CLINICAL TRIALS ADMINISTRATOR

An essential resource for managers of clinical trials

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CR Update: NIH research initiative

NIH's Roadmap/Common Fund has been working to improve CT research

CTSAs generate new tools, strategies

When the National Institutes of Health (NIH) of Bethesda, MD, rolled out its Roadmap for Medical Research about eight years ago, the chief goals were to speed up the lab-to-bedside research process, strengthen areas in clinical research, and develop regional translational resource centers. The NIH would provide grant funding, and research institutions would create new strategies and best practices.

"The Roadmap was a series of programs designed to overcome particular research barriers, and it began through co-funding from all NIH institutes and centers," says **Elizabeth Wilder**, PhD, deputy director of the NIH office of strategic coordination.

"With the 2006 Reform Act, Congress gave this series of programs its own budget and called it the Common Fund," Wilder adds. "So we have begun to refer to the programs as the Common Fund programs."

Originally, the Roadmap was envisioned to be a five to 10 year program, but its success will translate into ongoing programs and work.

"They're accomplishing their goals and moving to other sources of support," Wilder says.

One of the successful programs resulting indirectly from this effort is the Clinical Translational and Science Awards (CTSA) programs, which have brought research leaders at major academic research institutions together to solve clinical research (CR) problems facing the industry, says **Anthony Hayward**, MD, PhD, director of the division for clinical research resources at the NIH National Center for Research Resources.

"Resources that already existed at NCRR were merged with Roadmap money in 2006 to create the CTSA," he adds. "We expect to reach a target of having 60 CTSA sites by July, 2011."

These 60 academic health centers will be committed to working together to share best practices and implement them, Hayward says.

CTSA sites have raised the overall standard of education across programs and have developed new shared informatics tools and data sharing

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agreements, he notes.

"If you Google REDCap you'll find new tools that enable investigators to use a template for a database that can be adapted to their research needs," Hayward says. "Or Google ResearchMatch and you'll find new tools available that allow people to indicate they would like to be part of a clinical trial."

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EDITORIAL QUESTIONS

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ResearchMatch is a new and rapidly growing resource for investigators to use when recruiting clinical trial subjects. And CTSA funds have led to the creation of REDCap electronic data collection instruments, which have interoperability with electronic medical systems. *(See stories about ResearchMatch.org at p. 3 and REDCap at p. 5).*

"One of the things clinical researchers need is access to patients and community outreach," Hayward says. "So we have urged, encouraged, and then made it compulsory to have a community engagement activity at all CTSAs."

Also, CTSAs are encouraged to share and collaborate, and some have done this in community outreach, he notes.

For instance, three Chicago CTSA sites collaborated in a capacity-building project to increase clinical trial enrollment, says **Donna Jo McCloskey,** PhD, program officer at NIH's division for clinical research resources at the National Center for Research Resources.

"All three sites have two different focuses, including their engagement with a practice-based research network and engaging their lay community in clinical research," she says. "Their goal is to make the community aware of research efforts at each of their sites and to expand this."

The original 12 CTSA centers agreed to work together and make these collaborations work for their individual institutions. This hasn't always been easy.

For instance, the CTSAs at Yale University in New Haven, CT, and the Mayo Clinic in Rochester, MN, decided that a sharing agreement reviewed and approved by their respective legal departments would allow for the maximum flexibility in sharing.

It also would define how CR tools created in the collaboration or by the individual institutions would be shared and used, says **Cheryl Nelson,** associate director of administration for Center for Translational Science Activities at the Mayo Clinic.

"We tried to keep the agreement very simple so that the document could also be offered as an example that other sites and principal investigators could use when dealing with similar sharing programs," Nelson adds.

"We thought we'd send it around to our legal departments [for review and expected it to take about] two weeks," notes **Stacey Scirocco,** executive director for administration and operations at the Yale Center for Clinical Investigation.

Instead, the legal review took about a year to complete.

While the end result is that the institutions now have a legal document that could serve as a model for other institutions involved in collaborations that might create best practice tools, it proved to be more difficult to achieve than anticipated, Scirocco adds.

When the NIH Roadmap was launched with the theme of re-engineering the clinical research enterprise, it had established implementation groups to focus on these areas:

- Harmonization of clinical research regulatory requirements.
- Integration of clinical research networks.
- Enhance clinical research workforce training.
- Clinical research informatics: National Electronic Clinical Trials and Research Network.
- Translational research core services.
- Regional translational research centers.
- Enabling technologies for improved assessment of clinical outcomes.

As the CTSA stories show, research institutions are benefiting from the Common Fund's focus on collaboration and finding ways to spread best practices and research enterprise efficiencies.

For example, Yale and the Mayo Clinic have benefited from sharing successful tools and initiatives.

"We have a work group we call the IRB collaboration, and it's designed to identify IRB improvement initiatives that impact IRB processing times," Scirocco says. "Another aim is to facilitate scientists engaged in local clinics and other organizations to conduct human subjects research."

The CTSA project's main goal is to speed up initiation of clinical research and the overall timeline through a change of practices, she adds.

The Mayo Clinic has helped Yale with another goal of increasing minority inclusion in clinical trials, Scirocco says.

"Mayo has a great cultural advisor program that Yale is interested in modeling, and we want to learn more about their consent translations," she adds. "And we'd like to replicate it here and provide it as a resource for our investigators."

