditation practices throughout the world that are supported by the research community.

COMMENTS ON THE DRAFT REPORT

Within the Department of Health and Human Services, we received comments on the draft report from the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP). External to the Department, we solicited comments from the Pharmaceutical Research and Manufacturers of America (PhRMA), Public Citizen Health Research Group, Public Responsibility in Medicine and Research (PRIM&R), and Applied Research Ethics National Association (ARENA). We received comments from Public Citizen and joint comments from PRIM&R and ARENA, two organizations that reflect the perspectives of many engaged in ensuring and/or studying human subject protections. Based on the comments we received, we made some clarifications that are reflected in the final report. Below we briefly summarize their comments and offer our responses in italics. Appendix D contains the full text of each set of comments.

Food and Drug Administration

The FDA disagreed with our draft recommendation calling for it to improve the collection of data about the location and oversight of research submit in New Drug Applications. It elaborated that neither the purpose nor method of data collection we proposed were clear enough to warrant a commitment of scarce resources. *In this final report, we modified our recommendation to more clearly call for FDA to develop a database to track the location and growth of foreign research, (and suggested at least one way to do so.) With the significant growth taking place in foreign research that is submitted as part of New Drug Applications, we regard such an information base as an important means to help guide FDA oversight. FDA is developing other data bases to track IRBs and demographic information on clinical trials. As it works on these other databases, it might explore ways in which they could be developed to facilitate the tracking of information on foreign research*

At a general level, FDA agreed with our remaining recommendations. It did not elaborate on the specifics of how it would carry them out. It emphasized the importance of capacity building efforts in dealing with foreign IRBs and the minimal resources FDA now has to support such efforts. It also underscored its concern that it not discourage the submission of important, ethically conducted foreign research and thereby slow the approval of products that could benefit the American public. And it noted its limited authority in foreign countries as a constraint in carrying out the remaining recommendations. *We recognize the importance of capacity-building to address the concerns we raise in our report and of drawing on available, relevant data in support of New Drug Applications. At the same time, we urge FDA to recognize that our review presents a significant warning signal that it does not have sufficient assurances of human subject protections in a growing proportion of the research submitted to support New Drug Applications. Within the limits of its resources, it is important that FDA do all it can to draw attention to this situation and to foster corrective actions. Its relationships with sponsors can be particularly valuable in this regard. Finally, while we agree that resources and authority are limiting factors, we believe the FDA can use its technical expertise, its influence as the*

approving authority for drugs marketed in the U.S., and its prestige and experience in international circles to promote reforms, even in foreign countries.

Office for Human Research Protections

The Office concurred with the two recommendations we directed to it. It referenced its establishment of a new component office on international activities and underscored its readiness to engage in the kind of leadership we urged and to foster voluntary accreditation as a means of enhancing human subject protections. *We are pleased with the Office's positive response. Through its educational activities, its own oversight efforts, and its leadership position among Federal agencies, it has a major opportunity to help foster human subject protections in the emerging sites where so much research is now being done in support of New Drug Applications.*

External Comments

PRIM&R and ARENA expressed support for our assessments and recommendations. They emphasized the importance of fostering mechanisms for locally driven education, using approaches such as those that PRIM&R and ARENA have used in the United States. They strongly endorsed our recommendation for improved data collection and urged that FDA not just encourage, but in fact require attestations from all investigators conducting research to be used in support of New Drug Applications. *The educational approaches that PRIM&R and ARENA have taken over the years do serve as a good model for locally driven education efforts in emerging sites. We urge both FDA and OHRP to draw upon them as they proceed with their own efforts. We recognize PRIM&R and ARENA's sense of urgency about attestations for all research. Before any such requirement, we think it is important for FDA to try to use existing points of leverage to promote the wider use of attestations.*

Public Citizen was more critical, noting in particular that our recommendations were not strong enough in light of the serious problems we identified. It also noted that we failed to draw adequately on prior research and to give sufficient attention to deficiencies in the data collected by FDA. Public Citizen underscored the significance of our central finding that FDA can not assure the same level of protections in foreign trials as domestic ones. *Public Citizen's impatience with the current situation reflects that of other advocates we spoke with in the course of our inquiry and warrants consideration. We did draw on considerable prior research, much of it cited in the 65 endnotes in the report. What we did not do is cite specific incidents wherein human subject protections were compromised in foreign sites. Our aim in this report was to provide a systematic review of existing oversight, not to assess the adequacy of protections in foreign sites.*

APPENDIX A

Foreign Investigator Inspections

Between 1981, when FDA first began inspecting foreign sites where clinical investigators conduct NDA research, and 1999, FDA conducted 352 inspections in 41 foreign countries. Our analysis of the results of FDA clinical investigator inspections found that the outcomes of these inspections, based on FDA's classifications — FDA's overall evaluation of clinical investigator's compliance — were very similar to those given to domestic inspections.[59] For example, in both fiscal years 1998 and 1999, FDA found serious problems in about 3 percent of foreign and domestic inspections. (See table 1)

Table 1. Classifications of Foreign and Domestic Investigator Inspections

Fiscal Year	Location	Number of Inspections	Percent "Official Action Indicated" (OAI)	Percent "Voluntary Action Indicated" (VAI)	Percent "No Action Indicated" (NAI)	Percent Pending
1998	foreign	60	3	53	43	0
	domestic	286	5	54	41	0
1999	foreign	64	3	55	42	0
	domestic	242	2	52	45	1

Source: FDA data

OAI= FDA takes official action against investigator (e.g., sends warning letter outlining violations and requesting response or, for more serious violations, refuses to accept data).

VAI= FDA asks investigator to make voluntary changes.

NAI= Inspection reveals no objectionable conditions or practices; clinical investigator not required to make any changes.

In addition to classifying the investigator inspection overall, FDA can cite clinical investigators for specific deficiencies, based on observations made during investigator inspections. Our analysis found that, as with overall classifications, the deficiency codes given to foreign inspections have not been significantly different from those of domestic inspections (see table 2 on next page).

