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An FDA audit is no reason to panic: These 10 steps can help you prepare

Here's what to expect and what you can do

The problem with Food and Drug Administration (FDA) audits is that once you know inspectors are coming, there's really very little you can do. "You can't fix the data," says **Michael Hamrell**, PhD, founder and president of Moriah Consulting in Yorba Linda, CA. "At that point, you can just have the records available and accessible and show the inspectors what they ask for as quickly as possible."

But knowledge is power, and knowing how an audit works can help you sail through, says **Erich K. Jensen**, project manager of the education and certification core at the University of Michigan's Center for the Advancement of Clinical Research (CACR) in Ann Arbor. Jensen has developed a course designed specifically to highlight what happens during an FDA audit and what can be done to make the process as easy as possible.

The first thing is to understand that from the FDA's perspective, "if you did not document it, it did not happen," says Jensen, who has worked in the past with Parke Davis and Warner Lambert (now Pfizer).

"They want to see paper and electronic records," he explains. To a lesser degree, inspectors want to talk to personnel, but only as a means of leading them to records that validate what the interviewees tell them.

For the most part, the investigators, doctors, and study coordinators are the focus of FDA audits. Very occasionally, sponsors are audited, Jensen says. Contract organizations such as labs that do clinical pathology, pharmacies, or biomedical engineering departments that create medical devices may get a visit. IRBs also may be targeted. Usually, says Jensen, an audit covers phase III trials that involve multisite studies. The focus is most often on high patient enrolling sites.

Jensen has divided up a typical audit into 10 steps:

1. Selecting the site. A marketing application usually triggers an FDA audit within about six months, Jensen says. It can be faster if the drug or device is on a fast-track approval. Most often, the three highest enrolling sites are chosen, and if the IRB at a selected site hasn't been

audited in more than five years and is within easy distance of the audit site, then that IRB also may be targeted for an audit.

This all changes if there is a for-cause audit, Jensen adds. Those audits can occur for a variety of reasons, including an investigator who has had trouble before, if the study is of singular importance, or even if there is something in the media that prompts a lot of public attention.

For instance, while Jensen was at Parke Davis, the company was seeking approval for an Alzheimer's drug. The study was being run in the United Kingdom by a prominent physician who advertised in newspapers for patients. The FDA chose to audit that site because of the way enrollment was conducted and the media attention it generated.

For-cause audits also may arise due to patient complaints. The University of Michigan had one such for-cause audit last year at which the FDA spent three weeks reviewing records. Investigators doing a large number of studies or someone working on a study that isn't part of their everyday practice, such as an asthma study done by a cardiology group, also can trigger audits. If a study site has safety and efficacy results that differ greatly from another site or if lab results are "outside the range of biological expectations," then Jensen says the FDA may decide to do a for-cause audit. Lastly, studies that may have a major impact on medical practices may lead the FDA to your door.

2. Contacting the site. The FDA will call to arrange the visit if it is not a for-cause audit. In the latter case, says Hamrell, inspectors may just appear or give minimal notice of a visit. If they do show up unannounced, they already are in a mindset for finding a problem, he adds, and areas of concern on which they will want to focus.

For instance, if inspectors are concerned about enrollment, they'll ask to see appointment books and charts. They may even ask for phone numbers of the patients you have enrolled to check and see if they really were part of the study and showed up for appointments. In one case, Hamrell recalls, a physician made up patients, made up data, and now sits in jail for fraud. "That was a rare and egregious case, but it does happen."

Jensen says that even if an audit isn't a surprise inspection, the FDA will become suspicious if the audit date is delayed by too much time. If staff members are away on vacation, or there is some other legitimate reason for delaying the visit, the FDA likely will be amenable. But he says you want to make it happen as quickly as possible.

During the initial contact, the FDA may request some information in advance. In most cases, auditors probably have data from a drug or

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device marketing application already. However, they might want specific information. Jensen recalls a case where an investigator wanted a list of patients who were screened but not included in the study. "He was looking for some bias," he adds.

If the FDA doesn't request any specific information, Jensen says you can take the initiative and ask if there is something in particular investigators want to look at, or any particular information they would like to see in advance.

3. Arranging the visit. Visits usually last three to five days, Jensen says, although they can go anywhere from one day to six weeks. In a typical audit, inspectors target only a specific study. In a for-cause investigation, they'll review more than one trial.

