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HUMAN SUBJECTS RESEARCH

Undercover Tests Show the Institutional Review Board System Is Vulnerable to Unethical Manipulation

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Highlights

Highlights of GAO-09-448T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

Millions of Americans enroll in clinical studies of experimental drugs and medical devices each year. Many of these studies are meant to demonstrate that products are safe and effective. The Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) are responsible for overseeing aspects of a system of independent institutional review boards (IRB). IRBs review and monitor human subjects research, with the intended purpose of protecting the rights and welfare of the research subjects.

GAO investigated three key aspects of the IRB system: (1) the process for establishing an IRB, (2) the process through which researchers wishing to apply for federal funding assure HHS their human subjects research activities follow ethical principles and federal regulations, and (3) the process that medical research companies follow to get approval for conducting research on human subjects.

GAO investigated these three aspects of the IRB system by creating two fictitious companies (one IRB and one medical device company), phony company officials, counterfeit documents, and a fictitious medical device.

To view the full product, including the scope and methodology, click on GAO-09-448T. For more information, contact Gregory D. Kutz at (202) 512-6722 or kutzg@gao.gov.

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What GAO Found

The IRB system is vulnerable to unethical manipulation, which elevates the risk that experimental products are approved for human subject tests without full and appropriate review. GAO investigators created fictitious companies, used counterfeit documents, and invented a fictitious medical device to investigate three key aspects of the IRB system. These are the results:

Establishing an IRB. GAO created a Web site for a bogus IRB and advertised the bogus IRB's services in newspapers and online. A real medical research company contacted the bogus IRB to get approval to join ongoing human trials involving invasive surgery—even though GAO's investigators had no medical expertise whatsoever. Since the transaction involved privately funded human subjects research and did not involve any FDA-regulated drugs or devices, GAO's bogus IRB could have authorized this testing to begin without needing to register with any federal agency.

Obtaining an HHS-approved assurance. GAO also registered its bogus IRB with HHS, and used this registration to apply for an HHS-approved assurance for GAO's fictitious medical device company. An assurance is a statement by researchers to HHS that their human subjects research will follow ethical principles and federal regulations, which is required before researchers can receive federal funding for the research. On its assurance application, GAO designated its bogus IRB as the IRB that would review the research covered by the assurance. Even though the entire process was done online or by fax—without any human interaction—HHS approved the assurance for GAO's fictitious device company. With an HHS-approved assurance, GAO's device company could have applied for federal funding for human subjects research.

Obtaining IRB approval for human testing. GAO succeeded in getting approval from an actual IRB to test a fictitious medical device on human subjects. GAO's fictitious device had fake specifications and matched several examples of "significant risk" devices from FDA guidance. The IRB did not verify the information submitted by GAO, which included false information that FDA had already cleared GAO's device for marketing. Although records from this IRB indicated that it believed GAO's bogus device was "probably very safe," two other IRBs that rejected GAO's protocol cited safety concerns with GAO's device. No human interaction with these IRBs was necessary as the entire process was done through e-mail or fax. GAO's bogus IRB mentioned above also could have approved the fictitious protocol, which shows the potential for unethical manipulation in the IRB system.

GAO briefed HHS officials on the results of its investigation. The director of OHRP stated that, when reviewing assurance applications, HHS does not consider whether IRBs listed on the applications are adequate—even though HHS is required to do so by law. In addition, HHS officials stated that the department does not review assurance applications to determine whether the information submitted by applicants is factual.

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to discuss our investigation of vulnerabilities in the institutional review board (IRB) system. An IRB is an entity formally designated to review and monitor biomedical and behavioral research in clinical trials involving human subjects, with the intended purpose of protecting the rights and welfare of the research subjects. Each year, millions of Americans enroll in clinical trials of experimental drugs and medical devices conducted in over 350,000 locations throughout the United States. Many of these clinical trials are meant to demonstrate that products are safe and effective, and are sometimes conducted or sponsored by private pharmaceutical and medical device manufacturers. Although research subjects are required to give consent prior to their participation in these studies, a patient has the expectation that the product being tested presents a risk that is reasonable in relation to any anticipated benefits, and that all risks are fully disclosed. The Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) are responsible for overseeing aspects of the system of IRBs.

