When disaster strikes: In Katrina’s wake, IRBs struggle to regroup

Finding and protecting research subjects is institutions’ first priority

By now, everyone has seen footage of the horrible damage wrought by Hurricane Katrina on the Gulf Coast — more than 1,000 people dead, more than a million displaced, cities flooded and left in ruins.

But over the months since the hurricane blew ashore in late August, it has become apparent that Katrina also dealt a devastating blow to medical research in the New Orleans area, dispersing research subjects, destroying samples and wrecking facilities.

Now IRBs at Louisiana State and Tulane universities displaced by the storm are engaged in the huge task of locating subjects to ensure their safety and reconstructing IRB operations.

Most of LSU’s operations were moved to buildings on LSU’s Baton Rouge campus. The university set up an emergency web site, where IRB Chair Kenneth Kratz, PhD, posted notices directing investigators to get in touch, and to give the IRB a status report on all open studies.

Kratz says his staff is aggressively seeking out investigators and subjects, continuing to take on new trials, and continuing to oversee studies interrupted by the storm when possible, while dealing with a loss of resources, including staff laid off in the aftermath of the hurricane.

Tulane’s IRB operations and its Office for Grants and Contracts have moved even farther to the University of North Carolina-Chapel Hill, where Ina Friedman, MSN, NP-C, director of the school’s Office for Human Research Protection has set up shop at the invitation of former colleagues. There, the university gave her office space, a computer and laptop, fax and phone lines which gave her the capability to set up IRB meetings by conference call because members are scattered across the country.

“We are all over the place,” Friedman says. “But the Internet is an amazing thing, and once you find everybody, you go to work.”

She, too, is concentrating on locating subjects whose care has been interrupted by the hurricane, while taking the first steps toward helping the IRB regroup and move forward.
Both admitted to leaving so quickly that they left their laptop computers behind. “When somebody asks, ‘If this happened again, what would you do?’ I’d say, ‘Take your laptop because you’re crippled without it,’” Friedman says.

Kratz says the immediate aftermath of the hurricane left his IRB without any way for staff to communicate with each other. “You could not make a telephone call to New Orleans, you could not make a telephone call to the Baton Rouge area or the surrounding metropolitan areas across the lake,” he says. “It was impossible to get any number with those area codes for a long time.”

He notes that the university’s servers were down, so e-mail communication was impossible as well. “The only thing that was effective for a number of weeks was text messaging,” Kratz says. “Through text messaging, I was able to find my staff, which had been dispersed all over, to Houston and Georgia and Boston. Once I was able to find them and we all had alternate e-mail addresses, we could then start communicating by e-mail.”

Locating subjects is an uphill battle

The first priority has been finding subjects, many of whom have scattered to the winds and are on medications they can’t get elsewhere. It’s an uphill battle, particularly among the indigent patients LSU saw at the public hospitals where it operated, Kratz says. He estimates that for some studies, the school has lost contact with all of the enrolled subjects.

“We hope that those people, if they had some sort of illness, would get themselves to a physician somehow,” he says. “What’s problematic is that it may be difficult for them to relate to a physician in another town what the clinical trial was and how they were being treated. That has bothered me quite a bit.”

He says the IRB has advertised locally, asking subjects to call in to be reunited with their physicians, but for the thousands who have left the area and even the state, that won’t do much good.

Tulane’s IRB has faced a similar challenge in locating investigators and subjects, Friedman says. She, too, is concerned about the health of subjects who were participating in clinical trials. “Even if they were on a placebo, if they’re not being monitored, we don’t know if they need a
change in the therapy or some type of rescue therapy,” she says. “The same thing goes for people who have implanted devices. They need follow up.”

Friedman says investigators have been providing status reports on their subjects, and they and the IRB staff are working to try to find subjects.

Some investigators have set up their own toll-free numbers, and sent it out to physicians in the Gulf Coast area who specialize in the conditions being studied.

“For example, the people who see pediatric HIV patients have sent this number to all the pediatric infectious disease physicians in the Gulf Coast, asking them to be on the lookout for Tulane patients and to ask them to contact the 800 number if they identify them,” she says.

Survivor web sites on the Internet, such as those operated by the Red Cross, have been very helpful in locating people. She says The Times-Picayune, New Orleans’ local newspaper, has recently set up a site where physicians and patients can reconnect, and her staff have been examining that site to try to find subjects.