APPENDIX A

Table 2. A Comparison of Deficiency Code Distributions for Foreign and Domestic Investigator Inspections (1995-99)

Deficiency Code	Percent of Foreign Deficiencies (n=362)	Percent of Domestic Deficiencies (n=1781)
Problems with records availability	<1	<1
Failure to obtain patient consent	1	<1
Inadequate patient consent form	12	18
Inadequate drug accountability	12	10
Failure to adhere to protocol	30	27
Inadequate and inaccurate records	26	21
Unapproved concomitant therapy	–	<1
Inappropriate payment to volunteers	–	–
Inappropriate delegation of authority	–	<1
Failure to obtain or document IRB approval	–	<1
Failure to notify IRB of changes, failure to submit reports, etc.	–	1
Failure to report adverse reactions	9	10
Submission of false information	–	<1

Source: FDA data

APPENDIX B

International Research Guidelines

The Declaration of Helsinki.[60] Established in 1964 by the World Medical Association, these were the first somewhat detailed set of ethical guidelines for international clinical research. They are ethical principles directed at clinical investigators. Although the Declaration is not prescriptive about the oversight of investigators conducting human subjects research, the October 2000 revision does state that investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries and internationally. Moreover, it states that investigators should submit the research protocol to an independent ethics committee for review prior to conducting the research. In terms of conducting research in other countries, the Declaration states that

> Medical research involving human subjects is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

International Ethical Guidelines for Biomedical Research Involving Human Subjects.[61] These guidelines were developed in 1982 by the Council for International Organizations of Medical Sciences, in collaboration with the World Heath Organization. The purpose of these guidelines was to aid developing countries in applying the principles of the Declaration of Helsinki.

These guidelines do contain provisions for ensuring that ethical principles are adhered to, giving special attention to preventing exploitation of human subjects in developing countries. For example, the commentary for "Research involving subjects in underdeveloped communities," indicates the need for review by an ethical board:

> To guard against exploitation of individuals and families in socially and economically exploitable communities, sponsors and investigators who wish to conduct in such communities research that could be carried out reasonably well in developed communities must satisfy their national or local ethical review committees, and in the case of externally sponsored research the appropriate ethical review committee in the host country, that the research would not be exploitative. *The reason for choosing an underdeveloped community should be made explicit*.[62] [Italics added]

"Obligations of sponsoring and host countries," suggests another oversight provision—that an objective entity in the sponsoring country review the protocol:

> When externally sponsored research is initiated and financed by an industrial sponsor such as a pharmaceutical company, it is in the interest of the host country to require that the research proposal be submitted with the comments of a responsible authority of the initiating country, such as a health administration, research council, or academy of medicine or science.[63]

APPENDIX B

International Conference on Harmonization Good Clinical Practice Guidelines.[64] The International Conference on Harmonization, a collaboration between the United States, the European Union, and Japan, was established in 1990 to create international standards for the quality, safety, and efficacy of drugs to facilitate international trade. The Good Clinical Practice Guidelines include standards for overseeing human subject protections. Mostly, the guidelines hold sponsors accountable for ensuring these protections. Among other responsibilities, the guidelines state that the sponsor should verify that the investigator has adequate qualifications, has written informed consent before each subject's participation in the trial, and is only enrolling eligible subjects. The sponsor must also confirm that the protocol was adequately reviewed by the appropriate institutional review board.

There are also guidelines for institutional review boards. These spell out the institutional review board's responsibilities. For example, the institutional review board is responsible for reviewing recruitment advertisements, the informed consent document, and the amount of compensation to be given to research subjects. Other institutional review board responsibilities laid out in International Conference on Harmonization guidelines include reviewing the qualifications of the investigator who will be conducting the study and conducting continuing review of the trial. In addition to specifying review board responsibilities, it lays out guidelines for board composition, function, operations, and procedures.

Operational Guidelines for Ethics Committees that Review Biomedical Research.[65] This document, developed by the Tropical Disease Research group of the World Health Organization, provides guidance to countries and institutions for creating and operating their own research ethics committees. The group developed these guidelines because investigators in developing countries were conducting increasingly more research, but few people in these countries had experience setting up and running ethics committees. The existing international research ethics documents focused on ethical issues, not on how the ethical review committee should be staffed, organized, or operated.

APPENDIX C

Commitments in Clinical Investigator Attestation

1. 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.

2. I agree to personally conduct or supervise the described investigation(s).

3. 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 (IRB) review and approval in 21 CFR Part 56 are met.

4. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

6. 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.

7. I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

8. I will ensure that an IRB 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 IRB 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 IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

9. I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

APPENDIX D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

August 14, 2001

NOTE TO: Deputy Inspector General for Evaluation and Inspections
Department of Health and Human Services

FROM: Supervisory Policy Analyst
Executive Secretariat
Food and Drug Administration

SUBJECT: Final Comments to OIG Draft Report on Clinical Trials

Attached is a hard copy of the final comments already e-mailed to you by the Food and Drug Administration's Dr. David LePay and Ms. Catherine Lorraine, in response to a May 16 call for comments by Michael Mangano on the OIG's Draft Report, "The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects." These comments are in addition to the ones sent to you on June 29, 2001, by Dr. LePay.

If you have any questions, please feel free to contact me on 301-827-4450.

Walter D. Osborne

Walter D. Osborne, M.S., J.D.

Attachment

IG ✓
EAIG
PDIG ✓
DIG-AS
DIG-EI ✓
DIG-OI
DIG-MP
OCIG
ExecSec ✓
Date Sent 8-16-01

Examine ways in which it can obtain more information about the performance of non-U.S. institutional review boards reviewing clinical trials that provide data in support of New Drug Applications.

Agency response. The agency supports this recommendation in the context of capacity building. That is, the agency is largely unaware of other government or independent agencies that currently and comprehensively assess performance of non-U.S. IRBs in a way that would be meaningful to the assurance of human subject protection in studies submitted to FDA. FDA recognizes that one goal of capacity building can and should be the development of such other agencies with this oversight authority.

Help inexperienced non-U.S. institutional review boards build their capacity.

Agency response. FDA strongly supports this recommendation but cautions that the agency currently has virtually no resources available for this activity.

Encourage sponsors to ensure that all non-U.S. investigators participating in research for New Drug Applications sign attestations indicating that they will uphold human subject protections.

Agency response. FDA supports this recommendation but recognizes that it may not be possible to require that attestations be signed prior to or during the conduct of studies in countries outside the U.S. The agency does not want to adopt a requirement that might inadvertently prevent the submission of important, ethically conducted studies to FDA for review and thus slow or preclude the approval of a significant product that would benefit the health of American consumers. FDA will consider developing an attestation form specifically for foreign clinical investigators that they would be able to use. The agency believes that this would provide acceptable protection because it would reflect the investigator's compliance with

local laws and practices which assure equivalent human subject safe guards.

Encourage more rigorous monitoring of foreign research sites by sponsors.

Agency response. FDA supports this recommendation.