Unfortunately the IRB system sometimes fails to protect research subjects. For example, in 2002, a 47-year-old man died after his heart stopped beating while participating in an experimental trial of antipsychotic medication at a Texas research center. Before his death, the man spent 22 days suffering from fever, severe diarrhea, a rapid heartbeat, and kidney failure while under the care of researchers. The warning label for the experimental medication listed some of these serious side-effects and other signs of heart failure, but the IRB failed to ensure the risks were communicated to participants at the outset of the trial. During the clinical trial, the lead researcher continually delegated control of the clinical trial to a man who was unlicensed to practice medicine in the United States. In its follow-up investigation after the death, the FDA noted that the IRB repeatedly violated regulations governing the proper conduct of clinical trials and did not adequately supervise the clinical trial.

Most IRBs were historically located at academic institutions. However, independent IRBs are playing an increasingly prominent role in the protection of human research subjects.[1] Questions have been raised as to

[1]For the purposes of this testimony, we define an independent IRB as a private IRB that is not part of the same organization as the entity whose research is under the IRB's review.

whether all of these independent IRBs exercise effective due diligence in reviewing research protocols. Given the importance of IRBs in protecting human health and safety, you asked us to perform undercover tests to find out whether the IRB system is vulnerable to unethical manipulation. Specifically, we investigated three key aspects of the IRB system: (1) the process for establishing an IRB, (2) the process through which researchers who wish to apply for federal funding assure HHS that their activities related to human subjects are guided by ethical principles and federal regulations, and (3) the process that medical research companies follow to get approval for conducting research on human subjects.

To investigate the process for establishing an IRB, we created a fictitious IRB with phony company officials and only a mailbox for a business location. We then registered our fictitious IRB with HHS using its online registration form. We created a Web site that resembled those of other actual IRBs. We also advertised the services of our bogus IRB in various media, such as Web sites dedicated to the clinical trials industry and newspapers, in an attempt to persuade legitimate medical researchers to send protocols to our bogus IRB. In our advertisements, we stated that we were "HHS approved," in reference to our bogus IRB's registration with HHS. In addition, we emphasized the speed of our review process ("Fast Approval!"), customer service, and flexibility to customer needs in order to make our IRB look as attractive as possible.[2]

To investigate the process through which human subjects researchers who wish to apply for federal funding assure HHS that their activities related to human subjects are guided by ethical principles and federal regulations, we attempted to file a Federalwide Assurance for the Protection of Human Subjects for Institutions Within the United States (assurance) application using HHS's online application form, under the guise of a fictitious medical device company. We created a fictitious medical device company with phony company officials and only a mailbox for a business location, claiming that this mailbox was the facility where we intended to conduct

[2]Concerns about the speed of IRB reviews go back more than a decade. We noted in a 1996 report that some IRBs spent only 1 or 2 minutes on each review, often focusing mostly on reviewing the proposed research study's informed consent forms. See GAO, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72 (Washington, D.C.: Mar. 8, 1996). In addition, the HHS Office of Inspector General noted in 1998 that IRBs reviewed too many research protocols too quickly. See Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193 (Washington, D.C.: Department of Health and Human Services, Jun. 1998).

our human subjects testing. As part of filing for an assurance, we were required to submit information about the IRB that would be reviewing our research protocol, for which we listed our fictitious IRB.

To investigate the process that medical research companies follow to get approval for conducting research on human subjects, we created a research protocol for a fictitious medical device with no proven test history and bogus specifications, using information publicly available on the Internet. We designed our protocol so that it would contain vague information about certain aspects of our proposed study. Our fictitious device was a post-surgical healing device for women that matched multiple examples of "significant risk"[2] devices provided in publicly available FDA guidance. Our bogus medical device company then approached three actual, independent IRBs with information about our device and indicated that we wanted to submit our protocol for review and approval to conduct human testing. We selected these three IRBs by conducting a search online to identify independent IRBs, and then choosing three that we determined had less burdensome initial paperwork requirements than other IRBs for protocol submission. We fabricated additional documents requested by the IRBs for their initial review of our protocol, such as a curriculum vitae (CV) detailing our fictitious researcher's educational and professional experience,[4] and a medical license for our fictitious researcher. We created these counterfeit documents by using information found online and with commercially available hardware, software, and materials. After concluding the undercover portion of our investigation, we contacted two of the three IRBs to obtain information about their review process.