Friedman is optimistic that Tulane will be able to locate subjects at the most risk.

“We feel like we’ve gotten good responses from the investigators who see patients where we’re really concerned that the interruption of the therapy makes a big difference,” she says.

Both Kratz and Friedman say the problems they’ve encountered have led them to advocate creating centralized databases of research subjects at their institutions. The database would include primary and secondary contact information for subjects, so that the problems the IRBs currently are encountering could be avoided in the future.

Both noted that much of the contact information they had for subjects was useless, since people were no longer in their homes.

“If I were in a study, for example, I could give my sister’s name and phone number in New York,” Friedman says. “Maybe our 504 area code doesn’t work, but if we have alternate phone numbers and people checked in with their family, we can find them.”

Kratz says that when the idea had come up in the past, he was reluctant, citing concerns about privacy and other problems a separate database could pose.

“But in light of this, I think it’s important, because I’m concerned about some of these people,” he says. “Some may be on medications that should not be terminated quickly. You wonder what’s happening in those situations, and unfortunately, we just don’t know.”

Kratz says he’d like to ask investigators to give participants cards bearing as much information as possible about the trials and how to reach the investigators in an emergency.

Business as usual

In addition to locating subjects, the IRBs also are struggling to move forward, reapproving existing studies if the investigator and sponsor are willing, and even approving new studies when possible.

Both Friedman and Kratz have been in contact with the FDA and OHRP, which they say have posted guidelines on post-Katrina operations.

Kratz notes that in addition to the physical damage caused by Katrina, the destruction also has demolished revenue streams to the university, leading to furloughs and layoffs. He himself has had to lay off two IRB coordinators.

“In some respects, the reduced level of activity we’ve got is good, since we don’t have the magnitude of infrastructure to handle a lot of stuff right now,” he says.

Friedman and Kratz offer this additional advice to IRBs rethinking their disaster plans:

- **Make sure your information is stored somewhere off site.** Friedman suggests some place that is geographically remote, since a disaster such as Katrina can affect a very large area.

- Kratz says that luckily, his organization had recently switched to an IRB management software system in which information is stored on a server in New York.

  “Even though my staff were spread out throughout the country, we had immediate access to our IRB information,” he says. “It has made things a lot easier.”

- Friedman also suggests splitting physical samples such as blood and tissue, and keeping a set stored remotely as well. She says much of Tulane’s stored blood and tissue samples were lost because of weeks long power outages in the storage buildings.

- **Defer to other IRBs, when possible.** Friedman has deferred many studies, both existing studies and new requests, to other IRBs across the country with FWAs. “We are deferring as many of them as possible because logistically, you just can’t handle a load like you do when you’re set up in your own office.”
• Remember that IRB staff are affected by disaster, too. “Many of our clinicians, our investigators, lost their houses,” Kratz says. “They have personal problems they’re trying to cope with on top of work issues. Compound that with the financial situations of the institution — they’re worrying about their jobs, worrying about the people who work for them — it’s stressful for everybody.”

**Hurricane research proposals surge**

*Increase strains social-behavioral IRBs*

One unexpected result from Hurricane Katrina has been a sharp increase in proposals for social-behavioral studies, as social scientists seek to find out how Katrina survivors and evacuees have responded to the disaster.

That has created challenges for IRBs at Louisiana State and Tulane universities, as they attempt to absorb the increased number of proposals, while protecting a potentially vulnerable evacuee population.

Robert Mathews, PhD, chair of the social-behavioral IRB at LSU’s Baton Rouge campus, says he expected to see an increase in study proposals in the wake of Katrina, but the sheer volume of applications has surprised him.

“I would say that the number of proposals we handle has quadrupled,” Mathews says. “They began flowing in immediately and are still flowing in.”

**More frequent meetings**

He says that while special funding has been made available for Katrina-related research, the deadlines allow for only a short turn-around time for proposals. And because Mathews considers evacuees to be a population that needs special protection, he made the determination that all such proposals must be handled by the full IRB. That has meant a stepped-up schedule of IRB meetings.

“Our normal procedure for full board meetings is we only meet every other month, and we normally send out protocols two weeks prior to a meeting,” he says. “Obviously that couldn’t happen here. So I had to schedule special meetings about every three weeks. We had to hand deliver the protocols to every member on the board five days before the meeting so they’d have time to review them.”