Improve the collection of data about location and oversight of research submitted in New Drug Applications.

Agency response. FDA does not support this recommendation in its current form, because neither the purpose nor the method of data collection is clear enough for the agency to understand exactly what is being recommended. It should be noted that data collection efforts are expensive, and FDA would need to have a much clearer understanding of the cost effectiveness of the system and whether the information would actually contribute to the protection of human subjects.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Public Health and Science

Greg Koski, Ph.D., M.D., Director
Office for Human Research Protections
6100 Executive Boulevard, Suite 3B01
Rockville Maryland 20892-7507

SEP - 6 2001

TO: Janet Rehnquist
Inspector General
Office of the Inspector General

FROM: Director, Office for Human Research Protections

SUBJECT: Comments on the OIG Draft Report: *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, OEI-01-00-00190

The Office for Human Research Protections (OHRP) concurs with the recommendations in the draft report, *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*. OHRP recognizes the value of fostering integrated approaches to ensure protection of human subjects in research, whether conducted here or abroad, and whether it is federally or privately supported.

Toward this end, we announced last March the creation of a new component office, the Office of International Activities that will serve as a focal point and coordinating center for the Department's leadership in this area.

OHRP strongly supports the report's recommendation that voluntary accreditation programs offer an important, valuable and effective means of achieving the goals of strengthened protections for subjects and harmonization of policies and procedures for responsible conduct of human research through a non-regulatory means. The Department has strongly supported this goal domestically, and indeed has catalyzed the development and implementation of an accreditation process for human research protection programs through its contract with the Institute of Medicine (Report issued April 2001; "Preserving Public Trust: Accreditation of Human Research Participant Protection Programs").

OHRP stands ready to accept its leadership role and looks forward to working collaboratively with the Food and Drug Administration, National Institutes of Health, Centers for Disease Control and Prevention, the World Health Organization, World Medical Association, Council for International Organizations of Medical Sciences, the European Forum on Good Clinical Practice, the Global Forum on Bioethics, and other interested parties to address the important challenges identified in this report.

Melody Levine
for Greg Koski, Ph.D.

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June 29, 2001

Michael F. Mangano
Acting Inspector General
Office of the Inspector General
Department of Health & Human Services
330 Independence Avenue, SW (5th Floor)
Washington, DC 20201

Dear Mr. Mangano:

Thank you for allowing us to comment on the draft report on *The Globalization of Clinical Trials*. Public Responsibility in Medicine and Research (PRIM&R) and Applied Research Ethics National Association (ARENA) are dedicated to the protection of human subjects in research. We also have a concern for the public at large who may take medication based on unreliable data. We commend your office for reviewing this important topic and for recommending changes to improve this aspect of human research.

PRIM&R and ARENA are dedicated to advancing the ethical conduct of research. ARENA is a membership organization of 1200 members that promotes individual professional development opportunities and public policy awareness for those involved in the day-to-day application of ethical principles, government regulations, and other policies regarding research. PRIM&R is dedicated to educating, informing, and providing a forum for those involved in the ethical, legal and policy dimensions of research.

In general, PRIM&R and ARENA support the assessment and recommendations made by the Office of the Inspector General. We do, though, have some comments and recommendations for your consideration.

With regard to the second FDA recommendation, "Help inexperienced non-U.S. institutional review boards build their capacity," we believe that more can be suggested to improve non-U.S. IRBs. In the U.S., PRIM&R and ARENA have led the way in providing educational opportunities for IRBs. We recommend that sponsors, with cooperation from appropriate agencies in the foreign countries, foster the development of a system for providing educational resources, using the PRIM&R and ARENA model which has been successful here in the U.S. In the PRIM&R and ARENA model, non-profit organizations have provided IRB members, professionals, and researchers with high quality education experiences. IRB members, professionals and researchers have been given access to ethical and regulatory experts through conferences. The conferences have provided professionals and regulators with the opportunity for open dialogue and communication. In addition, PRIM&R has developed a number of innovative educational initiatives. For example, the IRB 101 course provides basic education on fundamental ethical and regulatory issues. The course is offered not only in conjunction with conferences but also "on the road" and is tailored to meet the needs of the local research

programs. The PRIM&R and ARENA educational offerings are developed with input from individuals in the field and are designed to provide education of ethical, regulatory, and practical aspects of protecting human subjects in research. The concept of encouraging sponsors to foster conferences and innovative education by working with not only U.S. human subject protection experts, but also appropriate agencies and local constituencies in foreign countries is complimentary to the suggestion that sponsors contract with experienced U.S. IRBs. This would be complimentary to the suggestion that sponsors contract with experienced U.S. IRBs.

In general, establishing a mechanism for locally driven education is ultimately preferable to "importing" foreign education, as those charged with developing it will likely be more aware of local issues and therefore more sensitive to them. In addition, a locally designed and produced educational infrastructure will ensure that those who are responsible for its development and implementation are also invested in its continuing relevance and success.

Another mechanism for fostering locally driven education is to establish individual membership associations. One possibility would be to expand ARENA membership recruitment efforts to include individuals from different countries. ARENA could set up divisions in different countries which would provide a framework for educational initiates and networking of professionals within that country.

In the future, a human subjects protection program (wherever it may exist) may need to include a requirement for the voluntary certification of IRB professionals, IRB members, and investigators, hopefully using a uniform international standard. Certification of IRB professionals is not yet widely accepted in the U.S., but there are indications that this requirement is being considered in some quarters. ARENA, for example, has initiated a program to provide certification of IRB professionals by their Council for Certification of IRB Professionals (CCIP). Passing the certification examination results in being credentialed as a Certified IRB Professional (CIP). This certification provides formal recognition of knowledge of IRB functions and human research subjects protection systems. Certification of IRB members and investigators is more controversial, but is being suggested by some Federal agencies.

The third recommendation for FDA action, "Encourage sponsors to ensure that all non-U.S. investigators participating in research for New Drug Application sign attestation indicating that they will uphold human subject protections," should be strengthened. The FDA can do more to encourage sponsors than is presently stated in this recommendation. As long as non-IND investigations that are ultimately used in the NDA are allowed, encouragement is likely not an adequate stimulus for sponsors to significantly change their approach. Sponsors are fully aware of such non-IND investigations as they plan and support them. At a minimum, the rules should be changed so that investigations in which the researchers do not have to sign attestations are not accepted in the NDA presentation. It is not clear from this proposed recommendation whether sponsors have to submit data that has not been collected under an IND as part of their NDA. If they are not required to submit this data, this allows discard of data not favorable to the NDA, and offers a strong motivation to continue doing such studies. There are, of course, other flaws in the system, but this change is one that could be implemented relatively quickly.