Once the date is arranged, let all the key personnel know the date and time of the visit — the investigator, IRB, and coordinator must know. In addition, depending on the subject of the investigation, lab and pharmacy personnel might need to know. General counsel should be notified, too, says Jensen, as well as any industry sponsor. In the latter's case, they often have quality assurance departments that will send out teams to help prepare for the inspection and do a mock audit.

Make sure you assign a site escort or facilitator to the investigator. He points out that the most likely candidate for this is the study coordinator or IRB compliance coordinator. This will be the main point of interaction throughout the audit.

Assemble all the relevant documents for the audit in one place, Jensen suggests, paying particular emphasis to requesting patient charts for the trial. If you are at a high-enrolling site, the FDA may say in advance what specific charts it wants. In one recent inspection at the University of Michigan, Jensen says there was three weeks notice and it took the entire time to locate all the required patient charts. In the recent for-cause inspection, the chart for the patient who made the complaint was put on the top of the pile. "It set a really positive tone that we didn't have anything to hide," he notes.

If it is a for-cause inspection, Jensen says to generate a list of all the studies the investigator has done.

Arrange a good workspace for the investigator. If it is a normal audit, don't put the auditors in a room with records from a bunch of different sites, he adds. "They may end up fishing." Ensure access to a photocopier, too. Even better, do the photocopying for the auditors, and make two copies of everything requested. That way, not only do you have knowledge of what they are looking at, but you can keep a record of the process. If you have future contact with the FDA about the audit, you can refer directly to the packet of information you made for yourselves.

4. Arriving at the site. Upon arrival, the inspector presents the site with a form 482. That lists out the regulations under which the FDA is given the authority to inspect. To see a sample of the form, see the FDA web site at www.fda.gov /ora/inspect_ref/iom/ exhibits/x510a.html.

There may be only one inspector or up to three in a for-cause investigation, Jensen says. In the latter case, one may come from the regional office to deal with compliance issues, while others may come from headquarters to review the medical or scientific aspects of the trial.

5. Showing data. The FDA will request that data and documents it wants to see related to the trial being audited. You don't have to show inspectors everything, though. You don't have to present financial information that is not related to the required financial disclosures of the principal investigators and their family members.

You do not have to provide information on salaries or budgets. You also do not have to provide personnel data such as performance appraisals and job ratings. But you do have to show inspectors any job descriptions and training records they request.

6. Interviewing personnel. While the investigator and trial coordinator of the specific study are the most likely people the FDA will want to interview, there may be questions better answered by others, says Jensen. For instance, if there are pharmacy questions, bring the investigational drug expert on your staff to the inspectors. "Pick the most knowledgeable and calmest people you have," he adds. "They will be asked a lot of really minor and seemingly bothersome questions."

Because the FDA is a government agency, nearly all its records and manuals are on-line, including the manuals for inspections. Jensen says he has seen inspectors follow the documents verbatim. A copy of the manual is available at www.fda.gov/ora/cpgm/default.htm.

Jensen says there is a lot of psychology involved in the FDA audit interviews. "Be cool, calm, and collect your thoughts. Be concise."

People often talk a lot when they are nervous. Avoid this temptation, he says. "If you have a closed question that requires only a yes or no answer, that's all you have to say." That said, the FDA is trained to ask open-ended questions. "But try to be short. Be polite, and be cooperative."

It's best to have the information you need at your fingertips, but if you don't, get it. If it will take some time to retrieve, tell the inspectors and explain why.

Never guess at questions, either, warns Jensen. If you don't understand the question, ask for a clarification. If you can't answer, say you don't have the expertise, but you will get someone who does. Don't answer outside the scope of the question or go off on tangents.

And don't ask the auditors unsolicited questions such as, "Is this all you wanted?" or "Did you also want this?" Don't answer hypothetical questions either, like, "How can you do this if you are running six trials?" If you aren't running six trials and never have, you cannot honestly answer the question and you should not try.

Lastly, Jensen says you should never sign affidavits. If an inspector asks you to sign something that summarizes what you just said, tell him or her politely that you have to contact your general counsel about signing anything.

7. Conducting the exit interview. This is usually done with the investigator and study coordinator at the end of the entire audit. However, Jensen recommends that you try to have a mini-exit interview at the end of each day. Ask how things are going and what you can do to prepare for the next day. "You should know along the way how things are going," he says. Such conversations can help to alleviate any misunderstandings and incorrect assessments.