Of Tulane’s three IRBs — two biomedical and one social-behavioral — only one biomedical board is operating, says Ina Friedman, MSN, NP-C, director of Tulane’s Office for Human Research Protection.

She, too, has seen a surge in Katrina-related research proposals and is expediting a number of them herself.

But Friedman also is worried about the vulnerability of the evacuee population, so any proposal involving more than minimal risk is going to the full board. “If the research is anything other than an anonymous questionnaire, I’m pretty much sending it to a full committee,” she says.

Friedman says she does have input from a few of Tulane’s social-behavioral board members at the IRB board meetings, which she currently is conducting via conference calls. She also regularly consults with the social-behavioral IRB at the University of North Carolina-Chapel Hill (UNC), where Tulane’s IRB is housed temporarily.

**Concern about PTSD**

Mathews says his principle concern about evacuees is the possibility that they may suffer from post-traumatic stress disorder (PTSD), which could come to light during a study.

His IRB discussed the matter at length and now requires researchers to be ready to refer subjects for treatment, including free treatment if the subject is impoverished.

If children being studied show signs of PTSD, the IRB requires that the child be withdrawn from the study immediately and that the parents be notified.

“They have to put into the consent form for these kinds of studies with children that there is a risk of becoming emotionally upset, and if their child becomes upset, we will notify the parent,” Mathews says. “And we felt it was important not only to tell parents that but in the consent form, to tell kids that if they get upset we’re going to tell their parents so they can get help.”

Friedman says Tulane’s IRB also is requiring referrals for help for subjects who need it. “In cases where [researchers] are looking for significant depression or suicidal ideation, they also disclose that this has to be reported to the appropriate authorities,” she says.
Mathews says that there was some discussion on his board as to whether subjects showing full-blown PTSD were even capable of giving consent to participate in research, but finally concluded that they should be allowed to participate, particularly in studies that might benefit them. “For example, there’s one study about helping people avoid substance abuse — it seems like they should be able to participate in those studies,” he says. “But it’s an issue that’s very gray at this point.”

Although most of the studies Mathews’ IRB is reviewing do not provide for compensation, some of the longer ones do. He says the board has taken care to ensure that the compensation is not so great that it could prove coercive, particularly to people who may have lost nearly everything they owned in the flooding.

He notes that some survivors of the Sept. 11, 2001, terrorist attacks were offered $100 for their participation in studies after that event. But Mathews says the economy of the New Orleans area is quite different from that of the Northeast.

“We felt like $100 would be excessive in this instance, so we were thinking more along the lines of $25 for an hour of participation would be more appropriate.”

Mathews advises IRBs who have to cope with a similar disaster scenario to take advantage of the information on OHRP’s web site.

He also notes that he was fortunate to have a clinical psychologist serving on his IRB.

“We had a lot of information about what those [psychological] effects would be like and where to refer people,” he says. “But if I didn’t have that asset, that would be a problem. So I would advise looking into that ahead of time — when people need help, where are you going to send them after an event?”

Is sharing results a moral obligation?

A re investigators morally obligated to provide research participants with the chance to see the results from the studies in which they enroll — and should IRBs require them to do so?

Some researchers argue that they should, calling it a matter of respect for the people who literally give of themselves — their time and their bodies — to help advance science.

But they say it’s not simply a matter of sending a letter with results to all participants in all studies. Some patients may not want to know the results. Some studies are so sensitive that they would require a carefully thought-out plan for approaching subjects with their results, perhaps through face-to-face interviews.

Ann Partridge, MD, MPH, an oncologist at Dana-Farber Cancer Institute and instructor in medicine at Harvard Medical School in Boston, has studied the attitudes of breast cancer patients regarding receiving results from clinical trials in which they’ve been enrolled.1

She says each study is different, and IRBs should approach the issue of results just as they would informed consent, tailoring the requirements to fit the study and the patient population involved.

“I think IRBs need to be sensitive to the varied nature of results,” Partridge says. “Investigators need to think through beforehand what are the possible outcomes of this study and worst case scenarios, what’s the most sensitive, patient-friendly, and also practical way of sharing those results.”

Few provide results now

Currently, few investigators provide results to their subjects, and it is not a common IRB requirement, says Conrad Fernandez, MD, FRCP, an associate professor of pediatric hematology and oncology at Dalhousie University in Halifax, Nova Scotia.