The Mayo Clinic has taken a look at Yale University's process for managing and working with affiliated IRBs, Nelson says.

"Yale has a very established process with specific operational, detailed procedures and templates that allow investigators to provide information to the Yale IRB and share information from the IRB to the affiliate," Nelson adds. "The Yale process allows Yale affiliates to utilize Yale IRB while Yale recognizes the local IRB review. It begins to address some of the aspects of a centralized IRB."

As part of the CTSA organizations' collaboration, they evaluate each other's tools, processes, and procedures and determine which items can be shared and used by each site and by other CTSA organizations.

The collaboration might result in the paired institutions coming up with a cost effective collaboration model that can be used by other institutions, Scirocco says.

"The idea is to look at what succeeds in both organizations and find a way to share the information," she adds. "The value of looking at each other's successes is that you can save a lot of time by documenting how that process works between the two institutions."

The NIH Common Fund has had some other notable successes, Wilder notes.

"Each of them has different goals and these are addressed in different ways," Wilder says. "One of the larger ones was the molecular library and establishment of small molecule screening centers around the country."

That program established a database that has been embraced by the chemical biological community, she adds.

The NIH Common Fund also has encouraged interdisciplinary research, helping to elevate this to a standard way of doing business in the research community within the past seven years, Wilder says.

"We were able to successfully put that in the forebrain of people's collective mentality," she says. "That program has been successful in testing new ways of doing interdisciplinary research." ■

ResearchMatch searches can be useful for clinical trial investigators

Some studies fully enroll in days

While ClinicalTrials.gov offers the public searchable information about clinical trials that might interest them, another research website offers investigators the potential of reaching their trial's enrollment goals without having to run an advertisement.

Called ResearchMatch.org, the website is available only to organizations that have received the National Institutes of Health's (NIH's) Clinical Translational and Science Awards (CTSA).

"However, we are in the process of expanding ResearchMatch to allow other academic institutions to participate, and we're very excited about that," says **Laurie Lebo**, PhD, ResearchMatch program coordinator at Vanderbilt University in Nashville, TN.

"In the next six months, we are expanding to academic medical centers," she says. "It might be made available to any research organization in the near future."

ResearchMatch was funded through CTSA as a national recruitment registry that matches volunteers interested in participating in research with investigators who need volunteers.

"It's a kind of eHarmony for research," Lebo says. "Volunteers spend five to 10 minutes entering data about themselves."

CTSA researchers who have an IRB-approved protocol can use ResearchMatch's search engine to find volunteers who meet their study's basic criteria, including age, gender, weight, she explains.

The search engine also divides volunteers geographically, according to how far they say they are willing to travel for a study.

"If someone has a rare disease and there are few studies conducted for that disease, then they might be willing to travel across the country," Lebo says.

The website also asks volunteers for some health data, including whether they have hypertension or other medical conditions. Volunteers also list their medications, and the search engine helps them find the correct spelling.

"If they know which letter their medication starts with and type it, then all the possibilities come up," Lebo says. "The next step is a text box where the volunteer can enter any additional information."

Vanderbilt has helped promote ResearchMatch at corporate health fairs, on Facebook and Twitter ads, and through word-by-mouth.

"I talk about ResearchMatch everywhere," Lebo says. "We have volunteers from every part of the country."

So far, ResearchMatch has about 12,000 volunteers registered, and investigator contacts have been made more than 25,000 times, Lebo says.

"Of those, 5,558 people [as of November, 2010] have said, 'Yes, contact me about participating,'" she adds.

About half of the people who've entered information in ResearchMatch are healthy volunteers, she says.

The website's early enrollment data show that one in five people will say 'yes' to being contacted about a study, and one in five of these people will enroll in a trial, Lebo says.

"I think ResearchMatch will be a more successful tool than ClinicalTrials.gov because with ClinicalTrials.gov, the volunteer has to go in every day and look to see which studies are available, and there is no place for the volunteer to enter information," Lebo says. "In ResearchMatch, they only enter information one time, so it's much easier for both the researcher and the volunteer."

Unlike ClinicalTrials.gov, ResearchMatch's search engine does not permit volunteers to shop around for a clinical trial or contact investigators.

"Volunteers enter their profile information, and then the investigator will contact them about a study," Lebo says.

Researchers send out an email that says the person might be a match for a study, and it asks if the volunteer would like to be contacted by the research team.

"When the volunteer says, 'yes,' then it is identifiable information that is released to the researcher," Lebo says.

"We send the researcher and coordinator a daily digest email to remind them of the volunteers they need to contact about their study," she adds.

The electronic tool has two other important features: First, it permits investigators to search its database to see how many people might meet their studies' criteria.

So if an investigator is writing a grant and needs to see how difficult it might be to recruit volunteers for the study, the database search will provide a strong clue.

"People who register with ResearchMatch are interested in doing research, so this information is much more valuable," Lebo says.

The second feature involves an automatic repeat search that works for at least 30 days.

"One of my favorite tools is that ResearchMatch allows you to set up an auto-contact rule," Lebo says.

The auto-contact rule works this way: The principal investigator (PI) sets up a search, and the electronic tool sends him or her a list of potential matches, without their identifiable information. Then the PI emails these people asking if they would be interested in learning more about the study. People are continuing to join ResearchMatch each day, so every night, the tool will send out a repeat search for the investigator. This continues for 30 days, and the PI can renew it. All of the additional matches are sent to the PI's

email inbox to be reviewed each morning.