The exit interview will be a recap of the findings and a description of any deviation from the regulations that the inspectors have found. The FDA may, at this time, suggest corrective action, although usually the site is responsible for that. Whatever you do, don't make suggestions to the FDA about what you might do differently at this time.

"I recommend that you give it some thought and time," he says. Tell the FDA that you will get back to them, rather than locking yourself into some new standard operating procedure when all that may be required is a simple small change to the existing policies.

8. Departure.

At this point, the auditor will present a Form 483 (available on line at www.fda.gov/ora/inspect_ref/iom/exhibits/x510b.html). Any observations on the form are not listed in a particular order or ranked.

Hamrell says most of what the FDA finds relates to "sloppy and careless work and a lack of attention to detail." For instance, there might be a missing document or an undated consent form. "A nurse will look at it, a coordinator will look at it, and an investigator will look at it. But no one will notice the problem."

He also has seen a lot of problems with sites not following a protocol. For instance, the study might require a blood draw at a particular visit, but a patient leaves without the draw. "Have a list," Hamrell says. "Check it off before the patient is out the door."

These things sound easy and straightforward, he adds, but they are constant issues that come up in audits.

Other common findings include inadequate and inaccurate records, failure to report adverse events, IRB problems, and inadequate drug accountability, says Jensen.

9. The report. These are forwarded from the local district office for evaluation at headquarters. Anyone can request a copy.

10. Outcome. There are three possibilities: No Action Indicated; Voluntary Action Indicated; and Official Action Indicated. The latter involves a warning letter. Samples can be found at www.fda.gov/cder/regulatory/investigators/default.htm

Having a finding other than No Action Indicated isn't the end of the world, says Hamrell. "It depends on what they are and how severe they are," he says. "It's like a speeding ticket. You may have to pay a fine, but if you do what you have to do, there is no lasting problem. Then again, if you're going 200 in a 25 zone and cause an accident, you may end up in jail."

The consequences for severe problems can be anything from disqualifying the investigator to criminal misconduct and jail time.

"The FDA isn't expecting perfection," Hamrell says. "We are all human. But if you make sure you have the proper procedures in place and you follow them, then you're going to have it a lot easier."

A lot of what happens is just plain carelessness, he concludes.

"Do it right the first time. Check and recheck your data. Review your procedures. If you delegate something to your staff, it still will all come

back to you. Have the checks and balances in place. If you are part of a busy medical practice and you've had a bad day, a busy day with a lot of patients coming through, it can be hard to get it all right. So check it and check it again," he points out. ■

Experts agree: Think recruitment through

Hot tips for warming up recruitment

You'd think it would be easy to recruit patients for studies — just put an ad in the paper or talk to patients at the clinic. Everyone wants to help science advance, right? Maybe, but that doesn't mean they want to be a subject in a clinical trial.

According to data reported in *How to Grow Your Investigative Site*, by Barry Miskin and Ann Neuer, published in 2002 by CenterWatch, it now takes about 4,400 patients to bring a new drug to market. Further, while some 3 million people per year begin studies, only 700,000 finish what they start.

"About 80% of studies have to extend enrollment periods by at least a month," says **Claire Driscoll**, MBA, executive vice president at Clini-Call Patient Recruitment services in St. John, New Brunswick in Canada.

Her company manages phone contact with patients and recruits them for studies through a call center. She has seen many of the mistakes that organizations make regarding patient recruitment. "One of the biggest problems I see is that people think if they hire a call center, patient recruitment will go through the roof. That's a misconception," she says. "It's only one part of a well-rounded strategy that you have to create before you even begin a study."

Indeed, problem No. 1 according to Driscoll, is most investigators and coordinators have no recruitment strategy at all. "A lot of people think they can choose just one thing, like putting ads in the paper or doing Internet recruitment. Worse, they'll say they'll just let the investigators do it for a while, and then if they run into problems, they come to us."

That creates some large challenges, she says. First, if it is a rescue effort, costs go up and time becomes critical. Money may become even more of an issue if the investigator did not budget for the contingency.

"You can't just try stuff willy-nilly," Driscoll says. "Start at the beginning, figure out who you are trying to reach, and create an appropriate strategy for getting to them." Recruitment, she adds, should be one of the first things an investigator and trial administrator discuss.

