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An essential resource for managers of clinical trials

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When do you really need to use a data safety monitoring board?

Experts discuss staying on top of adverse events

More clinical trials are using data safety monitoring boards (DSMBs) in recent years as investigators, sponsors, and clinical trials managers increasingly see the value of added checks and balances to subject protection, experts say.

Strictly speaking, few clinical trials are required by federal regulations to have a DSMB or data monitoring committee, but FDA guidance suggests a number of other types of trials should consider forming such a board. And this guidance is where clinical trials managers should begin looking when they want answers to the big question of whether to form a DSMB.

From a regulatory perspective, the only type of trial that's required by the FDA to have a DSMB is a trial in which there is a waiver of informed consent for emergency research, says **Susan Ellenberg**, PhD, director of biostatistics and epidemiology at the Center for Biologics Evaluation and Research of the FDA in Rockville, MD.

The NIH and the VA have their own requirements regarding DSMBs, but the FDA's requirement for an independent DSMB pertains to emergency research in which extra patient protections are necessary, she notes.

"The FDA put out a guidance document a few years ago, and we are in the process of revising it based on comments we received that suggest that in other areas, a DSMB could be an addition to the trial to ensure protection," Ellenberg says. "We recommended these kinds of data monitoring committees for trials that address mortality endpoints."

For instance, a data monitoring committee could assess the trial's information for signs that one treatment is saving lives while another is not, and so that trial may need to be stopped early, Ellenberg says.

FDA guidance also suggests that a DSMB might be considered in clinical trials in which an innovative treatment creates concerns that there might be serious adverse events, she adds.

It might be a mistake to routinely create a DSMB for every clinical trial because not every study needs one, says **Patricia Hibberd**, MD, PhD, professor of medicine at the Tufts University School of Medicine,

division of clinical research resource, and Tufts New England Medical Center in Boston.

"If every study needed a DSMB, we wouldn't have enough people to sit on these DSMBs," she says. "So I'm not advocating that every one have one."

While every trial needs oversight and monitoring, most don't need a DSMB, Ellenberg points out. "The vast majority of clinical trials do not need this extra layer of oversight," she says. "This is one more committee to have in a clinical trial, and with the complexity of doing a trial, you should only have them when they're really needed."

Likewise, it's a mistake to think that clinical trial managers and investigators can stop worrying about subjects protection because they have a DSMB, Hibberd notes.

"You still have to do your homework to make sure safety of subjects is maintained throughout the study," she says.

Very few clinical trials used DSMBs until the 1990s when the National Cancer Institute started to incorporate the boards into their trials, notes Ellenberg.

"So there's been a gradual increase [in use of DSMBs] as more people became aware that these committees could provide extra information," she explains. "Also there are more industry trials that have serious end points than there used to be."

Ellenberg and Hibberd provide these thoughts to consider when deciding whether or how to most effectively use a DSMB:

• **A DSMB makes recommendations to sponsors.** Data monitoring committees receive raw data regarding adverse events and a trial's progress, analyze the data, and make recommendations in a report to the sponsor, Ellenberg explains.

The information also could be made available to the IRB, she adds. "Because the sponsor is blinded to the results, you have to have somebody looking at the interim results, and it cannot be people who could change the trial," Ellenberg says. "So when the report from the DSMB goes back to the sponsor it doesn't reveal what interim data look like; it makes recommendations."

In trials where subjects might die before the trial ends, it's important to have a third party looking at the interim results to make certain the trial hasn't produced dramatic results that should result in a change, she says.

"The DSMB might make a recommendation to the sponsor to make a change in the trial to reduce adverse events, such as reducing dosage or adding another drug to mitigate or — in the worse case — to stop the trial," Ellenberg explains.

"You could have a trial where you see unusual

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adverse events only in women," Ellenberg says. "That's why you have a DSMB to have an independent judgment that is not colored by how much money it costs to get the trial going and how much money the company would spend to make it successful."

• **The DSMB's responsibilities need to be spelled out in advance.** "If you write a research protocol and say this needs to be monitored by an independent DSMB then it's your job to put together a DSMB and include experts of relevance for the particular study," Hibberd says.

For instance, here are some questions to consider:

— What will the DSMB do?

— Will the DSMB review adverse events?

— Does the DSMB need to look at summaries of adverse events?

— How will the DSMB be successful in having the appropriate oversight?

— Should the DSMB have regular meetings with the investigator?