ResearchMatch has proven to be especially useful to investigators conducting survey research, Lebo notes.

"It's fabulous for them," she says. "They get all of their participants within an hour." ■

REDCap data capture system pulls heavy weight for CTs

Free application is easy to use

One of the technological advances resulting from the National Institutes of Health's (NIH's) Clinical Translational and Science Awards (CTSA) project is a stream-lined, flexible, and interoperable data capture system called the REDCap (Research Electronic Data Capture).

More than 4,500 studies now use REDCap, and the REDCap Consortium includes 171 institutional partners. REDCap has a second web-based application called REDCap Survey, as well.

REDCap is a federally-funded project that provides code and technical support to nonprofit institutions or academic institutions that join the consortium.

Developed at Vanderbilt University in Nashville, TN, REDCap has received CTSA funding and is disseminated at no charge to consortium members, says **Janey Wang**, MS, MEng, project manager for the REDCap Project at Vanderbilt.

"What's nice about REDCap is it is a very simple data capture system that can be used for anything," Wang says. "You don't have to have a very fully finalized data collection instrument before you use REDCap."

All investigators need to do is think through data types and data elements they plan to collect.

"We're trying to empower researchers to be more [proactive] with data management," Wang explains. "REDCap saves them the cost of hiring additional personnel or constantly consulting a data management team."

New investigators can use REDCap for free, so long as they know which data elements they want to collect and can monitor these.

"The learning curve is not high, and we provide a lot of materials and resources for end users to explore REDCap on their own," Wang says. "Researchers find it's easy to learn in a cost-efficient way."

Here are some of REDCap's features:

• **Retrospective and prospective data collection:** REDCap has been used for clinical research, collecting everything from demographics and medical history to use in pilot trials and retrospective studies.

The application can extract data from medical records and restructure these in ways that are useful to investigators, Wang says.

"It has the capability to reduce data entry forms multiple times and put these in longitudinal format so end users define their studies' scheduled events along REDCap, as in baseline, visit 1, visit 2, etc.," Wang explains.

"Then it can create data entry forms for the study and designate which form they want to use at multiple times," she says. "If they have an adverse event form defined for their study, then they can use it for all events where they want follow-up."

REDCap can collect adverse event data without requiring every field to have an entry every time. This makes it more flexible for clinical trial use, she adds.

• **Data transfer system:** One of REDCap's most useful features is it's interoperability with electronic medical record (EMR) systems.

"If an investigator has some patients in the EMR repository and wants to pull out those data from the EMR, then REDCap can assist with this," Wang says.

This interoperability is being tested at Vanderbilt and four other academic research sites, Wang says.

"Each has a different EMR system, but we wrote the program to be flexible enough to allow interoperability," she adds. "It's being optimized in our shop to make sure we can accommodate the different systems out there."

It's challenging to use different EMR systems, but there is a huge need for this flexibility among researchers because it can save them a lot of time on data collection and input, Wang notes.

"You can pull data from the EMR on lab results, combined criteria, and it saves a lot of time," she says.

• **Data instrument share library:** The REDCap consortium website at www.project-redcap.org contains a library with a variety of validated study instruments that investigators can use.

One includes the Rand 36 Item SF Health Survey Instrument (Version 1.0), which is a short form for collecting quality of life data. Other instruments featured in the library are as follows:

— Ten-Item Personality Inventory-(TIPI).
— PROMIS Emotional Distress - Depression - Short Form 8b.
— Pittsburgh Sleep Quality Index (PSQI).
— Geriatric Depression Scale GDS Short Form.
— BRFSS 2009 Section 3: Health Care Access.

"Once investigators identify the correct instrument they want to use, they can import it into REDCap, and they won't have to develop a data entry form because it already exists," Wang says.

Researchers simply have to define the field and make sure the data entry form includes all the questions necessary and in the correct order, she adds.

"In a way, we're advocating the concept of using standardized instruments and standardized vocabulary and conventions for data elements," she adds. "Once data are exported they can change it freely, and the values are stored the same way."

This particular resource will continue to grow and increase in value to researchers as more instruments are added to the library, Wang says.

• **Technical support:** "The REDCap consortium is a very active group of people who are knowledgeable in terms of informatics, and they share information with others," Wang says.

Any technical problems sites have with REDCap can be answered through an archive of discussions or by members of the consortium.

"We don't have a team at Vanderbilt, so a lot of technical support is done by the consortium itself on a voluntary basis," Wang says. "Newcomers mostly feel it's well supported, and they are able to get feedback very quickly." ■

CASE STUDY

Expert offers tried and true strategies for balancing the books

CT site quickly turned red ink black

Collecting timely payments from sponsors is a common issue for clinical trial sites. Assigning payments to the correct budget also can be a problem. Mistakes in these areas can lead to cash-flow difficulties.

The good news is that clinical trial sites can improve their billing, budgets, and collections by establishing a thorough tracking program, one expert suggests.

"The big issue is that you could be losing money if you don't have a handle on what is coming in," says **Rachel Garman**, LPN, CCRC, research manager, oncology, at Cancer Care Northwest in Spokane, WA.