We performed this investigation from January 2008 to March 2009 in accordance with quality standards for investigations prescribed by the President's Council for Integrity and Efficiency.

[2]The FDA draws a distinction between "significant risk" and "nonsignificant risk" medical devices. A significant risk device, defined in 21 C.F.R. § 812.3(m), is one that "presents a potential for serious risk to the health, safety, or welfare of a subject"; a nonsignificant risk device does not present such a danger. For a significant risk device, the sponsor must submit an Investigational Device Exemption application to the FDA for approval before beginning clinical trials. For a nonsignificant risk device, the clinical trial must be approved by an IRB before it begins, but FDA approval is not necessary.

[4]A curriculum vitae generally provides information on a person's education, employment experience, professional memberships, publications, and other qualifications for employment.

Summary

Our investigation shows that the IRB system is vulnerable to unethical manipulation, particularly by companies or individuals who intend to abuse the system or to commit fraud, or who lack the aptitude or qualifications to conduct and oversee clinical trials. This vulnerability elevates the risk that experimental products are approved for human subjects testing with little or no substantive due diligence. We investigated three key aspects of the IRB system using fictitious companies, phony company officials, counterfeit documents, and a fictitious medical device. All communications and information submissions were conducted through the Internet or by fax. As a result, our investigators were never exposed to real-time activities, such as telephone conversations, face-to-face meetings, or site inspections, which would have revealed their lack of expertise, lack of an actual facility, and other fraudulent representations. The results of our investigation are as follows:

- Our bogus IRB received a research protocol and related materials from a real company that was seeking our IRB's approval to add one of its clinics as a new test site for ongoing human trials involving invasive surgery. Our bogus IRB could have authorized human subjects testing to begin at this new test site without needing to register with any federal agency, since the transaction involved a company conducting privately funded research and did not involve any FDA-regulated products.[5] We also registered our bogus IRB with HHS, after which HHS provided us with a registration number and listed our bogus IRB in its online directory of registered IRBs that review federally funded research. Our only communication with HHS as part of registering our IRB was through an online registration form, with no human interaction. The IRB registration process is meant to collect data that HHS uses during the subsequent assurance approval process. As such, HHS is not required to verify the information it receives during the IRB registration process.

- HHS approved our application for an assurance, submitted by a fictitious medical device company. An assurance is required for researchers to receive federal funding from HHS for research involving human subjects testing, and is also used by other federal agencies in their funding approval process. To obtain an assurance, HHS requires researchers to designate, among other things, one or more IRBs to

[5]After we received the protocol and related materials from the real medical research company, we notified it that we were unable to serve its business needs and destroyed the documents it sent us.

review the research covered by the assurance. We successfully used our bogus IRB to obtain HHS approval for an assurance on behalf of our fictitious medical device company, which would have allowed our fictitious medical device company to apply for federal funding for human subjects research. HHS provided us with an assurance number and listed our bogus company in its online directory of approved assurances, thereby helping our fictitious medical device company appear legitimate when we submitted a bogus research protocol to real IRBs, as described below. All contact with HHS was performed through an online application form or by fax.

- One of three IRBs approved our bogus research protocol for human subjects testing after only minor edits to our submission materials, even though we were a bogus company with falsified credentials and an unproven medical device. When we provided the IRB (IRB 1) with bogus information that FDA had already cleared our device for marketing, it did not attempt to verify this information. A search of FDA's online database would have shown no evidence that FDA ever cleared the device for marketing. The remaining two IRBs (IRB 2 and IRB 3) provided us with such thorough comments on our testing protocol and submission materials that we determined we did not have the technical expertise or resources to address their questions and gain approval. For example, IRB 2 noticed that our fictitious protocol mentioned previous testing of the device performed on animals, and requested that we provide a copy of the results from the fictitious animal testing. IRB 3 requested that we send it a copy of the diagram that our bogus researcher would use to record incision lines he made as part of the surgery involved in our fictitious study. All of our communications with the IRBs during their review of our protocol were done by e-mail or fax. After submitting the protocols, we obtained meeting minutes for IRB 1 that showed its board members thought our bogus protocol was "probably very safe" and voted unanimously to approve it. However, in follow-up calls to the two other IRBs, an employee of IRB 2 said the protocol was "awful" and called it "junk." A board member of IRB 3 said it was the "riskiest thing I've ever seen on this board" and indicated that IRB 3's board voted unanimously to reject the protocol. If we had been a real medical device company, we could have used the IRB approval we received to test our device on human subjects even though our research staff had falsified credentials and no research experience.[6] We also could have used our bogus IRB mentioned above to approve our fictitious protocol, which shows the potential for unethical manipulation in the IRB system.