In a study published this summer in Blood, the journal of the American Society of Hematology, Fernandez surveyed 450 authors of abstracts presented at the society’s annual meeting in 2003. Of the nearly 200 respondents, only 30% had a formal plan for returning research results to participants, although nearly 70% supported the idea.

Only 7% of respondents indicated that their IRBs mandated that research results be returned to participants. Fernandez says the results were consistent among U.S., Canadian, European, and other international researchers.

When asked why they had no plans to return results, “a substantial proportion indicated that they had just never considered it something that was an obligation,” Fernandez says.

Researchers also cite obstacles such as difficulty maintaining contact with subjects over time, and the potential cost of returning results.
Fernandez concedes that such an endeavor could be costly, depending on the type of plan required by a specific study.

For studies in which the results were expected to be uniformly good, the researcher could plan from the beginning to distribute results by letter, which could be relatively inexpensive, he says.

But Fernandez says other studies could raise issues that would require more careful treatment of results and subjects, particularly where individualized results are concerned. For example, genetic research could give a subject information such as a predisposition to illness that they might not want to know, for their own peace of mind or because of fears of losing insurance.

“Also results might be potentially harmful in other ways,” Fernandez says. “They may cause distress in reliving the initial event of their diagnosis and research participation. There may be distress because they happened to have been randomized to an inferior arm and did more poorly.

“They also may know of individuals who participated in the same study and if they got randomized to the positive arm, there may be survival guilt,” he says. “That’s very true for our pediatric patients — a lot of them know each other.”

In these cases, he says, the return of results may need to be in a face-to-face, even in a one-on-one setting and researchers may need to refer them to counseling or other services as needed, he says.

As an example, Fernandez cites research done on pediatric patients with Hodgkin’s disease, which showed that those treated with radiation therapy have an increased risk of breast cancer later in life. “That kind of information probably shouldn’t come in a form letter to a research participant to say, ‘Yeah, at 30 years everybody needs a mammogram’ and then sign off,” Fernandez says. “I think that really needs to come in a face-to-face or at least verbal contact with a plan in place for follow-up, both medically as well as psychologically.

“It could be very involved and expensive and time consuming,” he says. “However, there is cost from my point of view associated with getting informed consent for participation in studies, and that’s a moral requirement that we assume is part of the cost of doing business, so to speak, in research.”

He argues that returning research results is also a moral obligation the research community is obligated to assume.

**Guidelines for providing results**

How then, should IRBs and researchers plan for the release of research results?

Fernandez and Partridge contend that IRBs should have a policy requiring researchers to provide a plan to return results to subjects who wish to see them, or to provide an explanation why it shouldn’t be done.

“The researcher probably will be able to inform that plan very well because they can often anticipate what the nature of the results would encompass,” Fernandez says.

He suggests that subjects should be informed as part of the regular consent process that they will have an opportunity to receive results from the study when it’s completed, if they wish. The informed consent should lay out not just the benefits, but the potential risks of receiving the results. He says subjects probably should be informed more than once during the course of the study of this opportunity, as their attitudes about learning the results may change over time.

Results shouldn’t be released until the study has been closed and the results have undergone the normal peer review, he says. “You want to be providing results that have the same degree of veracity as you would to the scientific community,” Fernandez says.

However, they should be provided in a form that is more understandable to the laypeople in the study. For this reason, he says the current push to provide a clinical trials registry will not satisfy the needs of informing subjects about results from clinical trials.

“Those results, while theoretically accessible, aren’t accessible to the average participant,” Fernandez says. “The results need to be provided to participants in a format which they can understand — it’s not sufficient to just refer them to the journal and publication.”

An IRB could provide for review of the materials given to subjects to ensure they are understandable, but Fernandez says it wouldn’t necessarily have to be a requirement.

Fernandez and Partridge both say the timing of releasing results to study participants is important. They say subjects should learn about the results from researchers before they’re disseminated to the public at large through media coverage.

“Patients shouldn’t feel like the only way they heard about it was when it came out in The New York Times or on the nightly news,” Partridge says.
Fernandez says that results could be released to subjects after a manuscript is accepted for publication, which would still leave time to inform everyone before the article was actually published. A subject can only be informed of results if researchers know where to find him or her, which is seen by some as a significant obstacle to releasing results. But Fernandez says his studies have shown that subjects who want to see results believe it's their obligation to make sure researchers can contact them when the time comes.