— How will the meetings be conducted?

— How will the DSMB's recommendations be handled?

— How does information get from the DSMB to the IRB?

"All of those issues need to be sorted out, and that's the investigators' responsibility," Hibberd says. "If the pharmaceutical company is setting up the DSMB, their responsibility is the same."

With regard to the IRB, it's important to know who will be sending the DSMB's information to the IRB, or whether that will be done, she adds.

Extra steps

• **Best strategy is to set up DSMB early in process.** "I think honestly the best way to set up a DSMB is — before patient accrual occurs — for there to be a meeting between the principal investigator and the DSMB to review the processes and to agree upon the processes," Hibberd says.

"There may be certain trials where the DSMB wants to hear about every single serious adverse event as they occur, and if that's what the DSMB would like to do then we've got to make sure that happens," she adds. "In other circumstances, they may say we don't need to hear anything unless a certain threshold is crossed, and if you don't set up the process of when and how before the study starts then you may have a problem."

• **Sponsors may circulate DSMB report to investigators.** "There could be an agreement that the sponsor would circulate the DSMB report to investigators, and if there are any recommendations that impact how the trial is conducted, then that would have to be circulated," Ellenberg says.

If the DSMB says that things look good, but the data aren't up to date, then the clinical trials staff need to know that there is a problem in the process that needs to be corrected, she says.

"The DSMB might recommend a dose be lowered because of toxicity, and if the sponsor agrees, that information goes out to all cities because the protocol has been changed," Ellenberg says. "If they say everything is going well, there's no reason why the sponsor couldn't circulate that as well."

• **DSMBs pay attention to time limit issue.** "From the perspective of someone who has had experience in managing data monitoring committees and serving on them, one thing a DSMB will pay attention to is the time limit issue," Ellenberg says. "If a DSMB sees a high rate of dropouts, they'll be concerned about that because those kinds of problems harm the eligibility of the trial, and the DSMB will make a recommendation to the sponsor to tighten up the trial."

Also, DSMBs often consider aspects of trial quality in addition to data on safety because if a clinical trial reaches its end and doesn't produce useful information because the trial wasn't conducted rigorously enough then this becomes an ethical issue, she notes.

"Is it ethical to ask people to participate in a trial for which there is no useful result?" Ellenberg says. "So frequently DSMBs will make recommendations regarding quality."

• **Trials using DSMBs still need to include extra steps to ensure safety.** If the trial's risk will be high enough to require a DSMB, then investigators need to include more details to explain how they are going to be sure a study is going to be safely conducted, Hibberd notes.

"It's not enough to say, 'We're going to report adverse events,'" she says. "How do you know an adverse event has occurred? Are you going to ask patients, and how do you ask patients?"

For instance, should clinical trials staff ask subjects whether they've had any adverse events, or should they ask, "How have you been since the last time we saw you?" Hibberd says.

"What I see in a lot of protocols are descriptions of what an adverse event is and various definitions depending on how the protocol is regulated," she notes. "I couldn't care less what the term is, but I know the spirit is the same in all circumstances, so move on to the next level: 'How are you going to explain to the IRB that you're

going to be on top of them instead of giving a long definition of some regulatory definition of adverse events pasted in off a web page?'"

Also, clinical trials staff need to provide context to DSMBs regarding adverse events, Hibberd says.

For example, if there are three patients reporting headaches, it's not as useful to provide that information without the denominator of the number of people enrolled in the study, she explains.

"If there are three patients and every one has a headache, that's likely a major problem," says Hibberd. "If there are 3,000 patients and only three have a headache, then that's a very different matter." ■

The downside of the diversity drive

Race-based diversity or racist stereotypes?

At many professional meetings and workshops, clinical trial investigators and coordinators crowd into presentations offering advice on recruiting and retaining women and minority subjects.

The NIH Revitalization Act of 1993 required federally funded studies to include women and members of racial and ethnic minorities among their participants, both to remedy their historic exclusion and determine whether there are differences in the way women and people from different cultures and racial backgrounds respond to new medications.

However, the recent emphasis on the inclusion of racial minorities in clinical trials as a means of addressing health disparities between whites and blacks is reinforcing erroneous beliefs about race and medicine, warns **Otis W. Brawley**, MD, professor of medicine, hematology, and oncology at the Emory University School of Medicine and former director of the Office of Special Populations Research at the National Cancer Institute.