When Garman began working as the manager of the community clinical trial site, she was handed a budget that said the research activities were $80,000 in the hole.

"I did not see how we could be at that level," Garman says.

After an audit and closer look at the budgeting and accounting, she found $22,000 in lost funds.

Sponsor payments that were intended for specific trials were being deposited in the wrong accounts because no one had caught the mistakes. Fortunately, Garman was able to track down the lost money and have it re-deposited in the research account.

Garman also discovered that a very expensive piece of lab equipment was incorrectly charged to the research account.

"It was an error that made my department look bad," she says. "The clinical side should have paid for it, and returning this charge to the clinical side put us back in the black."

These mistakes were all avoidable on the part of the trial site.

"Sometimes it isn't the sponsor making mistakes," Garman notes. "On our end we missed stuff on invoices and billed items incorrectly."

After turning around the trial site's deficit within one year, Garman next tackled the entire billing and collecting process to make certain there would be no future mistakes of that magnitude. Here's how she did it:

• **Design billing tracking tools:** "They said we could use whatever we wanted as long as it was free," Garman says. "So we made Excel Spreadsheets, designing them to our tracking needs."

The tracking mechanism notes what money is coming in and what it is for. It also lists subjects' initials, time points for receiving payments, dates when money was received, comments, and how much was budgeted for any particular trial and visit.

"I had someone help me who is an Excel genius and could work the spreadsheets very quickly," Garman says. "But even if I had to do it myself, it

would be worth its weight in gold."

Each trial has its own spreadsheet because the payment particulars and requirements vary.

"Some trials have you submit the data electronically in order to get paid; some trials have you send an invoice," she says. "Each path is based on that specific need."

For example, in one trial the site doesn't receive payment until the investigator reviews the data and puts in an electronic signature. As a result, that trial's spreadsheet has a way for Garman to track whether the investigator has followed the requirements.

• **Keep track of what is billed and what is paid:** "I'm looking at the spreadsheets all the time," Garman says. "I have an amounts received column, and I check it to see if the money that came in is the amount I was supposed to receive."

If the amounts billed and paid match, Garman highlights the row in yellow. This way she can take a look at a sheet and easily see where the unpaid items are located.

When she catches an item that was billed, but not paid, she will check up on it to make certain the payment did not arrive in the accounting office and subsequently get put in the wrong place.

"I spend about eight to 12 hours a month checking on these spreadsheets, and some months it'll take longer," Garman says. "The important thing is that it's done in real time, so as soon as a check is received the accounting staff makes a copy and sends it to me."

• **Get accounting personnel on board with changes:** "I told the accounting office exactly what I needed to make my department function in an optimal setting," Garman says.

The accounting staff complied and now handles the research checks correctly.

Sometimes when Garman is expecting a specific research check, she'll contact the accounting office and let them know that it was billed that week and is expected to come in shortly.

"The tough part is when the odd check comes into the practice and it comes to me because it doesn't have anything to do with research," Garman says. "I weed it out and send out what's not mine."

• **Address late payments:** "This hasn't been a huge issue — just a couple of isolated cases," she notes. "But you have to be aggressive."

When a sponsor is late with a payment, Garman first sends out an email that says the subject was seen on this date and the payment has not yet arrived.

"I ask where they stand with this payment." she says.

Then if there still is no payment, Garman will send the sponsor a duplicate invoice by email in order to reiterate the request for payment.

"I send out emails for documentation purposes," she says.

For the rare occasions when the payment still does not arrive, Garman will call the point person about it.

"If we have somebody we're not getting payments from, we'll look at this issue when we do a study feasibility," Garman says.

The key to improving a clinical trial site's billing practice is to have checks and balances in place, she says.

"You need to keep a tight rein on it and verify why you haven't been paid," Garman says. "You can't have outstanding funds, and the longer they haven't been received, the harder they are to get." ■

ASK THE EXPERTS

Take this expert's advice on improving CT negotiations

Keep a sense of humor about it

Clinical trial sites can improve their clinical trial (CT) negotiation processes and reduce misunderstandings with sponsors and clinical research organizations by being clear about objectives and desires.

An expert in these types of negotiations provides *Clinical Trials Administrator* with advice on how CT sites can get the most from the CT agreement process in this question-and-answer story featuring **Robert L. Croog**, JD, corporate counsel and associate director of legal services at PTC Therapeutics Inc. of South Plainfield, NJ.

***CTA*: When working with clinical trial sites during the clinical trial agreement process, what are some of the chief issues or misunderstandings that can arise, and how can these be resolved?**

Croog: Misunderstandings can occasionally

arise because the legal language in a proposed draft is misinterpreted. This happens more frequently in international trials when the site and sponsor speak different languages, but it can happen with domestic sites, too. Usually, speaking on the phone or communicating by email to provide an explanation of a particular sentence or paragraph can resolve the matter. Sometimes, an explanation may not be enough, and the site may request an example be inserted in the text to illustrate how a provision works in practice.