"You can inform the individual about the potential benefits and harms of receiving research results," Fernandez says. "You can then say, 'We anticipate the results to be ready in about a year's time. Do you want to be contacted for that?' And some people may already vote with their feet at that stage. For those who do want to be contacted, it becomes incumbent on them to retain the contact."

Both Partridge and Fernandez say they hope to see more interest among IRBs and researchers in providing this type of information to subjects, because the interest among subjects is already there.

"I think thoughtful people are concerned about the pros and cons, so no one's wanted to push this," Partridge. "But we are pushing it more and more because there is more and more data that we can do this in a safe, patient-friendly, research investigator-friendly way that improves the process and improves communication with patients after a trial."

References

**Survey: Stroke patients favor emergency research**

A survey of patients who had suffered strokes found that most would be willing to participate in emergency research for stroke treatments, and if incapacitated, would accept surrogate decisions about enrollment by family members or even their doctors.

The study’s author, Carol Blixen, PhD, RN, a researcher with the Cleveland Clinic Foundation in Cleveland, says she plans to use this study and planned follow-ups to better define the attitudes of stroke patients toward emergency research.

She also hopes that the information will help refine a definition of the community consultation that is required by the FDA for waivers of informed consent in emergency research. Blixen says that people who have suffered strokes or are at risk for a first stroke make up a community whose opinions about research are more relevant than a definition of community that would be limited to geographic location.

"I think that this issue of community needs to be really tightened up," Blixen says. "We hope to come out with a model that, though not predictive, can be a way to systematically attempt to identify the relevant community for stroke. And that will provide a model for assisting researchers and IRBs to meet the rather cumbersome requirements of community consultation."

**Poster child for emergency research**

Blixen says she could foresee similar work being done with other conditions that have a strong emergency research component — acute cardiovascular conditions or brain trauma, for example — to identify relevant communities and determine their attitudes about emergency research. In many of these cases, patients are first encountered in an emergency room, and interventions must be administered quickly in order to save lives and preserve brain and other functions.

But Blixen considers stroke to be the poster child for this type of approach, because of its increasing prevalence.

"The burden of stroke will only increase in our country because of the aging population," she says. "In fact, it's been felt that the incidence of stroke will dramatically rise and lead to a stroke epidemic because of our aging population."

FDA regulations (21 CFR 50.24) address research done in emergency settings on patients who may lack the ability to give informed consent. The FDA allows for waivers of informed consent in these cases, but under strict requirements, including:

- Participation in such studies must hold out the prospect of direct benefit to the individual subject;
— Risks associated with the study must be reasonable in relation to what’s known about the medical condition and standard therapy; and
— The study should exclude emergency patients who emergency care personnel could reasonably infer would not agree to participate in a research study.

In addition, there must be an opportunity for “community consultation and public disclosure,” to ensure that the community from which the study participants will be drawn has a chance to be involved in the IRB’s decision-making process.

The FDA defines community as “the geographic area, e.g., city or region, where the hospital or clinical investigator study site is located.” The agency’s guidelines also state that the community can be characterized by analyzing the demographics of previous hospital patients with the condition being studied. Bliksen says confusion about this requirement can impede the progress of emergency research. Her study was an attempt to begin identifying what she calls the “relevant community” — specifically, patients who shared the condition being studied, and who were thus most directly affected by the research.

Bliksen recruited subjects who had suffered a stroke in the previous year and who helped reflect the racial, gender, and age distribution of stroke nationally. Participants were screened to ensure they had no problems with comprehension or speaking. In the end, a group of 12 patients was chosen. Researchers conducted face-to-face interviews with the subjects, gauging their understanding of research terms, their attitudes toward research and particularly emergency research, and their confidence in the ability of family members or doctors to give surrogate consent in emergency research situations. Overall, nearly all of the patients expressed approval for the idea of stroke research in general.

Eleven of the patients thought it was acceptable to treat patients who had had a stroke with a new and untested intervention, as long as the patient gave informed consent. But half had some concerns about giving such treatments without informed consent. One patient response showed the ambivalence some subjects felt about the idea: “...if a patient is fully informed of all the risks and then still says yes, I want to participate, then that’s fine. I wouldn’t expect the doctor to apply those new and untested methods to a patient who hasn’t given that informed consent.”