[6]We voluntarily withdrew our protocol from consideration by the two IRBs that rejected our initial proposal, before they conducted any additional review.

We briefed HHS officials on the results of our investigation. They told us that HHS does not review IRB registrations or assurance applications to assess whether the information submitted is factual. Moreover, although HHS is required by law to consider the adequacy of IRBs listed on assurance applications when reviewing applications,[7] the director of OHRP stated that his office would require more staff to do so. HHS officials also stated that the assurance process is not a meaningful protection against unethical manipulation. The director of OHRP acknowledged, however, that an HHS-approved assurance can lend credibility to a company because it means that HHS has recognized that company.

Background

The Secretary of HHS has issued regulations that form the "Federal Policy for the Protection of Human Subjects."[8] This policy is often referred to as the "Common Rule" because 17 other federal agencies that conduct, support, or regulate human subjects testing now follow some form of the policy.[9] The Common Rule lays out the basic policies that should govern any research involving human subjects that is approved, funded, or conducted by the agencies that follow the Common Rule, as well as by all entities that need these agencies' approval of their human subjects research.

Much of the Common Rule focuses on the role of IRBs in the testing process, as IRBs are the primary oversight mechanism for human testing. For example, the policy specifies that there must be at least five members of an IRB, with varying backgrounds, who are sufficiently qualified

[7]45 C.F.R. § 46.103(d).

[8]56 Fed. Reg. 28003 (Jun. 18, 1991).

[9]These other agencies are: Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, U.S. Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, Department of Transportation, Central Intelligence Agency, Social Security Administration, and Department of Homeland Security.

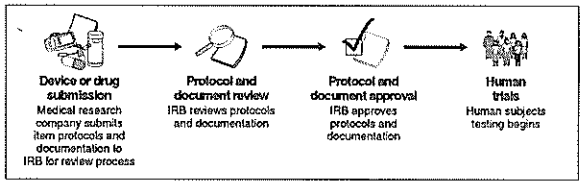
through experience, expertise, and diversity. The IRB must include members who have the professional competence to review the specific research activities being considered, as well as members with an understanding of a testing entity's internal protocols, the applicable law, and standards of professional conduct. Furthermore, among other requirements, the IRB should have members of mixed gender and mixed professions; should include at least one member with a scientific background and one with a nonscientific background; and should not have any members with a conflict of interest with the project being reviewed.

The IRB review process is intended to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. IRBs have the authority to approve, require modifications in, or disapprove proposed research. Figure 1 below provides a simplified illustration of the IRB approval process for human subjects research protocols. By law, clinical trials of experimental medical devices and drugs involving human subjects cannot begin until an IRB has approved the research protocol and any changes requested by the IRB have been made. To approve a research proposal, IRBs must determine that the following requirements are satisfied:

- risks to research participants are minimized;
- risks to research participants are reasonable in relation to any anticipated benefits, and to the importance of the knowledge that the research might produce;
- informed consent will be sought from each prospective study participant or the participant's authorized representative; and
- there are adequate provisions in place to protect research participants' privacy and to maintain the confidentiality of research data.[10]

[10]45 C.F.R. § 46.111, for HHS research, and 21 C.F.R. § 56.111, for FDA-regulated product research, describe these and other requirements for IRB approval of proposed research.