We strongly support the fifth recommendation, "Improve the collection of data about location band oversight of research submitted in New Drug Applications." More data about IRBs and investigators are needed both domestically and abroad. Registration of U.S. IRBs is a start. In general, it is difficult to advise the FDA and sponsors about how to oversee and/or conduct investigations abroad when we are not requiring the same level of activity in the U.S.

We certainly agree with the issues addressed in the first recommendation to the OHRP. However, when the OIG recommends an increase in the activities of this office, they should also recommend an increase in resources. Otherwise, OHRP is left with another mandate that, without funding, cannot be properly addressed.

The second recommendation for OHRP is a matter with which PRIM&R is most familiar, as the organization has spent almost three years developing a credible accreditation system for human research protection programs (HRPP). PRIM&R, along with our strategic partner in this effort, the AAMC, has founded and promoted the incorporation of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) to accomplish this goal. While AAHRPP is in its infancy, and it is not yet clear that AAHRPP's voluntary accreditation program will become widely accepted, we do have reason to believe that the community of regulated institutions will embrace a system of adopting voluntary performance standards, self-assessment, and accreditation site visits by their peers. We agree that an international accreditation program would similarly promote a better worldwide protection for human research participants with uniform standards. This will, however, take time and resources that are not yet available. The goal, though, is a worthy one and should be kept alive, and any opportunities to achieve this should be quickly embraced. It should be noted that the Institute of Medicine report to OHRP will not be completed until the middle of 2002, hence its impact on the currently perceived urgent need to initiate an accreditation process in the U.S. may not be great.

In the report, the problem of assuring the qualifications of the investigators is addressed. As stated in your draft report, this review of investigator qualifications occurs only after study subjects have already been placed at risk. This perhaps deserves greater attention, both in foreign and U.S. investigations, as it relates to the assessment of drug safety and efficacy, which may be relying upon possibly unreliable data. Many investigators involved in these studies do not appear to have specific training or expertise in the diseases being studied. The results of these studies provide the efficacy and safety data that ends up on package inserts and in advertisements. It seems essential to propose that the qualifications of the investigators of these trials be ascertained before the studies are initiated to assure their specific competency for doing the proposed clinical trials.

The data presented in Appendix A is somewhat disturbing as it suggests that U.S. investigators do not perform any better than their foreign counterparts, some of whom do not have to meet IND qualification criteria. If there is a contention that foreign investigators do not meet U.S. standards, the data presented do not support that conclusion. Since the OIG Report strongly suggests that the U.S. system should be the model for international investigations, more emphasis should be placed on improving the U.S. system.

Appendix B also raises concern. *The International Ethical Guidelines for Biomedical Research Involving Human Subjects* suggests that "an objective entity in the sponsoring country review the protocol," such as a health administration, research council, or academy of medicine or science. This suggestion delineates the difficulty and complexity in applying the various international ethical guidelines to non-U.S. trials when the U.S. does not hold the same standards. For example, the FDA does not require sites within the U.S. to have an objective entity first review sponsored research for scientific merit. Conversely, the international ethical guidelines do not recommend the use of for-profit, independent, or central IRBs for non-U.S. research, although this is a common practice in the U.S. As stated on page four of your draft report, this inquiry is focusing on sponsored research monitored and submitted in an NDA. However, the draft recommendations involving OHRP encompass federally funded research as well. We encourage the OIG to emphasize in its report the importance of integrated approaches for scientific merit review, ethical research review, trial monitoring, and data submission, both within the U.S. and internationally, regardless of funding source.

We respectfully urge that these comments and recommendations be considered in your final report on *The Globalization of Clinical Trials*. We would be happy to discuss any of these issues with you if that would be of help in this worthwhile endeavor.

Sincerely,

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Comments by Peter Lurie, MD, Deputy Director and Sidney M. Wolfe, MD, Director Public Citizen's Health Research Group on the Draft Health and Human Services Inspector General's Report: The Globalization of Clinical Trials (OEI-01-00-00190) July 5, 2001

While this report highlights the important issue of the increasing internationalization of medical research, it is lacking in three regards: 1. The report fails to draw adequately upon prior research in this area; 2. It fails to adequately emphasize the deficiencies of the data collected by the U.S. Food and Drug Administration (FDA); 3. The recommendations are too weak, even falling below those of the National Bioethics Advisory Commission (NBAC).

Moreover, it cannot be too strongly emphasized that the report's findings apply only to studies intended to result in FDA approval. Particularly because other government agencies may not be as attentive to ethical issues as the FDA and because some research occurs entirely without government oversight, it is important to change the report's title to clarify that it applies only to FDA-regulated studies. Nonetheless, the report's basic conclusion is irrefutable: more and more research is being conducted abroad and the great weight of existing evidence suggests that ethical review in foreign countries, particularly those with limited experience with research, cannot be demonstrated to be equivalent to U.S. review.

1. Failure to draw upon prior research

While an exhaustive review of published articles is beyond the scope of this report, the failure to include even a cursory review results in a document that is diminished inasmuch as it fails to establish that it is addressing a significant public health problem. In the absence of even a summary of evidence in the report that researchers are, for example, conducting research without adequate informed consent or taking advantage of the lack of available medical care to recruit patients and then not providing medically indicated treatment, the finding that there is much more international research is of interest, but does not generate the level of concern that is appropriate. Despite its omission from the report, there is a great deal of evidence of improper research in foreign studies, ranging from HIV vaccine preparedness studies in which informed

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consent was inadequate[1] to the Asian and African perinatal HIV prevention studies,[2] Ugandan tuberculosis prophylaxis study[3] and the proposed Latin American surfactant study,[4] in which known effective treatments were, by design, withheld from poor patients. At least some of these examples must be mentioned. Similarly, the report must at least acknowledge the possibility that research in developing countries is attractive to pharmaceutical companies because costs and ethical protections are lower.