"Race is not about genetics; it is a sociopolitical construct that was created 500 years ago to justify slavery," he notes. "It is a terrible, terrible way to categorize the population."

Clinical investigators should strive for a diverse subject population in order to better observe how drugs behave in different people and to ensure that people of all walks of life enjoy the same access to new treatments and the enhanced access to health care practitioners and disease monitoring that accompany them, Brawley says.

However, some investigators have taken the push for diversity a step further — advocating for proportionality of different genders and ethnicities in study populations in order to perform subset analyses on these different groups to discern any differences in response.

This practice can only serve to reinforce the erroneous belief that significant differences in biology exist in members of different races, Brawley says.

Some genetic differences do exist between people of different geographic origins, he says. However, area of geographic origin often has little to do with what racial category the person is assigned to in our society, he adds.

Sickle cell an example

"The best example of this actually is the sickle cell gene," Brawley explains. "We in the United States, primarily because of our racist and racial attitudes and the way we have been brought up, we tend to think of sickle cell anemia as a black disease. You can even find literature that calls the specific mutation of the sickle cell a black mutation."

But the same genetic mutation can be found in natives of southern Greece, southern Italy, and southern Spain, where there is a low but significant incidence of the mutation in people normally considered white," he says.

In sub-Saharan Africa there are a lot of people who have the mutation, but in southern Africa — for instance, in Zimbabwe or South Africa — people who have the mutation are either migrants from the northern part of the continent or the children of migrants, he explains.

"So I have defined a white population with this black mutation, and a black population that never had this mutation," Brawley says. "The mutation actually came about because 1000 B.C., there was a huge malaria epidemic that encompassed the Mediterranean, southern Europe, went into the Middle East, and then went down into sub-Saharan Africa. So area of geographic origin is actually a much better identifier of this trait, called sickle cell disease, than is race."

Categories created by government office

Our current racial categories — black, white, Asian, Pacific Islander, Native American, etc. — are re-created every 10 years by the federal Office

of Management and Budget (OMB) to prepare for the U.S. census.

The new categories are issued two years before the census in the preamble to the OMB's Directive 15, establishing how it will conduct the count of the population. The preamble always stipulates that the office is making sociopolitical categorizations.

"As an example of how it is a sociopolitical categorization is if you have a gentleman who was born in Bombay, India, and then migrated to the United States in the 1920s, that individual, according to OMB Directive 15, which has been reissued seven times over that individual's life, that person would currently be considered to be Asian; but 20 years ago, that person would have been called Indian; prior to that, the person would have been called white," Brawley says. "These things are very political, and they have nothing to do with genetics or how we metabolize drugs."

Difference in access to care

Disparities in access — to preventive health screenings, early diagnostic tests, regular health checkups, and early treatment — is the real culprit behind the disparities in illnesses between blacks and whites in this country, Brawley says. This fact is obscured by the furor over clinical trial subset analyses.

"It has become much easier for members of Congress to stress that they are forcing the NIH to look at these difference among the races in how drugs are metabolized and to define health disparities in genetic terms and throw $40 million at the problem through the NIH; it is easier to do that than it is to look at the real problems — disparities in care. I often like to point out that if we ever did find that one of my cancer drugs was metabolized differently in blacks than in whites, we already have data to show that blacks aren't going to get the new drug, anyway, so it doesn't really matter."

Disparities in access to care, and the resulting delays in diagnosis and treatment, also may partly explain the low rates of minority participation in clinical trials.

The June issue of the *Journal of Clinical Oncology* featured a report by Simon and colleagues[1] of a study they conducted of the dynamics of clinical cancer trial accrual at a single institution.

According to that report, Brawley says, the proportion of eligible patients who refused entry was significant, as was the proportion of patients who did not have a clinical trial available or who otherwise did not qualify for the studies.

The study also found that minorities with cancer were less likely to have a clinical trial available for their disease and stage of disease and were less likely to be eligible when a trial was available.

The authors did find that similar proportions of eligible black and white patients chose to participate when trials were available.

It is particularly noteworthy, Brawley indicates in an editorial accompanying the report's publication, that black women in the Simon study were more likely to have poor performance status and inadequate organ function.

More effort needs to be made to first ensure that black and white Americans have access to the same level of care and the same treatment before researchers go looking for differences in treatment response that they attribute to race, he says.