"A lot of investigators just kind of assume that recruitment will happen," says **Beth Harper**, MBA, senior vice president of global operations at Diane Anderson Company, a clinical trials consulting firm based in Dallas that specializes in patient recruitment.

Start with an in-depth assessment of the study and the targeted patient population, she says. "Make sure you have gone through any database of patients to identify patients who might meet criteria from the start."

Next, consider other physicians or investigators in your community who also might know some good potential patients, Harper says. "If you have a network, tap into it."

Only then should you consider which outside resources to use. Among potential strategies: advertising, placement of articles in the paper, and attendance at local health fairs, Harper continues. "Understand the potential sources for your patients and then put in place a plan for reaching them. Before you begin, estimate how much time it will take, what materials you'll use, and how much money you'll need to recruit the patients you require."

Harper says a frank discussion with the sponsor about resources required is a must. "Will you have to hire someone to go through charts and databases? Do you think you'll need to hire a call center? How much will you need for advertising?" Getting additional funds after the study starts will be much harder than answering those questions at the beginning and asking the sponsor for the appropriate funds then.

Another requirement: Make sure you get your recruitment materials approved early. It can take as long as four months, says Harper. "People often think if they just get through the regulatory paperwork, they'll be fine. But there are often materials that the ethics committee will have to approve, too."

Another problem Driscoll commonly sees is an overestimation of what it takes to get people involved in a trial. "Investigators will tell you they know 15 people who would be just great for the study. But converting good candidates into

people who want to participate in a clinical trial is neither easy nor instant," she says. "Chances are you won't convince all 15 of them."

If you are overseeing a multisite study, be sure to keep in touch with all the sites and monitor how recruitment is going at each. If one particular site is having trouble getting its share of patients, knowing early will help to identify the problem and correct it before your study becomes one of that 80% seeking an extension on the enrollment period.

Harper says administrators and investigators should have weekly meetings about recruitment to see where a study stands and what action, if any, needs to be taken to keep recruitment on track.

Large organizations, such as universities and academic medical centers also may have resources available to assist in patient recruitment. For instance, they may be able to help set up an Internet site to prescreen subjects or provide a toll-free number for screening.

If you do end up using a call center or other organization to help with recruitment, make sure your expectations of what they can do and how fast they can help are not unrealistic. "We can only generate referrals based on the calls we get, and the media planning drives that. If we've done the media part of the recruitment, too, it's not as much of an issue. But if the media doesn't target the right people then we might get hundreds of calls but few appropriate patients."

Part of what drives how successful efforts are is the difficulty of the protocol. If it's a simple one, the screen might take under a minute, and 200 calls can generate 150 potential patients. But harder protocols can require 500 people screened to get the same number of prospective subjects.

Call centers also may offer other services that can help with patient retention. For instance, CliniCall offers appointment setting and appointment reminder services, says Driscoll. "If they offer services like that, take advantage of them."

The costs for these services will vary widely, depending on the complexity of the study, the time frame in which recruitment needs to be completed, and any ancillary services you opt to sign up for. Regardless of what you choose to use, make sure you check references. "If you ask and they won't give you numbers to call, I would go elsewhere," Driscoll says.

Harper says letting a recruitment service know about your past recruitment efforts is key to building a successful relationship. "They should know what has worked for you in the past and what hasn't," she says.

The more you work with the company, the better the campaign will be. You can even work with them on the prescreening script, adds Harper. "Provide good feedback. Tell them how you want the relationship to work, what you need to see in advance, and if you have any good contacts for advertising."

Once you have a potential subject, keeping them involved in the study is often based on making sure they have a realistic understanding of the study. Harper says many patients enroll in studies because they think they'll be getting extra care with a physician. "Make sure that the reality and the message are the same."

Their experience in the study also must be good, and Harper says that means making sure that there is enough staff to handle the patients. "Don't take on more than you can realistically do," she says.

In the end, there is no magic formula, Harper points out.

"People always ask me what kind of ad design makes for the best recruitment. But that isn't what makes something work. It's the non-glamorous stuff like planning that will bring success. The rest is tactics and strategies. And those don't matter if you don't have a good plan, adequate resources, and a willingness to work hard." ■

HIPAA regulations still confuse and confound

If you don't get it, you're not alone

Just about a year ago, the Privacy Rule, which is a part of the Health Insurance Portability and Accountability Act (HIPAA) regulations, became enforceable. Already, complaints are coming in and investigations are being launched — some against mighty organizations such as Kaiser Permanente.