Recently, the NBAC released its report on the ethics of international research. Volume II of the report contains abundant and clear evidence of the deficiencies of both sponsoring and developing country Institutional Review Boards (IRBs).[5] This evidence, too, is lacking from the draft report, a deficiency of particular note because systematic studies of international research practices are few and far between. For example, U.S. researchers responding to the survey indicate that only 22% of pharmaceutical company/biotech studies were reviewed by U.S. IRBs. Elsewhere, the report clearly documents the inadequacies of developing country IRBs. As one developing country researcher stated, "They [local IRBs] are not really concerned about ethical issues, they are looking [at] technical [issues]. And you know, and who [is] giving you money, how much are you getting ... But now [we need to look at] the ethical aspects, what people are doing, is it right." Added another: "... but in terms of who is running these bodies and who is controlling what's really happening, you will be amazed. It is mostly people who have no idea about this. They just know it [ethics] is a word."

The NBAC report states that researchers should attempt to secure availability of effective treatments to both trial participants and members of the general community. Moreover, the NBAC concluded that "clinical trials in developing countries should be limited to those studies that are responsive to the health needs of the host country."[6] These are at the heart of claims that developing country study participants are sometimes exploited by multinational pharmaceutical companies. The absence of any discussion of this issue greatly undermines the report's credibility.

2. Failure to adequately emphasize data deficiencies

This report makes more clear than any previous report just how limited the data on the internationalization of biomedical research really are -- and this in the area (FDA-regulated studies) where the data are among the strongest. Even as there remains little question that more research on drugs intended for approval in the U.S. is being conducted abroad, and that an increasing proportion of the foreign trials are being conducted in developing countries with fledgling ethics infrastructures, the authors of the report can marshall little hard data on these trends. Even the data that do exist are subject to many caveats that emphasize the weakness of the FDA's oversight abilities, but many of these limitations are unfortunately relegated to the footnotes of the draft report. To emphasize the extent of the data drought, these footnotes should be elevated to the report's main body. To summarize, the report finds that:

Lack of data on foreign investigators

- The FDA only has data on investigators conducting research under Investigational New Drug (IND) applications
- Not all research on new drugs is conducted under an IND; the FDA first learns of some research only when the sponsor submits a New Drug Application (NDA)
- IND investigators, domestic and foreign, are required to submit a signed attestation confirming that they will comply with the basic tenets of human subjects research
- These attestations form the basis for the Inspector General's assessment of the growth in foreign clinical trials
- No attestation is required of research not conducted under an IND
- However, even foreign investigators operating under INDs do not always sign such attestations
- Sponsors are not required to submit the attestations to the FDA
- Despite these missing data elements, the number of non-U.S. clinical investigators increased 17-fold between 1990 and 1999
- These data show particularly high rates of growth in the number of investigators from Eastern Europe and Latin America

Lack of data on New Drug Applications

- FDA's database on NDAs does not track information by the location of the research
- Consequently, the FDA cannot describe the trends in NDAs containing data from foreign trials

Lack of data on foreign inspections

- The FDA does not know how many foreign clinical trial sites there are
- Therefore, there are no data on the proportion of foreign sites that are inspected as part of the evaluation of an NDA
- These inspections occur primarily to assure the integrity of the data, not to assure the protection of the volunteers
- Such inspections generally occur only after the study has been completed – too late to correct any unethical practices
- Despite the data limitations, there has been an estimated seven-fold increase in the number of foreign clinical investigator inspections between 1990 and 1999
- Many of the inspections appear not to be in the countries with emerging research programs: Poland had 100 investigators registered with the FDA in 1994-1996 and 190 in 1997-1999, but none of these have ever been inspected. Similarly, none of the 122 Argentinean investigators registered between 1994 and 1996 or the 271 registered between 1997 and 1999 has ever been inspected

3

- Although the FDA has such power, the report does not give any instances of foreign data being rejected because the study investigators did not collect the data ethically (this is an NBAC recommendation) or because an investigator refused to permit an inspection

Lack of data on foreign Institutional Review Boards

- Although there were 250 U.S. IRB inspections in 2000, the FDA has never inspected a foreign IRB
- FDA officials are unaware of a single regulatory agency outside of the U.S. that inspects IRBs
- Thus, the FDA does not know how many foreign IRBs there are, where they are located or how many IND protocols these IRBs have reviewed

Lack of data on foreign study participants

- The FDA cannot track how many participants have enrolled in foreign sites or any trends over time

3. Failure to issue sufficiently strong recommendations

Although the report describes the situation as "serious" and acknowledges that "FDA cannot assure the same level of human subject protections in foreign trials as domestic ones," the recommendations offered are not commensurate with the problems identified.

Recommendations regarding foreign Institutional Review Boards

Ideally, researchers working with INDs outside the U.S. would be required to provide the FDA with the name of the IRB from which they plan to obtain ethical approval and some evidence of its structure and rigor. The FDA could then work with foreign regulatory authorities and the foreign IRB itself to confirm the credibility of that IRB; those foreign regulatory authorities should actually inspect the IRB, something that has not been their custom to date, perhaps in conjunction with the FDA. The report's recommendation that the FDA merely "examine ways in which it can obtain more information about the performance of non-U.S. [IRBs]" falls well short of what is needed.

Recommendations regarding U.S. Institutional Review Boards

Here the problem with the report is not the presence of an inadequate recommendation, but the absence of any recommendation. Current U.S. regulations do not require U.S. companies conducting research in foreign countries to submit their study protocols to a U.S. IRB in addition to the foreign IRB. The NBAC clearly endorsed the need for double-IRB approval: "The Food and Drug Administration should not accept data from clinical trials conducted in developing countries unless those trials have been approved by a host country ethics review committee *and* a

U.S. Institutional Review Board."[6] (emphasis in original) This recommendation from the NBAC would actually be an improvement over existing ethical protections; the Inspector General should strongly endorse this recommendation.

Recommendations for the Food and Drug Administration

The report recommends that the FDA "encourage" sponsors to ensure that attestations are signed. We can see no reason that IND researchers should not be required to sign these attestations, regardless of where the research is conducted. Sponsors should be required to send all attestations to the FDA.

The report presents more than enough data to conclude that any detailed attempt to track trends in international research by the FDA under the present schema is doomed to failure. Some of the report's ideas -- such as the retrospective entry of data from NDAs and extending IRB registration to include foreign boards -- are laudable. Yet, the report's recommendations are couched in polite terms such as "could" and "consider." There is simply no sense of urgency in the report's recommendations, despite the data-collection disaster it describes.

Finally, the report notes that sponsors of gene therapy research are required to submit their monitoring plans to the FDA before the research is conducted. This requirement should be extended to all developing country research conducted with INDs. In addition, the FDA should be responsible for ensuring that all foreign research conducted with an IND is responsive to the health needs of the community and that the researchers have made good faith efforts to assure post-trial availability of effective treatments to the study participants and the general community, as recommended by the NBAC.