"A lot of people have taken what I have said to mean that 'Otis says blacks don't do worse with cancer," Brawley points out. "And that is not what I am saying. I am saying I don't think they do worse because of biological reasons, but because of sociological reasons."

To illustrate his point, he recounts the results of a research study at Cleveland-based Case Western Reserve University of white women with breast cancer.

"Now this type of study can never be done again — at least not with NIH funding — but it yielded some interesting information," he says. "The study found that white women who were poor have breast cancer at a lower age, and they have breast cancer that is more aggressive within stage — that there is something about poverty in white women that makes the breast cancer more aggressive. This is by comparing white women who were poor vs. white women who were not poor who had breast cancer. But now, when we look at black women vs. white women, we seem to be saying, 'Let's see, black women have disease at a younger age; they have more aggressive disease,' and then we immediately start saying, 'Maybe it is because they are black?' Ironically, maybe it is because they are black socially, not because they are black, biologically."

Reference

1. Brawley O. The study of accrual to clinical trials: Can we learn from studying who enters our studies? *J Clin Oncol* 2004; 22:1-2. ■

NIH announces new outside work restrictions

Federal agency explores new policies

In the wake of congressional hearings levying conflict of interest allegations at top scientists at the NIH, the director, **Elias Zerhouni**, has announced new restrictions on the types of paid consulting agreements federal scientists can accept with pharmaceutical and biotechnology companies.

"I have reached the regrettable conclusion that some NIH employees may have violated these [existing] rules and that the agency's ethics system does not adequately guard against these violations," he told members of the House of Representatives' Energy and Commerce Oversight and Investigations Subcommittee during a six-hour hearing on June 22.[1]

The subcommittee first initiated hearings on conflict of interest allegations following the December 2003 publication of an article in the *Los Angeles Times* that listed hundreds of consulting payments from pharmaceutical and biotech companies to a number of NIH employees.[2]

In January, Zerhouni told committee members that a blue ribbon panel would investigate the allegations and make recommendations for improving disclosure of potential conflicts of interest and instituting internal policies for monitoring compliance.

The panel's final report, issued May 6 and adopted by the agency's Advisory Committee to the Director, addressed three main areas: outside activities, financial disclosure and system management, and reform.

The panel crystallized its investigation into 18 specific recommendations and six general findings.

The recommendations included stricter limits on outside consulting for top-level manager-scientists at the NIH, a ban on scientists with human-subjects responsibilities holding interests in companies involved in such research (with some waiver leeway possible), and also set time and income limits on approved outside activities (with the exception of outside medical practice).

Following the report's release, however, subcommittee members charged that the changes were inadequate.

As part of the investigation, subcommittee chair Jim Greenwood (R-PA) contacted 20 pharmaceutical companies, asking them to reveal all consulting agreements they had with NIH employees, and found 264 reported agreements, at least 100 of which were unknown to NIH officials.

In response, Zerhouni last month announced additional changes to the NIH ethics rules, including:

- A ban on consulting agreements between senior NIH officials — which include directors, deputy directors, scientific directors, and research directors — and pharmaceutical and biotech companies. In addition, senior NIH officials cannot take consulting or speaking fees from not-for-profit organizations.
- A ban on consulting agreements for NIH employees involved with the agency research grant process.
- Limits on the consulting agreements that NIH employees can accept, such as a compensation limit equal to 25% of their agency salaries and a time limit of 400 hours each per year.
- A ban on stock options as compensation for NIH employees as part of consulting agreements;
- A ban on ownership of stock in pharmaceutical and biotech companies for more than 5,000 NIH employees — other agency employees could own only $5,000 of stock in such companies;
- A provision under which NIH employees could not serve on the boards of pharmaceutical and biotech companies.
- A ban on any form of compensation from universities and institutions that receive NIH research grants.
- A provision that would require NIH employees to refuse consulting payments until agency ethics officials could determine their legitimacy.

Some say rules still too lax

Some, however, don't think the new ethics rules go far enough, arguing that top-level NIH scientists should be banned from all paid consulting for the pharmaceutical and biotech industries.

"There is a strong argument for not allowing NIH senior scientists or scientists of any stripe for that matter to engage in paid consulting for industry," says **Merrill Goozner**, director of the Integrity in Science Project of the Washington, DC-based Center for Science in the Public Interest. "The NIH is the premier medical research institution in the United States, as well as a funding body. When they get tied up as individual scientists with individual firms, they may lose site of the primary mission, which is to find the causes and cures of disease."