While there has been concern that HIPAA could have a dampening effect on research, the good news is there is no evidence of that happening. The bad news is that most people are still confused by what the regulations require and how that affects the work they do.

According to **Mark Barnes**, a partner at the

New York City law firm of Ropes & Gray, one of the big things that makes HIPAA different from other federal regulations governing research is that this rule applies to virtually all clinical or interventional research that is done around the country. While most federal regulations relate only to federally funded research, this applies to it all.

"The other issue is that this is an overlay of the existing rules and regulations that was not designed to be consistent with those other rules," he says. The Common Rule for protection of human subjects and the rules and regulations of the FDA already are complex. "Now HIPAA comes along, and it has only one value, medical privacy. And even though it is only one thing, it gets complicated."

There are some basics that can help you get through the muddle, says **Kim Gunter**, JD, a partner in PricewaterhouseCoopers pharmaceutical and health sciences practice in Philadelphia:

1. It applies to everything and everyone — sort of. While most federal regulations only apply to federally supported or regulated research, this applies to all research. While most rules apply only to living individuals who are subjects, HIPAA relates to anyone who is the subject of information, living or dead.

But the National Institutes of Health (NIH) is quick to point out that HIPAA is about covered entities, not research. Covered entities are defined as health plans, health care clearinghouses, and health care providers who electronically transmit any health information in connection with transactions for which the department of Health and Human Services (HHS) has adopted standards. Generally, these transactions concern billing and payment for services or insurance coverage.

Researchers are covered entities if they also are health care providers who electronically transmit health information in connection with any transaction for which HHS has adopted a standard.

Hybrid entities may be exempt. These are entities that have both covered and uncovered functions. For instance, if a university has a research laboratory that functions as a health care provider but does not engage in specified electronic transactions, the university, as a hybrid entity, has the option to include or exclude the research laboratory from its health care component. If the lab is excluded from the hybrid entity's health care component, it is not subject to HIPAA.

2. When HIPAA doesn't apply. HIPAA always doesn't have to hamper you. If you are trying to determine whether a study is feasible or are preparing a protocol or if you are identifying prospective research participants, you may not have to follow HIPAA requirements. Keep in mind, however, that to make use of the preparatory to research clause, protected health information can't be removed from the covered entity. That means that if the information is in a physicians' office, there it must stay while it is being used in this fashion.

This is perhaps the biggest problem area that Gunter has seen. "For external researchers, not taking the information off-site is a huge problem," she says. "I have heard of this interfering with patient recruitment. If you do not know who the patient is, you can't contact them for authorization. You can use the data, but you can't use it off-site, and you can't use them without removing them from the office. Sending information over the Internet or fax is no longer an option, and for many researchers, they just don't ever go on-site."

Another exception is studies that get IRB or privacy board waivers. To get one, you must meet the following criteria:

- Use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals because there is a plan to protect health information identifiers from improper use or disclosure, a plan to destroy identifiers at the earliest legally acceptable opportunity, and written assurances that the information will not be used or disclosed to a third party except as required by law.
- Research could not be conducted practicably without the waiver or alteration.
- Research could not be conducted practicably without access to and use of the protected health information.

The other way to get an exception to HIPAA requirements is to de-identify the information. That involves removing 18 separate pieces of information from the data.

You also can use statistical methods to establish de-identification instead of removing the 18 identifiers.

This involves getting certification from "a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable" that there is a very small risk the information could be

used by the recipient to identify the individual who is the subject of the information. The person certifying statistical de-identification must document the methods used as well as the result of the analysis that justifies the determination.

3. Language is an issue. If none of those exceptions apply to your research, complying with HIPAA is not as simple as getting subjects to sign a HIPAA form along with their informed consent document. "Subjects already don't like informed consent forms," says Barnes. "There are a lot of required statements that have to be included. It makes them nervous. And it's well nigh impossible to convey that information at a sixth-grade reading level," Barnes says.

HIPAA has to be at that level, he says, but try saying the following so that a teenager will understand: The research team will collect data covered by HIPAA and only can use your medical information in the ways that are described and allowed by you in this form, but if this form allows them to give your information to people who aren't covered by HIPAA, then those companies and their agents can do what they want with it without penalty. "How can you possibly convey that in a simple manner?"