Recommendations for the Office for Human Research Protections (OHRP)

The report endorses the OHRP's proposed voluntary approach to IRB accreditation, both domestically and abroad. We can see no advantage to a voluntary approach over a mandatory one, particularly for domestic IRBs. Accreditation of foreign IRBs should also be pursued by requiring sponsors to provide detailed information on their study's IRB to the FDA when they apply for an IND. Sponsors would have a strong incentive to comply with such a regulation.

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1. Karim QA, Karim SSA, Coovadia HM, Susser M. Informed consent for HIV testing in a South African hospital: is it truly informed and truly voluntary? American Journal of Public Health 1998;88:637-40.

2. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. New England Journal of Medicine 1997; 337:853-6.

3. Whalen CC, Johnson JL, Lkwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. New England Journal of Medicine 1997;337:801-8.

4. Lurie P, Wolfe SM, Klaus M. Letter to Tommy Thompson, Secretary of Health and Human Services, regarding planned placebo-controlled surfactant study in Latin America. Available at: http://www.citizen.org/hrg/publications/1558.htm

5. Kass N, Hyder AA. Attitudes and experiences of U.S. and developing country investigators regarding U.S. human subjects regulations. In: National Bioethics Advisory Commission: Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume II: Commissioned Papers and Staff Analysis. Bethesda, MD, May 2001.

6. National Bioethics Advisory Commission: Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission. Bethesda, MD, May 2001.

APPENDIX E

Endnotes

1. This report focuses on those non-U.S. trials that are submitted to FDA in New Drug Applications. Many drug studies are conducted outside the U.S. that do not result in these submissions.

2. Joe Stephens, Mary Pat Flaherty, Deborah Nelson, "The Body Hunters: Testing Drugs on the World," *The Washington Post*, Sunday, 17 December, 2000, through Friday, 22 December, 2000.

3. 21 CFR sec. 56.102 (b)(21)(g).

4. FDA's Investigational New Drug regulations at 21 CFR sec. 312.120 (c) state, in part, that "foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the Declaration of Helsinki" and that "for each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the Declaration of Helsinki or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the Declaration of Helsinki and how they offer greater protection."

5. One difference between FDA regulations and International Conference on Harmonization Good Clinical Practice standards is that FDA is slightly more explicit in its institutional review board requirements, matters such as membership and quorum. In a few areas, the International Conference on Harmonization is stronger. For example, it requires the person obtaining consent to be identified through signature on the informed consent statement.

6. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193, June 1998.

7. FDA can reject the data in a New Drug Application if an investigator refuses to allow an inspection.

8. 21 CFR sec. 312.

9. 21 CFR sec. 312.120. "Foreign clinical studies not conducted under an IND." These state, in part, that "[i]n general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community." They must also be conducted under the principles of the Declaration of Helsinki, or the local country's standards, if they offer greater human subject protections:

(a) Introduction. This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical

principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval of a new drug based solely on foreign clinical data is governed by Sec. 314.106.

(b) Data submissions. A sponsor who wishes to rely on a foreign clinical study to support an IND or to support an application for marketing approval shall submit to FDA the following information:

(1) A description of the investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications, and bioavailability of the specific drug product used in the clinical study, if available; and

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under Sec. 314.126.

(c) Conformance with ethical principles. (1) Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" (see paragraph (c)(4) of this section) or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

(2) For each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the "Declaration of Helsinki" or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the "Declaration of Helsinki" and how they offer greater protection.

(3) When the research has been approved by an independent review committee, the sponsor shall submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. In this regard, a "review committee" means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

10. The Declaration of Helsinki is an international guideline for conducting human subjects research. It was first issued by the World Medical Association in 1964 and most recently revised in October of 2000. The October 2000 revision was a cooperative effort of medical representatives from 45 countries. For this updated version, see http://www.wma.net/e/policy/17-c_e.html, accessed October, 2000.

11. Because these guidelines are more explicit than the Declaration of Helsinki, they meet FDA's criteria of being the higher standard for protecting subjects.

12. In addition, FDA's database for tracking for tracking clinical investigators who conduct drug research does not accurately represent the number of foreign investigators working under an IND who have signed attestations that they will follow FDA regulations, because not all foreign investigators are required to submit them, and not all of those who are required to submit them may be doing so.

The clinical investigator database contains investigator information including name, site, address, and degree, based on information contained in the sponsor's IND submission (Form FDA 1571). This form requires sponsors to provide investigator information either by submitting the attestation form signed by the investigators (Form FDA 1572) or by providing information described in 21 CFR sec. 312.23(a)(6)(iii)(b), which includes "[t]he name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board." The majority of information in the database does come from attestations.

However, because sponsors are not required to submit attestations and because the database does not identify the source of the investigator information, the database can not be used to determine how many foreign investigators have signed attestations. According to 21 CFR sec. 312.53 (c), sponsors of research conducted under an IND must obtain a signed attestation from an investigator "before permitting an investigator to begin participation in an investigation."

13. Department of Health and Human Services, Office of Inspector General, *FDA Oversight of Clinical Investigators*, OEI-05-99-00350, June 2000.

14. Figure 2 does not fully reflect the growth of clinical investigator inspections where the NDA contains foreign data because FDA tracks investigator inspections by the site at which the investigation occurs, not by the content of the data contained in the NDA. As a result, even clinical investigator inspections that occur in the U.S., which are not reflected in Figure 2, may be part of an NDA that contains data from foreign research that goes uninspected.

15. This includes phase 1, 2, and 3 trials. B.L. Natorff, "Clinical Trials in Central and Eastern Europe," Presentation at the 36th Annual Meeting of the Drug Information Association, San Diego, CA, 12 June 2000.

16. The number of approvals includes trials that, despite approval, may have never been launched or may have stopped prior to completion. W. Allen, "Russian Market Meets its First SMO," *Centerwatch* 7 (February 2000) 2:4.

17. K. Kaitlin, "Global Drug Development and International Harmonization: the Emergence of China as a World Pharmaceutical Player," *Drug Information Journal* 32 (1998): 1187S; S. Wanless,

"Ethical and Policy Issues in the Oversight of Human Subjects: Private Sector Roundtable," Presentation at the 39th meeting of the National Bioethics Advisory Commission, Washington, DC, 7 April 2000; C. Statuch, "Clinical Trials is Russia: Are They Really as Good as They Sound?" Presentation at the 36th Annual Meeting of the Drug Information Association," San Diego, CA, 13 June 2000;

and J. DeSilva, "Site Selection for Clinical Trials," *Drug Information Journal* 32 (1998): 1257S.