Figure 1: IRB Approval Process for Research Protocols Involving Human Subjects (Simplified)



Source: GAO.
Note: FDA may have oversight functions in this process, depending on the risk level of the device or drug under review and other factors. However, the graphic is intended to provide a simplified illustration of the interaction between an IRB and a medical research company seeking to obtain the IRB's approval for an experimental drug or device.

When seeking to obtain research participants' informed consent to participate in a study, researchers must make sure they offer the potential participants sufficient opportunity to consider whether or not to participate without undue influence or possibility of coercion. In addition, consent forms must contain language that is easily understood, and cannot contain any language that causes or appears to cause the participants to waive their legal rights, or that minimizes or appears to minimize the liability for negligence of the researcher and the sponsors of the research. In addition to reviewing proposed research protocols, IRBs are responsible for conducting continuing review of research at least once a year, or more frequently if the research represents a higher degree of risk to the human research subjects.

IRBs also play a central role in the process by which entities apply for federal funding for human subjects research. An entity must have an approved assurance in order to receive federal funding for research involving human subjects testing from HHS and other federal agencies. An assurance is basically a declaration submitted by an entity engaged in human subjects research that it will comply with the requirements for the protection of human subjects under 45 C.F.R. Part 46. HHS has jurisdiction over human subjects research that is supported through federal funding, and approves assurances for federalwide use.[11] As such, other federal

[11]Federal funding includes grants, contracts, or cooperative agreements under the Public Health Service Act (codified as amended in scattered sections of 42 U.S.C. chapter 6A).

agencies that have adopted the Common Rule may rely on an assurance from HHS for any human subjects research they sponsor. To obtain an assurance, HHS requires an entity to declare to HHS that its activities related to human subjects are guided by ethical principles and federal regulations—the Common Rule—and to designate one or more IRBs to review the research covered by the assurance. In order for the application for assurance to be approved by HHS, all IRBs listed on the application are required to be registered with HHS. IRB registration involves providing HHS with basic information about the IRB, such as the name and contact information for the organization operating the IRB and for its head official, and the names and qualifications of its board members. In evaluating an application to determine whether or not to approve an assurance, HHS is required to consider, among other things, the adequacy of the proposed IRB in relation to the research activities of the entity that submitted the assurance.[12]

Results of Investigation

Establishing an IRB

We succeeded in getting a real company to send a research protocol and related materials to our bogus IRB for its review. As mentioned above, we created a Web site for our bogus IRB that resembled those of actual IRBs, and then advertised the services of our bogus IRB online and in newspapers to attempt to persuade legitimate medical researchers to send protocols to us. In our advertisements, we stated that we were "HHS approved," in reference to our bogus IRB's registration with HHS. We also sought to make our IRB look as attractive as possible by emphasizing the speed of our review process ("Fast Approval!") and flexibility to customer needs. The company that sent materials to us was seeking our bogus IRB's approval to add one of the company's clinics as a new test site for ongoing human trials involving invasive surgery. Our bogus IRB could have authorized human subjects testing to begin at this new test site—even though it was a fictitious IRB, with no medical research expertise whatsoever. Moreover, because this transaction involved a company conducting private (i.e., not federally funded) research, and did not involve any FDA-regulated products, our bogus IRB could have approved

[12]45 C.F.R. § 46.103(d).

the research to begin without needing to register with any federal agency.[13] We also received inquiries from five other real companies, which expressed interest in our bogus IRB's services. However, none of these five companies submitted any materials for us to review.

All IRBs that review federally funded human subjects research are required to be registered with HHS.[14] After we registered our bogus IRB with HHS, HHS provided us with a registration number and listed our bogus IRB in its online directory of registered IRBs that review federally funded research. Our only communication with HHS as part of registering our IRB was through an online registration form, with no human interaction. The IRB registration process is meant to collect data that HHS uses during the subsequent assurance approval process. As such, HHS is not required to verify the information it receives during the IRB registration process. However, our investigation of the assurance process, as described below, shows the importance of IRB registration data as they relate to HHS's evaluation of assurance applications. Moreover, if our bogus IRB had been an actual IRB that did not intend to review federally funded human subjects research, it would not have been required to submit any registration information. IRBs that intend to review privately funded human subjects research are not currently required to register with HHS or any other federal agency, although recently implemented regulations will change this as of July 2009.[15]

HHS's Federalwide Assurance Process

We found that the process for obtaining HHS approval for an assurance lacks effective controls. As mentioned above, we formed a fictitious medical device company with phony company officials and a mailbox for

[13]As mentioned above, after we received the protocol and related materials from the real medical research company, we notified it that we were unable to serve its business needs and destroyed the documents it sent us.