NIH scientists need to remain completely open to pursuing the best possible research avenues and solutions, and accepting money from companies that have a stake in research outcomes inherently compromises this function, he contends.

Researchers with the best of intentions still will be unconsciously influenced in favor of a particular company's pursuit if they routinely receive consulting fees — no matter how seemingly insignificant — from the same company.

Lowering income limits from 50% to 25% will likely make little difference, he says.

"Do they really believe that a person might be unduly influenced by compensation equal to 26% of their salary but not 25% of their salary?" he asks. "That just flies in the face of what conflict of interest is all about. If a scientist is accepting money from a company with a financial interest in the research area that scientists supervises, how will we ever be sure that their decisions are not biased in favor of that company?"

In explaining the rationale behind the recommendations, blue ribbon panel members likened the atmosphere at the NIH to that of a university balancing education and research interests, says Goozner. But, he argues, the NIH, as a taxpayer-funded federal entity, should be held to higher standards.

"A university researcher can stay on a narrow path [of study] and pursue that and, if some company is interested, then perhaps they can get consulting arrangements from it," he says. "We don't want that in our NIH scientists; we want them to take broad views of their field and always pursue the most productive path whatever that might be. Once you engage in a financial relationship with anybody, that is a reward for pursuing a particular path."

Although some have argued that too many restrictions on employees' ability to earn outside consulting, writing, and teaching fees will hurt the ability of the NIH to attract top scientists and limit productive cooperation between research and industry, thereby lengthening the time it takes for advances in technology to reach the market — Goozner argues there are better ways to address these issues.

"If industry wants to consult with an NIH scientist, they should, just like any other researcher out there should be able to," he says. "This is not to say that they should cut off all contacts with private enterprise. Because these companies are pursuing for-profit avenues, then perhaps they should pay for the privilege. But that money should go into a general fund, if not back to the U.S. Treasury, not to the individual scientist. If there is an issue with holding and attracting quality people at NIH then the level of salaries — and, already they are among the most highly paid people in government — then that should be addressed directly, rather than trying to set them up with the right to earn up to 25% of their salaries."

Perception of misconduct is dangerous

A relatively small number of questionable arrangements — not widespread misconduct — and a lack of transparency in its regulations and oversight procedures necessitated the blue ribbon panel and Zerhouni's reform efforts, notes **David Korn**, MD, senior vice president of the division of biomedical and health science research at the American Association of Medical Colleges in Washington, DC.

"You have two main issues: One relates to the consulting arrangements with companies that provide products for study to the NIH and to institutions that receive funding from the NIH; and, the second issue, is the receipt of honoraria and sponsored lectureships by senior NIH officials from institutions receiving large grant funding," he says.

During the tenure of former NIH director Harold Varmus, there was an increased emphasis at the institutes on recruiting and retaining the top scientists in the individual fields to service at the federal agency, he explains.

To do so, Varmus and others at the institutes felt they had to create parity in compensation and other privileges between key positions at the NIH and positions at a comparable level at private research institutions and universities. Scientists were allowed, within the scope of regulations governing all federal employees, to maintain outside consulting arrangements and, in some cases, federally permitted consulting positions at the NIH were used to augment the salaries of some officials whose pay grade would limit them to a salary beneath what they were earning in the private sector.

Further complicating matters, there were no overall guidelines at the NIH governing disclosure of outside relationships, and monitoring of such relationships. Different institutes and offices had different policies about who must disclose what and to whom. Different positions would be governed by a number of different federal

regulations and guidance regarding permitted outside work and disclosure requirements.

Following the *L.A. Times* report, Zerhouni initiated an investigation and discovered several questionable relationships — among them senior NIH directors with paid consulting contracts from private companies whose products were studied with NIH funds, and one situation in which the a director had a paid consulting relationship with a company whose product was under direct study at an NIH center. Zerhouni also discovered that many of these relationships had never been disclosed — either internally or externally.

"I think Dr. Zerhouni responded quite vigorously to what was reported in the media, by establishing a coherent set of guidelines on who could accept outside consulting work, setting limits on the amount of money that could be involved, and establishing a clear, transparent process for reporting potential conflicts of interest and for ongoing monitoring," Korn says.

However, a key bone of contention has been the pervasive belief, within the NIH, in the need for parity in compensation with the private research community. Many government scientists have come to accept as gospel that they should be compensated as well as their private colleagues and should not have to give up any perks in order to engage in government service, he says.