Helen Hayes Hospital in West Haverstraw, NY, has developed HIPAA language written at an eighth-grade level. **(See sample language at right.)** Additional help is available from the NIH, which has sample authorization language available at http://privacyruleandresearch.nih.gov/authorization.asp#samplelang.

4. Find a privacy officer. You don't have to hire one, but someone has to have the responsibilities of dealing with privacy issues and complaints. In addition, there has to be a privacy board at your institution. This can be a committee of an IRB, or the IRB sitting as a privacy board. The membership and record-keeping requirements of these boards are like IRBs — unaffiliated members are a must, no member may vote on issues or studies in which he or she has a conflict of interest, and privacy boards must include members of varying backgrounds.

5. Check your policies and procedures. Gunter says to check over anything in your current crop of policies and procedures that relates to confidentiality and make sure it complies with privacy laws. If you aren't sure, do some reading, she says. The NIH web site has a section on how HIPAA relates to research. The document is thorough, and about as simple and understandable as this law can be made, "but you'll have to read it through more than once, and it won't give you guidance on all potentialities."

Your general counsel may also be able to help, but Gunter says that office is probably best qualified to tell you about how state laws compare; in cases where state privacy laws are more

Sample HIPAA language

A. "Under current laws, you have control over who has access to your medical records. Any medical information about you that comes up as a result of this research study can be shared and discussed with all the members of the research team for the duration of this study. The research team may include, in addition to Helen Hayes Hospital staff, researchers from other hospitals, universities, drug companies, or government agencies. Some members of the research team may not be required to follow federal laws that protect the privacy of your health information.

B. Although you have a right to see and get copies of your medical records, medical research studies often require that research subjects not be able to see information collected for the research while the research is in progress. Health information about you that becomes available as a result of this study may not be available to you for as long as the research is in progress. You will, however, be made aware of all available information that may make this study dangerous to you, or that may make you want to reconsider your participation in this study.

C. Helen Hayes Hospital needs you to sign this consent form in order for you to participate in the research study. If you choose not to sign this consent form, you will not get the treatments that are part of this study, but you will in no way lose any of the benefits or privileges of any regular Helen Hayes Hospital patient.

D. Even if you sign this consent form you can take back at any time your permission to have your medical information shared by the research team, although some of this information may have been shared already. In order to take back your permission to share information, you have to give a written notice to a member of the research team."

Source: Helen Hayes Hospital, West Haverstraw, NY.

stringent than HIPAA, they take precedence.

6. Get training. You and your staff should be taking seminars on this topic regularly. There is provision in HIPAA for it to be modified annually, Gunter says. The next potential modification comes this summer. There is also technical assistance and guidance that is issued by the government regularly. If you opt not to follow the guidance but to follow the law as it is written for a particular issue — and Gunter says the choice is yours — be sure you cite the law or the guidance as appropriate, and document what you do.

Barnes says he doubts there will be any big changes in the near or medium term. There was a conference at the end of March that included a half-day devoted to how HIPAA has impacted research. In the long term, there may be some changes, but for now, only interpretation of the law is likely to change.

Although it is convoluted and confusing, Gunter contends HIPAA is a good thing.

"It brings us more in line with what is happening internationally," she says. "And since more research happens across boarders, then being more in line with what others are doing is probably a good thing." ■

Protecting children in clinical drug trials

Advocate proposes new laws

Federal laws aimed at encouraging drug companies to study how well their products work in children have had the unintended consequence of weakening already vague protections that prevent child research subjects from being exploited, a leading human subjects research advocate claims.

Passage of the Better Pharmaceuticals for Children Act (incorporated into the Food and Drug Administration Modernization Act [FDAMA]) in 1997 and the preceding Prescription Drug User Fee Act (PDUFA) in 1992 have created an environment in which children have become valuable research commodities, says **Vera Hassner Sharav**, MLS, president of The Alliance for Human Research Protection (AHRP), a nonprofit research advocacy organization based in New York City.

These laws, which provide financial incentives to pharmaceutical companies to perform research involving children, set in motion radical shifts in public policy away from protecting children by setting limits on permissible research risks to a policy aimed at broadening the inclusion of children in trials as test subjects, she notes.

In particular, FDAMA provides an additional six months of patent exclusivity for the manufacturer of pharmaceuticals that have undergone testing in children. Such an extension of patent rights can represent millions of dollars in profit.