[14]While the registration requirement is currently only HHS policy, HHS recently issued a final rule that will require registration by formal regulation. This regulation, effective July 14, 2009, also expands the amount of data an IRB is required to provide during the registration process. 74 Fed. Reg. 2399 (Jan. 15, 2009).

[15]FDA regulations cover some human subjects research that involves experimental drugs or medical devices, even though IRBs reviewing the research are not required to register with any agency. However, FDA does not currently maintain a comprehensive list of all IRBs involved in testing experimental drugs or devices on human subjects. On January 16, 2009, FDA issued a final rule that requires all IRBs reviewing products that fall under FDA regulations to register with HHS. This rule is effective on July 14, 2009. 74 Fed. Reg. 2358 (Jan. 15, 2009).

its business location—where human subjects research would supposedly be conducted. We then submitted an application to HHS for its approval of an assurance on behalf of our fictitious medical device company. As part of the application, we named our bogus IRB as the IRB responsible for reviewing the research covered by the assurance. HHS approved our assurance application, provided us with an assurance approval number, and listed our bogus medical device company in its online directory of approved assurances. Our only communication with HHS as part of this application was through an online application form and a faxed signature to complete the application. We did not have any real-time contact with HHS, whether by telephone, in person, or through a site visit.

We do not know what verification HHS performed, if any, in its review of our assurance application. However, if HHS had performed basic screening of the assurance application, HHS would have found discrepancies that would have warranted further investigation, such as the fact that we used only a mailbox as our business location. As mentioned above, in evaluating an application to determine whether or not to approve an assurance, HHS is required to consider the adequacy of any IRB designated on the application, as the IRB will be responsible for overseeing the research activities of the entity that submitted the assurance application. By approving our assurance application, HHS essentially deemed our bogus IRB as adequate to oversee human subjects research, as conducted by our fictitious medical device company. Moreover, by obtaining an approved assurance from HHS, our fictitious medical device company can apply for federal research funding from HHS or other federal agencies.[16] In addition, we used the assurance approval to boost the credibility of our fictitious medical device company by posting our assurance number on the fictitious medical device company's Web site.

The IRB that approved our fictitious medical device protocol, as discussed below, is listed on HHS's Web site as being involved in more than 70 assurances on behalf of actual medical researchers. Each of these assurances is a first step for the medical researcher to apply for federal

[16]Although assurance approval from HHS allows us to apply for federal funding for our research, it does not necessarily mean that we would have been awarded such funding. However, as our investigation was designed to test HHS's controls during its process for evaluating assurance applications, we determined that the actual process of applying for federal funding for human subjects research was beyond the scope of our investigation.

funding for human subjects research, with this IRB formally designated to oversee the research.

IRBs' Research Protocol Approval Process

We were able to get an actual IRB to approve a fictitious protocol for human subjects research, which raises concerns that other IRBs may conduct protocol reviews without exercising due diligence, thereby exposing research volunteers to significant risk. For this test, we created a research protocol for a fictitious medical device with no proven test history and bogus specifications, and sent the protocol to three actual, independent IRBs under the guise of the medical device company we created for obtaining an assurance from HHS in our second test, as mentioned above. Our protocol offered only vague information about certain aspects of our proposed study and was designed using information publicly available on the Internet. As mentioned above, our fictitious device was a post-surgical healing device for women that matched multiple examples of "significant risk" devices provided in FDA guidance. In addition, we fabricated additional documents we needed to submit along with our protocol, such as a CV detailing the educational and professional experience of a fictitious researcher at our company, and a bogus medical license for the researcher. We succeeded in getting our fictitious protocol approved by an IRB, even though we were a bogus company with falsified credentials and an unproven medical device. If we had been a real medical device company, we could have begun testing our "significant risk" experimental device on actual human subjects. We also could have used our bogus IRB mentioned above to approve our fictitious protocol. This shows the potential for unethical manipulation in the IRB system.