"However, it is pretty apparent that this opinion is not shared by many members of the [Congressional] oversight committee," Korn adds. "Following the initial release of the blue ribbon panel's report, the committee responded basically by saying, 'No way. You have not gone far enough [in restricting outside work].'"

It's a trade-off

Whether federal scientists should be expected to surrender more of their freedom to earn outside contracting fees in the service of maintaining the integrity of the agency and public confidence in it, is a legitimate question for discussion, he adds.

To be sure, top scientists in the private sector most likely would sacrifice as much as 30%-50% of their annual earnings if they were to come to work for the NIH and accept salary alone. However, the world of the federal NIH researcher also is often very different than that of the typical academic investigator, Korn notes.

Private researchers must continually hustle for grant money to keep their projects going, whereas NIH scientists have a budget and, often, a longer time frame to study their interventions.

"It's not directly equivalent, but there that is valuable, the NIH can be a much more comfortable, insular place that the private arena," he says. "And I don't know that I agree that there must be absolute parity between people involved in intramural research and those who do extramural."

There also is something to be said, he adds, for commitment to public service even in the face of personal sacrifice — something that is lacking not only here, but in many other areas of public life as well.

While it is true that most NIH scientists could make more money in the private sector — that also is true of most U.S. senators, representatives and others employed by the federal government.

Ultimately, however, it will be up to Congress to decide the issue.

"They could decide to do an experiment with this next appropriations bill and absolutely eliminate any outside work by NIH employees," he says. "Then, we would see whether there would be a mass exodus of talent. I think that there are some who probably would leave if they had to give up their outside work, but more would not. I could be wrong, however. It might be interesting to find out."

Above all, it is important for the NIH to maintain unquestionable standards of integrity; it is to keep the public's trust, Korn says.

Although, in this whole controversy, it has not been proven that NIH scientists use their influence to help secure funding or favorable reviews for products of companies they had outside relationships with — the perception exists that they could have, and that the public might never have been able to find out.

"I think the NIH may have gotten a little isolated and forgotten that when you are a publicly funded agency charged with maintaining the public good — in this case researching ways to cure disease and mitigate suffering; then you have to worry about perception," he says. "You will be held to a different standard whether you think you ought to be or not."

References

1. Weiss R. NIH scientists broke rules, panel says. *Washington Post*, June 23, 2004:A19.

2. Willman D. Stealth merger: Drug companies and government Medical Research. *Los Angeles Times,* Dec. 7, 2003: A1. ■

CAM studies should meet research standards

Expert notes challenges in this field

While interest in complementary and alternative medicine (CAM) research increases in the United States, there remain some significant challenges to properly designing these studies, an expert states.

"I personally don't subscribe to the view that because CAM studies are difficult to design that we can't maintain the rigor expected of other products, including pharmaceutical products," says **Patricia Hibberd**, MD, PhD, professor of medicine at Tufts University School of Medicine and division of clinical research resource at Tufts New England Medical Center in Boston.

"We have got to understand those challenges and how to deal with them," she says.

Here are some of the challenges of designing a CAM research protocol:

1. What is the composition of the product under study? "First, in order to know what you're studying and to understand what the effects of the product are, you've got to know what the product is and, for patient safety, what's in there and what's not," Hibberd explains.

"I don't have a lot of patience for studies where someone says it will cost a lot to buy a standard product," she adds. "I think, ethically, we're required to get something to meet standards."

Since many CAM products are not regulated as drugs or biologics and the manufacturers do not make health claims that are approved by the FDA, then they may include items in the product which are not listed on the label, Hibberd notes.

"So it ends up being challenging figuring out how to do some of these studies," she adds. "We need to step up to the plate and say, 'How do we know what's in the product and what's not, so we're not putting patients at risk.'"

The challenge for the researcher is to take the dietary supplement or other CAM product and learn precisely what is in the supplement and in what exact proportions, Hibberd suggests.

"If we can't do that then should we be studying it in that format, or should we be studying something else that does meet that standard?" she asks.

2. When should safety be a top consideration and when should a data safety monitoring board (DSMB) be used? Too often, there is a tendency for CAM researchers to have an attitude that people have used this CAM product for 100 years, so why should safety be a major concern? Hibberd asks.

However, this overlooks the importance of conducting CAM research as rigorously as any other type of clinical research, she adds.