18. B.L. Natorff, "Experiences of a CRO Operating in Central and Eastern Europe," *EPC International*.

19. P. Loveday, "Clinical Trials in Russia: Are They Really as Good as They Sound?," Presentation at the 36th Annual Meeting of the Drug Information Association," San Diego, CA, 14 June 2000.

20. S. Wanless, "Ethical and Policy Issues in the Oversight of Human Subjects: Private Sector Roundtable," Presentation at the 39th Meeting of the National Bioethics Advisory Commission, Washington, DC, 7 April 2000.

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R.J. Taylor and F. Knox, "A Clinical and Regulatory Perspective on Conducting Clinical Trials in Latin America," *Applied Clinical Trials*, 1999. http://actmagazine.com/articles/act.taylor.cfm, accessed May, 2000; P. Loveday, "Clinical Trials is Russia: Are They Really as Good as They Sound?" Presentation at the 36th Annual Meeting of the Drug Information Association," San Diego, CA, 13 June 2000.

21. L.R. Ptak, "The Globalization of Clinical Research," *Journal of Pharmacy Practice* 9 (December 1996) 6: 418.

22. K.L. Miller and S.L. Pryce, "Better, Faster, Worldwide Too— Update on Pharmaceutical Contract Support Organizations," *Hambrecht & Quist, L.L.C., Industry Report* (4 January 1999): 1.

23. Association of Clinical Research Professionals, *ACRP's White Paper on Future Trends: Faster Time to Market* (1998): 7.

24. S. Engel, "Holding On," *R&D Directions* 6 (September 2000) 8: 109.

25. The three largest contract research organizations are Quintiles, Paraxel, and Covance. The number of countries where contract research organizations are located is constantly changing. Quintiles: "Quintiles Signs Letter of Intent to Acquire Pharmacia's Clinical Development Unit in Stockholm," 30 November 2000,
http://www.quintiles.com/press/press_releases/press_release/1,1286,723,00.html, accessed December, 2000;
Covance Inc.,"Corporate Information," http://www.covance.com/aboutcvd/index.html, accessed December,

2000;
Paraxel International Corporation, "Parexel And Acadia Collaborate to Incorporate Pharmacogenomics Into Neuropsychiatric Drug Development," 28 November 2000 http://www.parexel.com/main.htm, accessed December 2000

26. Kendle International Inc., "Clinical Development in Asia," http://www.kendle.com/asia.html, accessed December, 2000. Information on its plans for global expansion in *1999 Annual Report*.

27. Pharm-Olam International, Inc. From DataEdge "CRO Capability Assessment Service," http://www.dataedge.com/crop.html, accessed December 2000
http://www.norma.dk/htm/exp100.htm

28. W. Allen, "Russian Market Meets its First SMO," *Centerwatch* 7 (February 2000) 2:4.

29. NORMA ApS, "Development," http://www.norma.dk/htm/con100.htm, accessed December, 2000

30. If during the investigator inspection FDA finds evidence of an ethical violation (e.g., lack of institutional review board approval of the protocol prior to conducting the research), it can refuse to accept that investigator's data in the NDA.

31. This is the only information that FDA receives about the board review of research conducted at sites not under an IND application that FDA does not inspect. According to the FDA medical officers that receive these submissions, this is generally very basic information, such as the name and address of the review board and a statement that the board reviewed and approved the protocol.

32. Foreign regulatory agencies, analogous to FDA in this country, may inspect the institutional review boards within their countries. However, FDA officials were unaware of any foreign regulatory agencies that did so. For example, the European Medicines Evaluation Agency, the regulatory agency that oversees all clinical research in the European Union, inspects many different entities involved in clinical trials, but does not inspect institutional review boards. Some regulatory agencies' investigator inspections involve reviewing certain aspects of the institutional review board. FDA does not routinely collect or maintain information on the way different countries' regulatory agencies oversee institutional review boards. Because the extent and type of clinical research inspections conducted by regulatory agencies varies significantly by country, FDA cannot rely on this oversight mechanism to protect human subjects in non-U.S. trials.

33. See endnote 11.

34. According to FDA's protocol for clinical investigator inspections, the FDA inspector should: obtain copies of the protocol and all approvals and modifications; determine whether the protocol changed and whether these changes were approved by the institutional review board before

implementation; obtain consent forms and determine whether consent was sought prior to the subject's entry into the study; determine whether the consent form is compliant with FDA or International Conference on Harmonization -Good Clinical Practice standards; obtain the name, address, and chair of the institutional review board; and determine whether the investigator maintains copies of all correspondence with the institutional review board and whether the investigator reports all deaths, adverse events, and unanticipated problems to the institutional review board. Food and Drug Administration, "Bioresearch Monitoring for Clinical Investigators: FDA Compliance Program 7348.811," 1 October 1997. http://www.fda.gov/ora/compliance_ref/bimo/7348_811/default.html, accessed October 2000

35. Antoine El-Hage, "Preparing for FDA Visits," Presentation at FDA's Clinical Trials 2000 Conference. Rockville, MD, October 6, 2000.

36. For example, an FDA official mentioned a flight to South Africa that cost about $5,000.

37. In some locations, such as parts of Japan and Brazil, lodging alone can be exorbitantly expensive. The listed maximum Federal employee travel rates for certain foreign cities with high costs of living fail to reflect the actual cost of lodging in these cities. Because no hotels are available for U.S. government rates, FDA officials state that they sometimes must exceed maximum rates by up to 300 percent. For Federal per diem allowances see: U.S. State Department, "Maximum Travel Per Diem Allowances for Foreign Areas," Section 925, a Supplement to the Standard Regulations (Government Civilians, Foreign Areas). http://www.state.gov/www.perdiems/2000/0004bperdiems.html, accessed April, 2000.

38. According to FDA guidance, sponsors are responsible for: the selection of adequately qualified and trained monitors; written monitoring procedures; preinvestigation visits to ensure that investigators understand the protocol and understand their obligation to obtain IRB approval prior to conducting the study, as well as to obtain informed consent from each study subject prior to enrollment in the trial; periodic visits to the site throughout the trial, which are to be documented in writing; and a review of subjects' records to ensure that they are accurate and complete. FDA guidance states, "proper monitoring is necessary to assure adequate protection of the rights or human subjects and the safety of all subject involved in clinical investigations and the quality and integrity of the resulting data submitted to the FDA." Food and Drug Administration Office of Regulatory Affairs, "Guideline for the Monitoring of Clinical Investigations," January 1988. http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html accessed October 2000. See also 21 CFR 312.53 "Selecting investigators and monitors."