The publication section of the agreement is another area where misunderstandings can arise. The site, existing in a world of academic freedom, in which great value is placed on disseminating knowledge by publication, may not want to limit the right to publish results of the study. The sponsor, being a business heavily invested in the outcome, wants to publish results in a way that will preserve its ownership of intellectual property (IP), in due course after careful review to ensure accuracy of reported findings — and confidentiality is key until the analysis is complete. Usually it comes down to mutually agreeing on a reasonable period of time for sponsor review before publication, per standards accepted in the academic and biotech industry. If there are a number of centers in the study, it's important that the site understands, and that it's reflected in the agreement, that a multi-center publication occur before any one site's, or investigator's, publication. Again, market standards indicate reasonable periods for a site or investigator to wait for the multi-center publication to go first, and these periods will be set forth in the agreement.

Sometimes, investigators or their sites want the agreement to ensure their right to be named in any publication. The ICMJE guidelines are helpful in this regard. The important thing is that a unified approach be taken, fair to the study centers collectively.

One of the most frequently negotiated areas of the agreement is the IP section. Since the average cost of discovering, studying and bringing a drug to market in today's economy is upward of a billion dollars, you can imagine that it's a section of the agreement to which the sponsor will pay special attention. I have found that sites understand how important this is to the sponsor's business (i.e. recouping investment) and will agree, consistent with market standards, to reasonable terms relating to any inventions or discoveries made in the course of the study, or resulting from the protocol or the carrying out of the agreement. Often there will be some negotiation to find the right language that both sides are comfortable with.

CTA: **What are some important areas to address in CT agreements that sponsors and/or CT sites sometimes overlook?**

Croog: Sometimes overlooked is the possibility that the study protocol may be amended after the agreement is signed. If the protocol is an attachment to the agreement, language should be included in the agreement to anticipate and allow for protocol amendments, so the parties won't have to also amend the agreement later.

Another area that may be overlooked is the warranty of non-debarment. The FDA maintains a list of practitioners and institutions excluded from practice, for violations of one sort or another. The FDA can exclude study results obtained by debarred persons or institutions. Not only is it important to include a warranty by the site that none of the study personnel has been debarred, it should add that none have committed any action that could reasonably lead to debarment. Moreover, the sponsor should require the site to affirmatively alert the sponsor if any debarment-related issue arises after the agreement is signed, during the study, and even up to five years beyond its end (or if earlier, until a marketing application is filed with the FDA in connection with the study). Having this type of language in place can assist sponsors in meeting their reporting obligations to the FDA.

If the site or the sponsor is new to clinical trial practice, the other party may want to inquire to make sure both sides understand all their respective responsibilities with regard to Good Clinical Practice (GCPs), patient confidentiality requirements, record-keeping, internal procedures and policies for shipping and handling drugs, and safety. Everyone is a professional in the field, but best practice is to check if they're new.

CTA: **What are some best practice strategies for making this CT agreement process go as smoothly and fairly as possible?**

Croog: Channels of communication that are smooth and open (both internal and external), being organized, are key to success. Often the parties are in a rush to complete the agreement and begin the study. Legal departments may handle the agreement, but sometimes sites' technology offices may need to review the IP section, and of course the investigator must be kept closely in the loop. Clinical, regulatory and finance departments

of sponsors each play critical roles and need to be questioned as appropriate and kept informed and up to date by the legal department, as issues may arise that require their input. With all these organizational stakeholders, it's important that between the site and the sponsor, there is one main point of contact at each for communication about the agreement.

Often clinical research organizations (CROs) are involved in a study. It's important to delineate their role in the agreement, as an agent of the sponsor, and provide some details of their role in the study. Will they provide monitoring services only, or also handle receipt and payment of invoices?

Professional courtesy and a sense of humor can assist in the process of working through an agreement.

It pays to show sensitivity to local culture and regulatory set-ups. This is more important in the international context. Sites outside the US will often be subject to regulatory requirements that influence the agreement in ways that US sponsors dealing with domestic sites will not be accustomed to. Inevitably, if the sponsor wants to conduct studies abroad, it will have to show greater flexibility where regulatory requirements limit what sponsors and sites can agree to. In the international arena, it helps the sponsor and the site to have a good CRO that can act as go-between, and communicate across language divides, and do so in a way that not only translates, but explains, each side's position to the other. ■

COMPLIANCE CORNER

Yale's QI self-assessment tool assists with better site compliance

It also helps with internal audits

Many clinical research institutions have limited resources for internal audits or quality improvement (QI) checks, so the key is to create proactive tools and policies to improve overall site regulatory compliance.

Yale University of New Haven, CT, has mastered this strategy through its creation of a quality improvement self-assessment tool and checklist.

There only are enough staff resources for about seven quality improvement reviews per quarter, says **Tracy Rightmer**, JD, CIP, compliance manager of the human research protection program at Yale University.

"So we focus on smaller, investigator-initiated studies, federally-funded studies, and others that are not industry-sponsored because those have outside organizations that monitor their activities," she explains.

The studies selected for audits are randomly chosen, based on criteria of greater-than-minimal risk.

The compliance office recommends that researchers improve their processes before a QI visit by completing a self-assessment tool. This tool also serves as a way to educate investigators and research staff on what is expected of them in terms of regulatory documentation, IRB documentation, subject recruitment procedures, informed consent process, subject selection criteria, adverse event reporting, drug/device dispensing accountability, and case report form source documents.