In a report published in the *American Journal of Bioethics*,[1] Hassner Sharav presents case studies detailing incidents in which children have been included in research projects that placed them at significant risk of harm without the potential for direct benefit to the child subject (in violation of federal human subjects research protections laws). In fact, in many instances, children are included as research subjects in trials that do not seem likely to yield scientifically valid information for any population.

"Children are being used in ever more speculative experiments, often in the absence of a therapeutic intent, but with a significant chance of harm and/or discomfort," says Hassner Sharav. "The Nuremberg Code provides the best standard for justifying research involving human subjects: 'The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.'"

The code also requires that human subjects give informed consent for participation — that they be informed of all the potential risks and benefits of participation in a given study and then consent to participate free of undue inducement or coercion.

"Children, however, are not capable of exercising the human right to informed consent. Therefore, they need additional protections to prevent their exploitation," she adds.

Parents or guardians must consent to involve children as research subjects, because children are not able to give adequate informed consent themselves. Parents often do not understand the risks involved in research, and may themselves have conflicts of interest that prevent them from putting the interest of the individual child first.

Federal regulations adopted in 1983 preclude the inclusion of children in research involving "greater than minimal risk" unless the project

poses a potential direct benefit to the child.

However, there are no strict definitions of "minimal risk" or "direct benefit" in the regulations, and these terms have been open to wide interpretation, Hassner Sharav argues.

And under the regulations, children may be included in studies that present more than minimal risks to them, if the study will yield generalizable knowledge about the subject's disorder or condition, which is of vital importance. And if all of these standards are not met, inclusion of children still is permissible in studies that present significant risk to them if them if the investigator can demonstrate that the proposed project presents "an opportunity to understand, prevent, or alleviate a serious problem affecting the welfare of children."

These standards provide so much room for interpretation that individual IRBs have wide room for discretion in approving studies that pose considerable risks for children, Hassner Sharav says.

"As currently constituted, IRBs cannot claim to be independent," she argues. "IRBs are compromised by an inherent conflict of interest, and their decisions bear this out."

As examples, she cites a 1996 study approved by the IRB at the National Institute of Child and Human Development that approved an obesity experiment conducted on 100 obese and 92 normal-weight children ages 6 to 10.

The experiment involving fasting, blood tests, X-rays, and a two-day overnight hospital stay during which the children were subjected to painful, invasive procedures. The procedures included insertion of an intravenous (IV) line for 18 hours; a battery of intensive measurements of metabolic rates; a two-hour hyperglycemic claim study involving a second IV line for two hours; blood sampling at five-minute intervals; a three-hour hyperinsulinemic clamp study for two hours with two IV lines; and infusion of glucose and insulin for two hours.

The IRB unanimously approved the study under the federal minimal-risk category, justifying its decision by stating to an investigator from the federal Office of Human Research Protections (OHRP) that: "Several members of the committee explored the meaning of minimal risk and what a child might encounter in a visit to the doctor or while playing in traffic. It was felt that spending several hours in the clinical center in a clamp experiment would be safer than playing actively on sidewalks and streets."

The experiment was later suspended by the OHRP.

The Alliance for Human Research Protection has formulated 10 recommendations for improving research protections for children that include a national review board to oversee research involving children, and the establishment of a fund — supported by fees from drug and device manufacturers — to cover the cost of research oversight.

A national review board could serve in the capacity of a Supreme Court for research by rendering judgments about the appropriateness of specific studies to establish national standards for approval, Hassner Sharav notes.

"The board would be an independent body with one-third of its members nonscientists or not under the influence of industry," she says.

Individual institutions also should have specific child protection committees that function in conjunction with, but independently of, the institutional review boards.

A different view

While Hassner Sharav raises some very compelling ethical points in her report, she doesn't give appropriate equal weight to the need to test pharmaceuticals in children to determine their effectiveness and a safe dose, notes **Howard Trachtman**, MD, a pediatrician and clinical researcher at Schneider Children's Hospital in New York City.

Patient advocacy groups, including advocacy groups for children, have driven much of the change in the drug evaluation and approval process that she finds so many faults with, he says. They have done so precisely because they felt that continuing to prescribe drugs for children in the clinical setting, which had previously largely been tested only in adults, was unethical.

"Vulnerable populations can be vulnerable in two ways," Trachtman notes. "One, you can abuse them and take advantage of them, and the other is that you can be overly protective of them."