The IRB that approved our bogus research protocol (IRB 1) required only minor edits to our submission materials, and did not verify that the information contained in our protocol and related materials was correct or authentic, or even that our medical device company actually existed. For example, we provided IRB 1 with bogus information that FDA had already cleared our device for marketing because our device was found to be

substantially equivalent to an existing, legally marketed device.[17] IRB 1 did not attempt to verify this information even though a quick check of FDA's online database would have shown no evidence that FDA had ever cleared our device. By taking advantage of this lapse, our investigators—who lacked technical expertise in this subject—bypassed any requirement to develop a risk assessment for a device that, under normal circumstances, would be considered "significant risk" according to FDA guidance. Meeting minutes from IRB 1's board meeting show that it accepted the bogus information about FDA clearance of our device as evidence that our device did not require any further risk assessment. See figure 2 below.

Figure 2: Excerpts from IRB 1's Board Meeting Minutes, during Review of Fictitious Medical Device Protocol

B) NEW SPONSOR SUBMISSIONS

1) Medical Device Studies

(a) Device [redacted] Study of Safety and Efficacy of [redacted]

1. Note: This Device falls under a 510k and risk assessment is not required.

(i) For Review: Protocol, Version [redacted]

2. • Decision/Vote: Approve # Voting: 7 # For: 7 # Against: 0
[Abstain/Recuse]: 0 Names(s): [Enter member's name]

3. [Device] [redacted] is probably very safe; this is a pilot study & first-time use in humans. [redacted]

Excerpts from meeting minutes
1. "...risk assessment is not required."
2. Unanimous approval of item with no dissenting votes (7/7)
3. Device referred to as "...probably very safe..."

Source: IRB 1

[17]FDA's 510(k) premarket notification process includes a determination of whether each new device (1) has the same intended use as an existing, legally marketed device, and (2) the new device has the same technological characteristics as the existing, legally marketed device, or has different technological characteristics and submitted information shows that the new device is as safe and effective as the existing device. If FDA determines that the new device is substantially equivalent to a legally marketed device, the manufacturer may market it immediately. For more information about the 510(k) process and the more stringent premarket approval process, see GAO, *Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process*, GAO-09-190 (Washington, D.C.: Jan. 15, 2009).

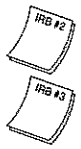
IRB 1 "conditionally approved" our protocol after a full board review, but requested that we modify our informed consent form for study participation in order to make the language understandable at a fifth-grade reading level. We modified our informed consent form as requested by using medical information found on the Internet, after which the board members of IRB 1 voted unanimously to approve our fictitious medical device protocol (see fig. 2 above). IRB 1 approved our fictitious protocol, thereby authorizing us to begin human testing, after only contacting us by e-mail or fax, and never by telephone or in person. IRB 1's board meeting minutes indicate that it believed our device was "probably very safe," as shown in figure 2 above. Although our protocol mentioned fictitious animal studies that we conducted on our device to ensure its safety, IRB 1 approved our protocol without ever seeing proof of these studies or any other evidence that our device was reasonably safe for use in human subjects. On its Web site, IRB 1 advertises the speed of its reviews and states that it performs a "triple check" for quality. IRB 1 has approved research protocols for experimental drugs tested by major pharmaceutical companies.

The remaining two IRBs (IRB 2 and IRB 3) provided feedback on our protocol that was so extensive we determined we did not have the technical expertise or resources to gain approval. The extensive nature of the feedback IRB 2 and IRB 3 provided on our initial submission materials indicated that they follow a much more thorough review process than IRB 1, which approved our protocol. For example, IRB 2 noticed that our fictitious protocol mentioned previous testing of the device performed on animals, and requested that we provide a copy of the results from the fictitious animal testing. In addition, IRB 3 requested that we send it a copy of the diagram that our bogus researcher would use to record incision lines he made as part of the surgery involved in our study, and raised a number of questions about the timing and locations involved in our fictitious testing. The documents and information that IRB 2 and IRB 3 requested would have taken extensive time and research to fabricate, and demanded a level of technical expertise that we did not possess. IRB 1 approved our protocol without obtaining any of the additional information requested by IRB 2 and IRB 3.[18] Our contacts with IRB 2 and IRB 3, during their review of our protocol, were done entirely by e-mail.