For example, a researcher might decide to provide triple doses of vitamin C to subjects and perhaps thinks there is no reason to worry about safety because everyone uses vitamin C, Hibberd says.

"But we have to look to see if high doses of vitamin C have adverse consequences," she says. "I wouldn't consider doing a research study unless I had that information, even if it is appropriate to hypothesize that a higher level of vitamin C would be appropriate."

One rule of thumb is that if a particular patient population might warrant the establishment of a DSMB in a pharmaceutical product trial, then a DSMB should be used for a CAM trial as well, Hibberd notes.

"We need the same approaches to determine whether or not adverse events have occurred — as in a clinical trial, and we need the same oversight with a DSMB," she says. "What ever standards we'd expect for good clinical research outside of CAM, why should we consider CAM differently?"

Trial design and the double blind

3. How does a clinical trial in CAM research use control groups and blind the study? "One of the areas that is very hard in CAM research is to blind subjects to what treatment group they're in, particularly if you're doing an intervention, for example," Hibberd says.

For instance, suppose an investigator wants to study the effects of tai chi and randomizes some subjects to engage in tai chi and others to not, she points out. "It's obvious to folks who are getting it that they're getting it."

"I understand it's hard, but our job if we're trying to understand CAM therapies is to come up with the strongest possible scientific design," Hibberd says. "And there are some great examples of how researchers have figured out how to do sham acupuncture for studies."

Likewise, perhaps a sham tai chi program could be created to provide a blinded quality to the study.

One methodological problem with this is that the tai chi master could be a charismatic person, and so the study might inadvertently study the effects of one group leader over another, Hibberd says. "The better conceived the design, the easier

these protocols will be for the IRB to review."

4. What is the justification for the study? "If we have absolutely no idea at all how something might work then it really is difficult to justify why we're doing a study," Hibberd notes.

For example, suppose an investigator is designing a study for a particular herb to see if it provides some therapeutic benefit when used to treat a particular condition, she says.

"If you asked for a rational basis for setting up the study for people with a particular illness, then you might not have a good reason for doing this particular study," Hibberd says.

"When trying to design scientifically valid research, and those are the ones the IRB really wants to be able to feel confident that the scientific rationale makes sense, then it really is hard when we don't know much about how these products work," she says. "So you have to work backward and say a particular product is being used widely in this condition and, therefore, maybe we're going to try to study whether it works."

Still, it's difficult to answer skeptics who ask how a trial will determine how something is working and why it's working, Hibberd notes.

"I personally think it would be helpful if some CAM researchers would stop jumping on 'I want to study a particular approach in this disease or that disease and, instead, say, 'I've got to understand how these things are working rather than come up with a rationale for doing research,'" she says.

From an IRB's perspective, it's better to know that there is a reason for doing a study, Hibberd notes. "Why waste people's time?" she says. "A lot of these therapies are not likely to be risky, but some could be." ■

Demand-driven research yields greater benefits

Push toward practical uses

Current health care research and service development all too often misses the target, according to presenters during the "Translating Research Into Practice: Advancing Excellence from Discovery to Delivery," conference held in Washington, DC, in July.

Sponsored by the **Agency for Healthcare Research and Quality** (AHRQ; Rockville, MD), the event brings together clinicians, researchers and business leaders to focus on more efficient and productive ways to deliver health care and related services to the end-user patient, which is the backbone of the agency's Translating Research Into Practice (TRIP) program.

"We have done our best to turn this [traditional research methods] on its head and create demand-driven types of research," said **Cynthia Palmer**, program officer of AHRQ's Integrated Delivery System Research Network, told conference participants. "We need to get away from helping other researchers do more research and help the decision makers and the end users that are out there looking for the solutions."

She said the move from purely academic types of research to more practical applied approaches is a shift in mindset for many, but it must happen because current research efforts often take too much time to reach the benefit of patient care.

"By focusing on topics that are actionable," Palmer said, "we are fostering research that builds the collaboration and a dialog between the people that produce the findings and the people that we hope to use the findings."

The way to build what Palmer and others at the conference called "demand-driven research," is to begin creating collaborations and dialog with decision makers and researchers. This helps both sides by revealing expectations and creating understanding.

"If you define evidence as decision makers do, they are more inclined to understand and use that information," she explained.

"What is really needed across the country are targeted tools that inform decision making to guide rational resource allocation," said **Lucy Savitz**, PhD, senior health services researcher for RTI International based in Research Triangle Park, NC.