Most said they would be willing to participate in emergency research if the opportunity arose.

In cases where they were unable to consent for themselves, nine of the 12 patients surveyed would want a family member to give consent before being entered in a trial. Those nine said they had a “high level of confidence” in the ability of their family members to make the decision to enroll in a study.

**Family, doctors seen as surrogates**

In cases where neither the patient nor a family member could provide consent, 11 of the 12 subjects said they would trust their doctor to make the decision of enrolling them in a study. “Some people even said they trusted them more than their families,” Bliksen says. “That was surprising.”

She says the results were consistent across gender and even racial lines, despite the fact that other studies have found African-Americans to be more distrustful of research and research institutions.

Bliksen says she already has applied for grants to expand this study, interviewing a larger group and including Hispanics. She also is seeking out not just stroke patients, but people with risk factors for stroke, since the attitudes of stroke patients may be influenced by their having survived a stroke already.

With more results in hand, Bliksen hopes to convince the FDA to refine its requirements regarding community consultation in emergency research, to include the idea of seeking out those who have the condition or illness being studied.

“We’re very excited about the possibility of what the results of the larger study might offer, both on a policy level and on a clinical level for researchers,” she says.

In the meantime, Bliksen suggests that IRBs should take the initiative to ask investigators to provide more of these types of community consultations themselves.

“They may find that this kind of inquiry into the defining the relevant community would be helpful in them looking at what investigators are doing,” Bliksen says. “Someone saying they’re going to put posters up in City Hall or in supermarkets, that’s not good enough for community consultation. Researchers may have to go a step further in getting a consensus from the relevant community about what they’re going to be proposing.”

**Reference**

OHRP offers guidance on review of trial web sites

Clarifications welcomed by many

In late September, OHRP issued guidance concerning IRB review of clinical trial web sites. The guidance, which can be viewed at OHRP’s web site, states that IRB review is required when information on a clinical trial web site includes more information than the study title, the purpose of the study, the protocol summary, basic eligibility criteria, study site locations, and how to get more information on the study.

Among the additional information the guidance points to as necessitating IRB review are descriptions of risks and potential benefits, and solicitation of “identifiable information.”

In reviewing any risk or benefit information, the guidance says the IRBs should try to ensure it is presented in “a balanced and fair manner.” IRBs should also review incentives being offered and determine whether they could cloud a potential subject’s judgment. The guidance also notes that eligibility questions that solicit information that could link answers to the respondent require IRB review. Additionally, the IRB should review plans for maintaining confidentiality of that information and ensure that the web site includes explanations of how that information will be used. In most cases, informed consent is required if any personal information is going to be collected.

Lastly, the guidance notes that IRBs do not have to review clinical trial web sites that include only directory listings and basic information about clinical trials.

“One area that is a potential gap is the approval by central IRBs of advertisement materials for markets in which there are one or more local IRBs — who has jurisdiction?” says Robert “Skip” Nelson, MD, PhD, associate professor at the University of Pennsylvania and physician at the Children’s Hospital of Philadelphia.

“An individual in Philadelphia, for example, could go to the web site, and then be referred to the local investigator. The local IRB has jurisdiction over that investigator but may have never seen nor approved the web site. Even if the local investigator knew of the site and told the local IRB, the web site may have been reviewed and approved by the central IRB. All is well if everyone agrees, but what should happen if the local IRB disagrees with the central IRB? Who wins?

Should the local IRB tell the local investigator to not use the site? Refuse referrals? Disapprove the study?”

Nelson’s solution is that the local IRB would provide input to the central IRB, which can then take the advice at their discretion.

This kind of conflict can be completely avoided if local and central IRBs communicate well, says Erin Thacker, MS, CIP, lead administrator of New England IRB in Wellesley, MA. “I would hope that a local IRB would call us if there was a problem,” she says, or better yet, that the two organizations would talk about web site content before it goes live.

The guidance in general is not going to change what New England IRB does in most cases — primarily because most of the studies they do are conducted under FDA regulations. “Those requirements say pretty much the same things about clinical listings,” she says. “These are a little bit more specific when it comes to confidentiality issues, though.” This clarification is welcomed, though, not least because some unnecessary paperwork will be eliminated, she says. Thacker will not have to approve the most general web sites.