[18]As mentioned above, we voluntarily withdrew our protocol from consideration by the two IRBs that rejected our initial proposal, before they conducted any additional review.

We later interviewed representatives from IRB 2 and IRB 3 to obtain additional details about why they did not approve our protocol. Representatives from both IRBs expressed concern that our protocol did not contain adequate information about the safety of our fictitious medical device. For example, the manager of IRB 2 said that she worried that our device could cause infection in patients, or possibly even cause patients to develop sepsis.[19] In addition, a board member from IRB 3, who claimed to have 15 years of experience reviewing research protocols with this IRB, stated that our protocol lacked any evidence that our bogus medical device was actually safe for implantation into a human body.[20] He also said that IRB 3's board voted unanimously to reject our bogus protocol. Figure 3, below, shows additional examples of IRB 2's and IRB 3's comments on our fictitious medical device and protocol.

Figure 3: Examples of Statements by IRB 2 and IRB 3 Regarding Our Bogus Medical Device and Protocol



Protocol was "awful" and a "piece of junk"
"Did somebody else approve it [the protocol]? Oh, boy ..."

Protocol was the "riskiest thing I've ever seen on this board"
Protocol was the "worst I've seen ... too risky"

Source: GAO.

None of the three IRBs questioned us about the authenticity of our bogus CV and counterfeit medical license. As mentioned above, we fabricated these documents by using information found online and with commercially available hardware, software, and materials. Our bogus CV contained information on our fictitious researcher's human subjects research background, which we created by using phony drug and device names and with information that we accessed on the Internet. Our counterfeit medical license contained a bogus license number with a similar format to real license numbers used by the state we claimed our license was from.

[19]Sepsis is a life-threatening illness caused by a human immune system's overreaction to bacterial infection, which may lead to organ failure and death.

[20]We did not verify the accuracy of the claims from IRB 2 and IRB 3 about the health risk posed by our fictitious medical device.

Briefing with HHS

We briefed HHS officials on the results of our investigation. They stated that HHS receives around 300 IRB registrations and 300 assurance applications every month, and that OHRP currently has three employees who review all registrations and applications. According to HHS officials, the department does not review IRB registrations or assurance applications to assess whether the information submitted is factual. HHS officials said that the department reviews assurance applications to ensure that applicants have submitted all of the necessary information and meet minimum standards. Moreover, although HHS is required by law to consider the adequacy of IRBs listed on assurance applications when reviewing applications,[21] the director of OHRP stated that his office would require more staff to do so. However, HHS officials added that they would not consider additional evaluation of IRB registrations or assurance applications to be worthwhile even if the office had increased resources.

HHS officials stated that the assurance process is not a meaningful protection against unethical manipulation. They stated their belief that anyone submitting false or misleading information as part of the assurance application process would likely be detected during the subsequent process of applying for federal funding for human subjects research. However, our work shows that an unethical company could leverage an HHS assurance for purposes unrelated to the federal funding application process. For example, representatives from one of the IRBs that rejected our protocol stated that the HHS assurance number listed on our bogus medical device company's Web site gave our company credibility because it meant that HHS had recognized our company. When we discussed this with HHS, the director of OHRP acknowledged that an HHS-approved assurance is meaningful in this regard.

Mr. Chairman, this concludes our statement. We would be pleased to answer any questions that you or other members of the subcommittee may have at this time.

[21]45 C.F.R. § 46.103(d).

Contacts and Acknowledgments

For further information about this testimony, please contact Gregory D. Kutz at (202) 512-6722 or kutzg@gao.gov. Contacts points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. GAO staff who made major contributions to this testimony include Matthew D. Harris, Assistant Director; Matthew Valenta, Assistant Director; Timothy Persons, Chief Scientist; Christopher W. Backley; Ryan Geach; Ken Hill; Jason Kelly; Barbara Lewis; Andrew McIntosh; Sandra Moore; James Murphy; and Seong B. Park.

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