The regulatory documentation section includes references of specific regulations to which the questions pertain. Here are some examples of the self-assessment tool's questions about regulatory documentation:

- Is the approved protocol (and consent) on file?
- Is there a subject enrollment log? # of subjects included; # of subjects excluded.
- Has the protocol been monitored by the PI or outside monitor as described in the protocol DSMP? Is there a monitoring log? How often is the study monitored?
- Are all personnel who interact with subjects or their identifiable data listed on the protocol? Have all personnel completed the required HSPT and HIPAA training?
- Is there a staff signature log? Is the staff signature log complete? Does the staff signature log include delegation of responsibilities?
- Are lab tests required? Is a copy of normal lab values on file?
- If eligibility or treatment decisions are based on test results or when study results are shared with subjects, are they done in a CLIA-approved certified lab?
- Is there a COI on this protocol? If so, has the HIC management plan been adhered to?

The point of quality assurance visits is to help investigators and clinical research staff with their documentation and compliance, Rightmer notes.

"We give them an idea of what to expect during the visit, and this reduces some anxiety," she adds. "This is something we do to help them with the process and to work collaboratively to ensure all safeguards for the protection of human subjects are being followed."

The QA reviews are time-consuming and involved, but can be made easier for both the site and QA coordinator if the site has been conducting its own internal audits and monitoring. The self-assessment tool provides a simple structure for doing this. For instance, the self-assessment checklist gives investigators prompts on what is required in subject recruitment procedures, the informed consent process, and subject selection criteria. Here are the checklist questions for these three areas:

- Are recruitment methods stated in the protocol?
- Are approved recruitment materials (original and all revisions) on file?
- Have changes to the recruitment materials been made since the last reapproval?
- If yes, was an amendment submitted to the IRB?
- How many versions of the consent form are there (i.e., how many times has the ICF been amended)?
- How many different consent forms are being used in this study (e.g., healthy volunteers, adult subjects, minors)?
- Provide the approval and expiration date for each version of the consent form.
- Are all the original consent forms approved by the HIC on file?
- List the subject files chosen for inspection (this may be a sample of subject files or all subject files).
- Was any invalid consent form used?
- If yes, was a protocol violation submitted to the IRB?
- Did each subject or his/her [legally authorized representative] sign his/her own consent form?
- Did each subject or his/her [legally authorized representative] date his/her own consent form?
- Are there copies of enrollment notes written for each subject and kept in each subject's chart?
- Did each subject or his/her [legally authorized representative] receive a copy of the signed consent form? Is subject's receipt of a copy of the signed consent form documented?
- Is there an inclusion/exclusion criteria checklist?
- Does each record indicate that the subject was included/excluded appropriately?
- If subject was included inappropriately, was a protocol deviation submitted to the IRB?
- Does the inclusion/exclusion criteria checklist for each subject include the dated signature/initials of the person obtaining the information?

Typically, CT sites receive a short report with recommendations following the QA visit.

"We'll provide them with templates with enrollment logs and inclusion/exclusion criteria checklists, and things like that," Rightmer says. "Depending on the findings, we will require corrective actions and a time line for completing those corrective actions."

There is a follow-up to make sure those corrective actions have been completed, she adds. ■

International research requires lengthy capacity building

Don't just parachute in and fly out

International HIV vaccine trials underway in resource-poor settings provide good examples of how clinical research (CR) can be done in both ethical and culturally-sensitive ways despite a wide variety of obstacles.

Even without recent reminders of past callous behavior by researchers, such as the recent news of U.S. public health investigators intentionally infecting Guatemalans with sexually transmitted diseases (STDs), there have been rumors and tall tales of immoral research behavior circulating among some international populations.

For instance, some people in sub-Saharan Africa still believe that AIDS was a creation of white people to eradicate blacks.

HIV researchers working in these international settings continue to do their work as carefully and sensitively as they can in hopes of dispelling these rumors and false beliefs.

"Those who are engaged in the day-to-day combat against AIDS are facing rumors and misconceptions all the time, and they have mixed success," says **Robert J. Levine**, MD, professor of medicine and lecturer in pharmacology at Yale University School of Medicine in New Haven, CT. Levine also is a senior fellow in bioethics and was co-founder of the Yale

Interdisciplinary Center for Bioethics at Yale.

One success involves the increased use of condoms in Africa, despite some regions' cultural bias against condom use, he notes.

"There is increasing cooperation with clinical trials, but there's even more cooperation with treatment regimens," Levine says.

International documents, including those that address the ethics of international vaccine research, have a strong expectation for capacity building in countries hosting research.

"It's my view that capacity building is most important when you have as prolonged interaction with the people of a country as you do in a vaccine development program," Levine says. "You don't just parachute in and do research and leave."

Vaccine research is an especially long-term investment since it can take seven to 10 years or longer.

"This is not a transient contract," Levine says. "It's most important to do capacity building when you have this long of an engagement."

While HIV vaccine research is fairly prominent on the international scene now, building capacity in an international setting is important for any type of research, including influenza vaccine studies and others, he notes.

The best way to build this capacity is through continued contact with the community after and between trials.

"This is one reason why vaccine trials have been so popular in Uganda and Thailand," Levine says. "The United States has been collaborating with people in the major cities of those countries for many years, so a new study is not a big thing."

When an international community has no context or past history with researchers, then capacity building is resource intensive and time-consuming, often taking years to build the trust and relationships necessary for a successful trial, he adds.

Until this foundation of trust is solid, it would be difficult to have ethical and practical debates with research communities about the responsibilities of investigators and sponsors after the study ends.