Felix Gygi, PharmD, MBA, CIP, chief executive officer of Chesapeake Research Review in Columbia, MD, says another positive aspect of the guidance is that it takes the potential for interpretation out of one aspect of the IRB’s work. “There was a presumption that anything that had to do with research had to be reviewed,” says Gygi, who also serves on the Secretary of Health and Human Services’ advisory community on human research protection.

“Whenever you get official guidance on something, you eliminate individual interpretation.” He also notes that guidance means no one will have to search through all the letters of determination to find out whether this issue has come up for any IRB.

Clinical results too good to be true?

Most likely they are

Clinical trials that show a treatment effect early on face a dilemma. If the effect is real, one ethical argument goes, then it is imperative to give all involved access to the drug as quickly as possible, starting with the placebo group.
The problem is that efficacy early in a clinical trial may not be real, but instead a mere statistical fluke. For that reason, Gordon Guyatt, professor of clinical epidemiology and biostatistics and medicine at McMaster University in Hamilton, Ontario, calls that ethical argument “honest but misguided.”

In the Nov. 2 issue of the Journal of the American Medical Association, Guyatt and his colleagues cast a critical eye on clinical trials ended early. While the words describing such trials are often nothing short of bombastic — an editorial that accompanies the JAMA paper has one researcher saying it was “vital to tell the world immediately” of their results — the first look often doesn’t hold up.

Because in clinical trials, it’s a number, not a picture, that is worth a thousand words. And according to the authors’ analysis, the numbers paint a sobering picture.

Ninety percent of 143 trials that were stopped early for benefit ended up failing to provide a full interim statistical analysis of the truncated trial, and only about two-thirds of them provided a statistical justification for their decision at all. In the remaining third, in the words of the authors, “a statistical approach to monitoring the trial was either not used or not specified in the report.”

To evaluate whether the decision to stop early is statistically sound, or whether it is even possible to evaluate whether the decision is sound, the authors, who are from McMaster University, Ontario; the Mayo Clinic College of Medicine in Rochester, Minn.; the University of Toronto; Basel University Hospital in Switzerland; the University of Buffalo in New York; and the Italian National Cancer Institute, Rome, analyzed such trials for three pieces of information: the planned sample size, the interim analysis that led to the decision to stop a trial early and the statistical rule used for the decision to stop a trial early. Fewer than half of the trials reported all three numbers.

Most troubling was one particular inverse correlation: The larger an observed effect, the less data it was based on. That is, the more of a chance that it was due to a statistical phenomenon called, fittingly, the random high.

Since dramatic findings are the ones most likely to be published in high-impact journals and influence clinical practice, it is problematic that many of those dramatic findings turn out to be statistical flukes.

The authors described typical truncated trials as being disproportionately industry-funded drug trials in cardiology, cancer, and HIV.

Guyatt explained that the reason serious diseases are disproportionately represented is that clinical trials are most often stopped for benefit when there is the perception that doing so will save lives: “If you’re decreasing runny nose, that’s a much less compelling reason,” he said.

The authors also noted that a majority of those trials were published in only five high-impact general medical journals, including JAMA.

For clinicians, the authors recommend a healthy dose of skepticism when evaluating reports of large benefits in clinical trials, including cross-checking with what is already known about a drug. They cited an example of a clinical trial that was stopped early for benefit despite results that were inconsistent with the researchers’ expectations, with earlier clinical trials, and with clinical practice, calling the data “likely too good to be true.”

For those running clinical trials, Guyatt has an equally blunt message: “If you can avoid it, don’t stop early under any circumstances for benefit. If you are forced to have a stopping rule” — which grant reviewers sometimes will insist on — “choose an extremely conservative rule and don’t stop until as late in the trial as possible.”

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Can Alzheimer’s patients participate in research?

Survey respondents say, “Yes”

Is it ethical to enroll an elderly person with Alzheimer’s disease in a new research study, even if he or she doesn’t really understand what it entails? What if the research has real risks, is unlikely to benefit the patient, but could lead to advances that will help future patients with Alzheimer’s?

Questions like these are likely to arise more often as potential treatments evolve that require more involved and invasive research, and as potential new therapies such as vaccines, gene therapy, and new drugs are being tested, the need for research must be balanced with the need to protect vulnerable adults, according to Scott Y. H. Kim, MD, PhD, of the University of Michigan Medical School in Ann Arbor. This
continues to be an area with unsettled policy, and there is little data to guide policymakers. Kim and his colleagues conducted a study of what adults at risk of Alzheimer’s disease think about participating in research.