If a sponsor brings questions to FDA about a non-U.S. non-IND study, FDA will very likely give input and comments, even though such a submission is not required.

39. R.J. Taylor and F. Knox, "A Clinical and Regulatory Perspective on Conducting Clinical Trials in Latin America," *Applied Clinical Trials*, 1999. http://actmagazine.com/articles/act.taylor.cfm, accessed

May, 2000.

40. J. Lee, "Clinical Research in China," *Drug Information Journal* 32 (1998): 1271S.

41. S. Puri, Covance Asia, as cited in CC. Lang, "The Current Status of Clinical Trials in Malaysia," *Drug Information Journal* 32, (1998): 1245S.

42. "Russian Market Meets its First SMO," *Centerwatch* 7 (February 2000) 2:4.

43. S. Shin, "The Current Status of Clinical Trials in the Republic of Korea," *Drug Information Journal* 32 (1998): 1220S.

44. P. Sidley, "Drug Firms in Bind Over Clinical Trials" *Business Day,* 28 August 2000.
http://allafrica.com/stories/200008280121.html, accessed October, 2000.

45. N. Kass and A. Hyder, (Draft) "Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations," *A Commissioned Paper for the National Bioethics Advisory Commission*, (15 June 2000)*:* 25.

46. Ibid., 13, 78, 93, 167-8.

47. Nuffield Council on Bioethics, *The Ethics of Clinical Research in Developing Countries*, October, 2000.

48. World Health Organization's Division of Tropical Disease Research, "Developing the Ethical Review Process," *TDRnews* 61 (February 2000).
http://www.who.int/tdr/publications/tdrnews/news61/ethical.htm, accessed November, 2000.

49. World Health Organization, *Operational Guidelines for Ethics Committees That Review Biomedical Research*, Geneva, 2000.

50. World Health Organization's Division of Tropical Disease Research, "The Ethics of Biomedical Research: Sustainable Activities Begin in Asia and the Western Pacific," *TDRnews* 63 (October 2000).
http://www.who.int/tdr/publications/tdrnews/news63/ethics.htm, accessed November, 2000.

51. In prior reports, we raised concerns about how well such protections are being met in clinical trials in the U.S. and have made recommendations to FDA and other Department of Health and Human Services components. Many Department efforts are currently underway to improve human subject protections in the U.S.

52. National Bioethics Advisory Commission, Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. April 2001.

53. Our interviews, review of the literature, and attendance at conferences suggest that to varying degrees those conditions can be described as follows:

(a) A fragile foundation for independent review: Foreign institutional review boards may lack the support to conduct a review that is sufficiently independent of the research interests. For host countries and their research institutions, participation in clinical trials conducted by international pharmaceutical companies can bring money, prestige, and the opportunity to develop a local research industry. For physicians, clinical trials can present an opportunity to participate in cutting edge research on a multinational scale, and may substantially enhance the income they receive for patient care. For potential subjects, clinical trials can represent the only opportunity to access medications that might help their medical conditions.

(b) A political and cultural environment that may not accord sufficient emphasis to individual autonomy: Human subject protections are based on the principle of individual autonomy. In some environments it can be difficult to ensure the kind of substantive and procedural protections regarded as essential in FDA and international research guidelines.

(c) A limited base of experience in providing human subject protections: The expertise that develops with experience in conducting ethical reviews of clinical trials is lacking in areas where research has not been conducted extensively. Countries with little experience hosting such trials are unlikely to have much of a knowledge base to tap in handling the various aspects of the ethical review process.

54. National Bioethics Advisory Commission, Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Chapter 5: "Ensuring the Protection of Research Participants in International Clinical Trials" April 2001: 82.

55. Ibid.

56. The director of the Fogarty International Center identified bioethics training for researchers in developing nations a priority initiative for the center when he assumed the center's leadership in 1999. The Center awarded grants for training investigators from developing countries to Johns Hopkins University School of Public Health, Albert Einstein College of Medicine, Harvard School of Public Health, Case Western Reserve University, and the University of Toronto. The Center awarded planning grants to University of Cape Town, University of Chile, and University of Pretoria School of Health Systems. "FIC International Bioethics Grants May Support IRB Improvement," *The Blue Sheet* 43 (October 18, 2000) 42: 15.

57. National Institutes of Health, "New Initiatives to Protect Participants in Gene Therapy Trials," 7 March 2000. http://www.nih.gov/news/pr/mar2000/od-07.htm, accessed 5/00. FDA requires sponsors of gene

transfer research to submit their monitoring plans for review prior to conducting research; "FDA Inspecting All NME Applications for Appropriate Clinical Trial Monitoring," *The Pink Sheet* 62 (October 16, 2000) 42: 24. FDA has recently expanded its compliance inspections of sponsor monitors to include examining all new molecular entity applications to ensure appropriate clinical trial monitoring.

58. 45 CFR sec. 86.

59. Outcomes of foreign and domestic clinical inspections, in terms of corrective actions, are comparable (see appendix A). However, FDA officials have stated that they usually detect some problems when they visit areas of the world where clinical investigators are inexperienced in conducting research under FDA or International Conference on Harmonization - Good Clinical Practice guidelines. Each year FDA inspects more countries that it have not previously inspected. One FDA official noted that when inspectors go into new regions they "usually find some kind of problem there that recapitulates historically what [they] have seen first in the United States when [they] started in the '60's and then in the European Union in the '70's and '80's." That is, clinical investigators experience a learning curve in properly conducting these trials. (See D. Lepay, "Ethical Issues in International Research: Overview of FDA," Presentation to the National Bioethics Advisory Commission, Baltimore, MD, 2 December 1999.

60. World Medical Association, *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects,* adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and most recently revised October, 2000. http://www.wma.net/e/policy/17-c_e.html, accessed October, 2000. These guidelines have been revised five times since their original adoption: in 1975, 1983, 1989, 1996, and 2000.

61. Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (1993): 9.

62. Ibid., 25.

63. Ibid., 44.

64. International Conference on Harmonization, *Consolidated GCP Guideline,* finalized May 1996; in implementation phase. http://www.ifpma.org/ich5e.html#GCP, accessed May, 2000.

65. World Health Organization, *Operational Guidelines for Ethics Committees That Review Biomedical Research,* Geneva, 2000.