For instance, in HIV vaccine research, it's expected that some people will be infected with HIV because the vaccine or control substance doesn't work and they haven't followed the researchers' instructions to follow safe sex practices. So what happens to these people?

Is it the responsibility of the study sponsor to provide them with lifelong antiretroviral therapy?

"In the United States, if you are exposed to the HIV virus or anthrax virus you immediately are given post-exposure treatment," Levine says. "Do we owe that level of care to people in other countries?"

Or should the sponsor make antiretroviral treatment available and affordable to study volunteers?

There are a number of ways these can be handled, and research projects have had no consistent answer to these questions, so it's a debate that has to be made at the community level after investigators have done the groundwork necessary to build capacity and trust. ■

CNE/CME OBJECTIVES / INSTRUCTIONS

The CNE/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.

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 letter of credit. When your evaluation is received, a letter of credit will be mailed to you.

COMING IN FUTURE MONTHS

CNE/CME QUESTIONS

1. Which of the following was one of the original goals of the National Institutes of Health Roadmap for Research announced in 2003?
A. Harmonization of clinical research regulatory requirements.
B. Integration of clinical research networks.
C. Regional translational research centers.
D. All of the above were among the original goals

2. ResearchMatch.org is a national study recruitment registry that works in which of the following ways?
A. It gives potential study volunteers a list of open studies, along with investigator contact information
B. It enables researchers to find potential volunteers who meet their studies' basic criteria
C. The website serves as a clearinghouse for under-enrolled studies and potential volunteers
D. All of the above

3. Which of the following questions would *not* be important to include in a quality improvement checklist that addresses best practices in subject recruitment?
A. Do you anticipate meeting recruitment goals?
B. Are recruitment methods stated in the protocol?
C. Are approved recruitment materials (original and all revisions) on file?
D. Have changes to the recruitment materials been made since the last reapproval?

4. True or False: To improve a CT site's billing collection process, it's a good strategy to compare the amounts received column of a spreadsheet with the billed column.
A. True
B. False

Answers: 1. D; 2. B; 3. A; 4. A

CLINICAL TRIALS ADMINISTRATOR
An essential resource for managers of clinical trials

It's performance and results — and not just the economy — impacting research sites

Wages, however, are another story

Clinical trial sites might be experiencing an upward or downward cycle of business, but they can't blame it on the economy, some experts say. Sure, there is high unemployment overall and some depressed industries, but in the world of clinical research, things are booming for sites that demonstrate success in enrollment and performance.

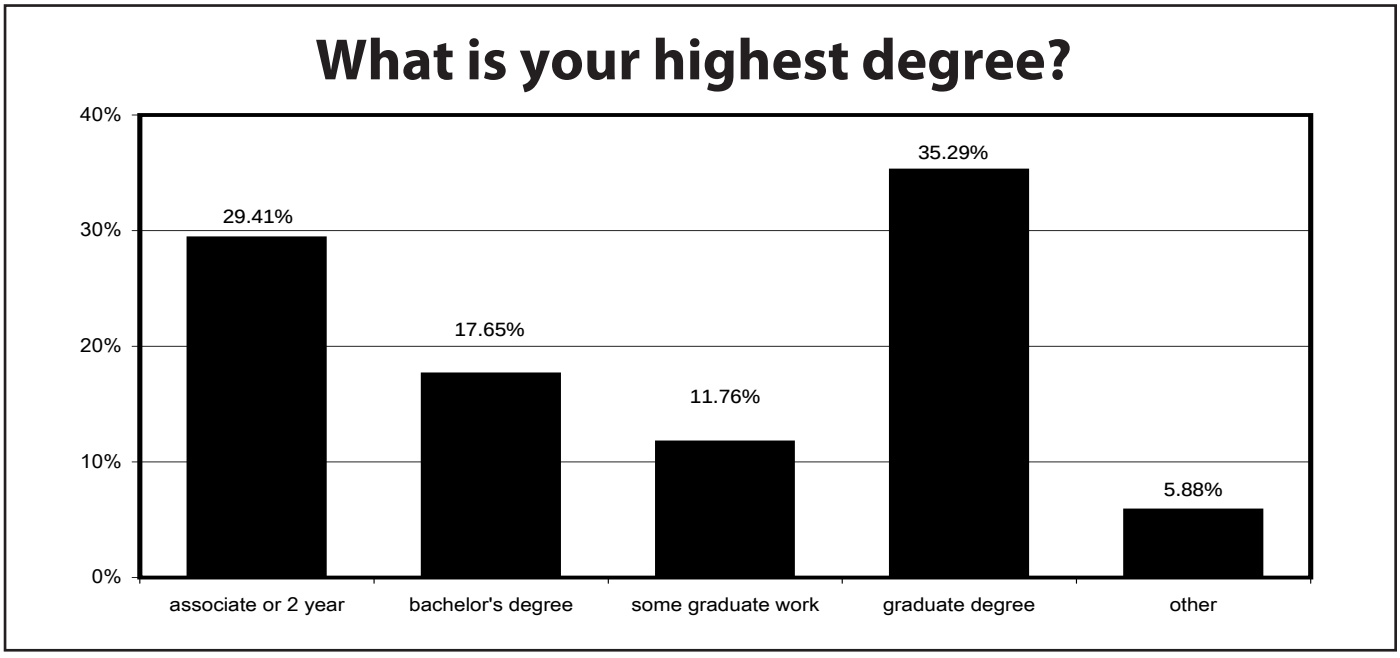
"We've been expanding staffing, actually growing," says **Tammy Anderson**, CCRC, CCRA, CRCP, director of the clinical trials office at Virginia Commonwealth University in Richmond, VA.