People at heightened risk for Alzheimer’s disease — 229 people who were more than 70 and had at least one close relative with the disease — took part in the study, which was published in the Nov. 8, 2005, issue of Neurology, the journal of the American Academy of Neurology.

Testing patients OK, to a point

The participants were given 10 research scenarios and asked if the research portrayed was acceptable if it involves people with Alzheimer’s disease who cannot give informed consent on their own but are enrolled with a family member’s permission.

They were asked to consider three perspectives: whether the research was acceptable from a societal perspective; from their own perspective (whether the participants would want a loved one to make the decision for them); and from the perspective of a surrogate (how they would make a decision for a loved one).

The 10 scenarios ranged from low-risk studies involving observation or routine blood draws to higher-risk studies like testing a potential vaccine or a neurosurgical gene transfer intervention. The survey participants were told about the risks and any potential benefits to subjects or to society.

More than 90% of the participants felt that minimal risk studies as well as randomized clinical trials of new medicines should be allowed with incompetent Alzheimer’s subjects if family members give permission, according to Kim. A smaller percentage, but still a majority, approved of such surrogate decision making for studies involving gene transfers Alzheimer’s protein “vaccines,” spinal taps and brain tissue sampling.

In general, participants endorsed family consent for research most strongly when applied to themselves as future research subjects and least strongly when placing themselves in the position of the surrogate having to decide for a loved one. For example, for a study that would involve a lumbar puncture, family consent for research was endorsed by 69% when applied to themselves as future subjects; by 65% from a social policy perspective; and by 61% as something they would allow for a loved one.

The participants perceived the highest risk from studies involving gene transfer, Alzheimer’s vaccine and brain biopsy or tissue sampling. But despite the risk, more than 50% said they thought it was acceptable for society to allow such studies, and a majority said they would probably or definitely take part. When asked if they would consent to allow a loved one to take part, the percentage saying probably or definitely yes fell just below 50% for gene transfer and biopsy.

Participants were more likely to find the research scenarios acceptable if they had a generally supportive attitude toward biomedical research. The study participants were already taking part in an Alzheimer’s disease anti-inflammatory prevention research study; the researchers note that the participants therefore could be more supportive of research than the typical person at risk for Alzheimer’s.

However, those taking part in the study were fairly typical demographically to people taking part in other studies of Alzheimer’s disease, so they may be quite similar to those likely to be considered for future research studies, Kim adds.

“Right now, Alzheimer’s studies being done in one state could be illegal in others, and most states such as Michigan have no clear law on this issue. Though individual research institutions such as universities do their best to protect research participants, they deserve better policy guidance than what they have now,” he says.

“Our study aims to provide data about the attitudes of key stakeholders that policymakers can use.”

For more information and to see full results of the study, go to the American Academy of Neurology web site, www.aan.com.
CE/CME Objectives

The CE/CME objectives for IRB Advisor are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research.

CE/CMEquestions

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.

The semester ends with this issue. 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.

21. IRBs in the New Orleans area have been able to reach most of the subjects in clinical studies in the aftermath of Hurricane Katrina by relying on local television and newspaper advertising.
   A. True
   B. False

22. Of respondents to a survey of presenters at the American Society of Hematology’s 2003 annual meeting, how many were required by their IRB to offer to provide results to study participants?
   A. 1%
   B. 7%
   C. 30%
   D. 70%

23. The FDA’s community consultation requirements for a waiver of consent in emergency research currently do not include a requirement for consulting patients with the condition being studied.
   A. True
   B. False

24. The reason for the high number of clinical trials for serious diseases such as HIV and cancer being stopped for benefit is the perception that doing so will save lives.
   A. True
   B. False

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When looking for information on a specific topic, back issues of IRB Advisor newsletter, published by Thomson American Health Consultants, may be useful. To obtain back issues, contact our customer service department at P.O. Box 740060, Atlanta, GA 30374. Telephone: (800) 688-2421 or (404) 262-7436. Fax: (800) 284-3291 or (404) 262-7837. E-mail: ahc.customerservice@thomson.com. Managing Editor: Alison Allen.

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