He also takes issue with the contention that the potential for financial gain is the driving force behind the expansion of clinical research in children.

"My sense, in reading [Hassner Shirav's] article, was that she was putting all doctors into this group and that we were all doing this for the same reason, which is to make money,"

Trachtman explains. "That is not fair to everybody. There are clearly examples you see in the newspaper where investigators get rich off clinical trials in terms of supplementing their income, but I don't think that is very relevant in pediatrics."

The profit motive in pharmaceutical research, while admittedly powerful, is less forceful in the pediatric community because fewer children are ill and pediatric physician investigators are not as sought after as their adult counterparts.

Most pediatric researchers primarily are motivated by the belief that they are doing whatever they can to find good treatments for their patients to find a cure for life-threatening conditions that affect children, Trachtman adds.

In his experience as an investigator, parents also are highly motivated to learn all that they can about a potential drug or treatment, and they are concerned primarily about its potential to benefit their child vs. the risks involved, he notes.

Children are vulnerable to abuse and exploitation in a number of settings — not just research — and improvements in enforcement of existing protections and oversight systems should be sufficient to protect them without depriving them of the benefits of participation in what could be a very helpful and empowering experience, says Trachtman.

Adding more layers to the oversight process would not have the results that Hassner Sharav and others desire, he states. The solution to improving protections for children, he notes, is in strengthening the quality and support for existing oversight structures.

Because research inherently involves experimenting on test subjects, it is easy to demonize human subjects research as being disrespectful and potentially damaging to human beings without seeing the essential benefits it can provide, he notes.

"The view that the research enterprise is this dark force is not fair," Trachtman says. "Most people that I see, they always want what is best for their kid. Well, where did that best drug come from? It had to come from somewhere; it didn't pop out of the sky. The importance of ethical practice and all of the precautions are definitely justified. It is not reigning in some sort of criminal enterprise, but it is needed to make sure that a basically good enterprise is done right."

Reference

1. Sharav V. Children in clinical research: A conflict of moral values. *Am J Bioethics* 2003; 3(1):Infocus. Web site: www.bioethics.net. ■

On-line university offers controversial course

Wired magazine created a stir by publishing that the human body was worth $46 million, bucking the traditional contention that the human body was worth 97 cents, or $17.18, adjusted for inflation. Now, the educators at New Canoe University (NCU) have developed a course to enable students to tap into some of that intrinsic value and live to enjoy it.

The new course is called, "Body Bucks: How to Sell Your Body to Science While You're Still Alive," and teaches students that income opportunities are literally coursing through their veins.

"By selling body fluids and participating in medical experiments, a human being can earn $20,000 or more per year," says **Bob Heyman**, NCU co-founder and instructor for the course. "Think about it; this is literally the only 'business' out there where you can always carry your assets with you . . . and they're renewable resources to boot."

Heyman says individuals can rent their bodies to drug companies for $150 per day or more. "Additionally, many college students have found

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that supplying their blood, sperm, eggs, and hair to various sources is an easy way to finance their education. We've compiled some of the best ideas and sources into a course from which others can profit."

Before putting a kidney up for sale on eBay, warns Heyman, individuals have to be aware of U.S. laws.

"Participating in medical studies or selling your body fluids is legal, but selling vital organs is illegal in the United States. The course focuses on the parts of the body such as bone marrow, blood, sperm, and hair that can be sold legally." ■

CE/CME objectives

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- review pertinent regulatory mandates;
- develop practical clinical trial oversight strategies;
- review best practices shared by facilities that successfully conduct clinical trials. ■

CE/CME *questions*

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

13. Which of the following situations could cause an FDA audit?
    A. a death of a subject in your study.
    B. a new administration comes into office.
    C. an investigator is conducting a large number of studies.
    D. a marketing application is filed with the FDA.

14. Which of the following is a possible outcome of an FDA for-cause audit?
    A. voluntary action indicated
    B. official action indicated
    C. no action indicated
    D. all of the above

15. Of the 3 million people who participate in studies every year, how many complete what they start?
    A. 700,000
    B. 300,000
    C. 500,000
    D. 2.7 million

16. HIPAA covers:
    A. investigations that are paid for by federal money
    B. investigations using only live subjects
    C. statistically de-identified data
    D. all research that uses protected health information

Answer Key: 13. C; 14. D; 15. A; 16. D