Savitz said practice change is best accomplished through knowledge utilization. She explained that research is not a one-way flow of communication but rather that there is a bidirectional flow of shared learning between research and practice — or there should be.

When this doesn't happen, research results don't translate to practice and you get underused vehicles. That was the term used to describe electronic medical records and clinical reminder systems in one of the TRIP breakout sessions.

"In 1977, we completed a study that said that the electronic medical record would be in widespread use in 15 years, and that statement is as true today as it was 20 years ago," said **Peter Goldschmidt**, president of Bethesda, MD-based

World Development Group, a health care business development and consulting company specializing in quality management and decision support technology. He previously served as director of the Health Services Research and Development Service of the Department of Veterans Affairs.

"In all seriousness, the electronic medical record has enormous potential to improve the quality of care," he said.

One of the electronic technologies being used and discussed at TRIP sessions is Microsoft Windows-based Logician software from GE Medical Systems, based in Waukesha, WI, used to help with a tobacco cessation program in a primary care setting. The software allowed researchers to track patients through primary care clinics to help physicians with identifying and targeting patients that fit the criteria for smoking cessation programs.

Research showed that this approach was more direct and had a more measurable impact on patients than traditional informational techniques.

It was specifically more measurable because the software is able to maintain a more precise record of the steps taken to flag smoking cessation patients and track them through the process via their health care record. It is intended to put physicians in greater control of the message and the plan of care. It also was cheaper than commonly used mass media or literature-based methods, according to the presentation. ■

AMA wants all clinical trial results in database

An initiative started by the American Medical Association (AMA) to create a national clinical trials registry appears to be gaining momentum around Washington.

It started in late June when the AMA House of Delegates approved a proposal calling for the Department of Health and Human Services to establish a new registry that would ensure all trials, with negative or positive results, are made publicly available.

The AMA also called for institutional review boards to require companies to register in the database as a condition of approval for all trials.

Proposal gaining support

Since the release of the proposal, a few lawmakers have reportedly jumped on the bandwagon by asking the National Institutes of Health and the FDA to provide guidance as to what can be done to improve such a database, which currently is available under the FDA Modernization Act of 1997.

The law requires companies and other organizations to make public studies of experimental medications for serious or life-threatening diseases. The FDA reportedly does not enforce the regulation.

However, trial data that are available can be found on ClinicalTrials.gov, an Internet databank of study information launched in February 2000 by the NIH's National Library of Medicine.

Indeed, the Chicago-based AMA took up the issue out of concern that negative or null trial results were not being published. **Joseph Heyman**, an AMA trustee, said the association believes that pattern of publication might distort the medical literature, affecting the validity and findings of systematic reviews, the decisions of funding agencies and, ultimately, the best practice of medicine.

Also, the AMA contends that investigators and authors are reluctant to submit poor trial results because they don't believe the medical journals will publish them.

Journals are more interested in publishing studies that are likely to affect clinical practice, and, as a result, confirmatory trials with negative results and trials that show no significant result are less likely to be published, the AMA said. ■

COMING IN FUTURE MONTHS

- Detailed training programs for clinical trials staff
- Software that will make your job easier
- Recruiting members of the deaf and hard-of-hearing community
- Studies on the impact of violent images on children

CE/CME objectives

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.

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*

5. Which of the following instances is not a good reason to form a data safety monitoring board for a clinical trial?

A. A DSMB might be considered in clinical trials in which an innovative treatment creates concerns that there might be serious adverse events.
B. A DSMB is required by the FDA for a trial in which there is a waiver of informed consent for emergency research.
C. A DSMB might be employed to assess a trial's information for signs that one treatment is saving lives while another is not, and so that trial may need to be stopped early.
D. All of the above are good reasons to form a DSMB.

6. With which level of research do all of the investigational drug exemption regulations and rules apply?

A. Significant risk research
B. Nonsignificant risk research
C. No risk research
D. All of the above

7. The newspaper that initially published allegations of conflict of interest on the part of top scientists at the NIH was:

A. *The New York Times*
B. *The Washington Post*
C. *The Los Angeles Times*
D. *The San Jose Mercury-News*

8. According to our article, what government agencies establishes the racial/ethnic categories used in the U.S. census and many government forms?

A. The Congressional Budget Office
B. The Government Accounting Office
C. The Office of Management and Budget
D. None of the above

Answers: 5-D; 6-A; 7-C; 8-C.