While other sites might see fewer studies come their way, the Virginia Commonwealth University Office of Research has seen an increase in studies, she adds.

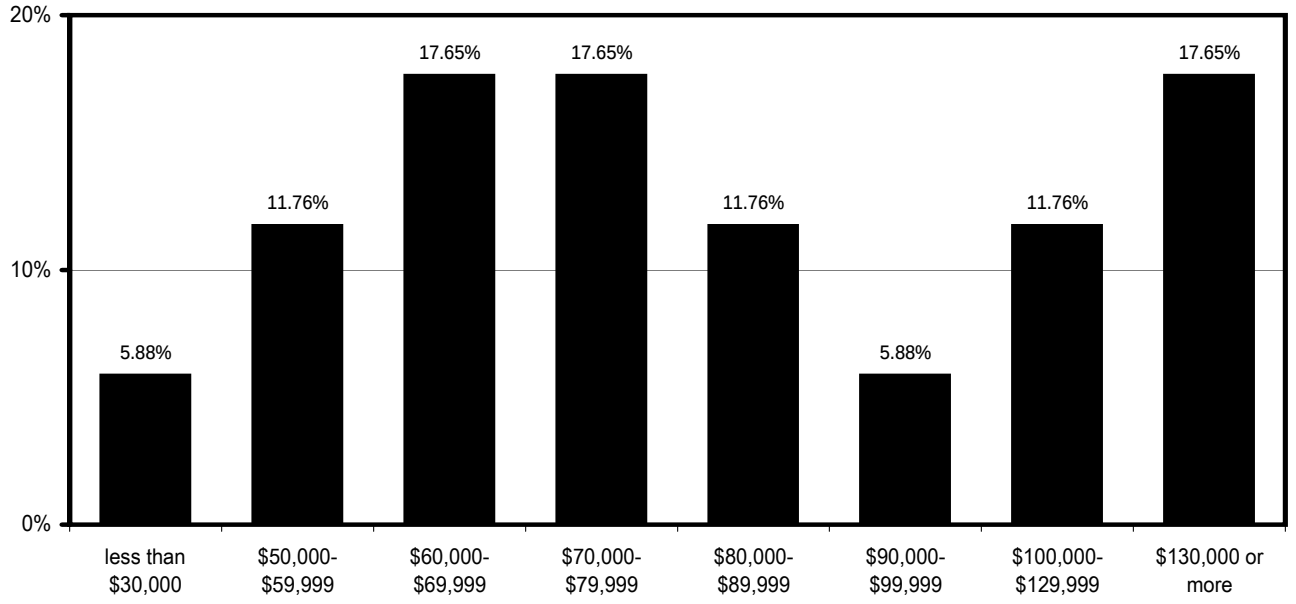
One key is to proactively work with sponsors to build direct collaborations, Anderson says.

Another ingredient in the CT site's success is the site's efficiency and track record.

"There's a misconception where people think business is slow because of the economy or because there aren't as many trials in the United States, which is true," Anderson explains. "There aren't as many trials and a larger percentage are going



What is your annual gross income?



overseas, but there still is a lot of clinical trial work being done in the United States."

The reality is that CT sites that operate efficiently and meet their enrollment projects are getting more contracts, she says.

"There's a new trend where sponsors are requiring more efficient sites and sites that are experienced and have compliance and training issues in place," she adds.

CT business fluctuates, but it's been an upward trend for the VA Sierra Nevada Health Care System's research office, says **Elizabeth E. Hill**, PhD, RN, associate chief of staff for research at the Reno, NV, site.

"We're getting more business," Hill says.

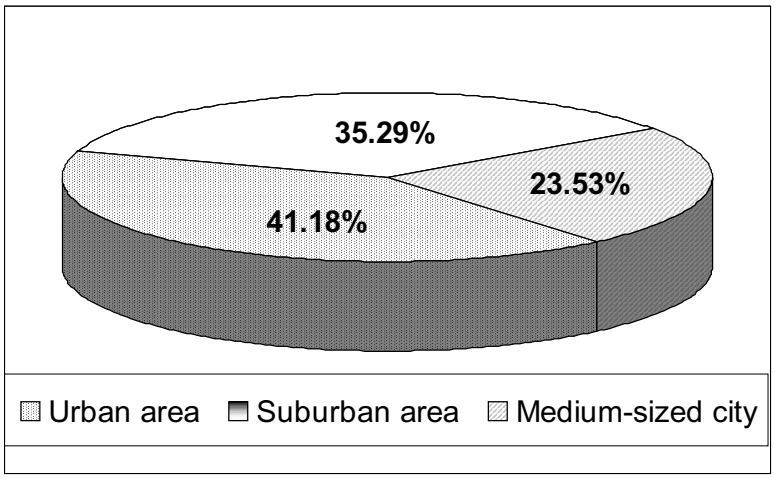
The hard part is finding experienced staff, Anderson and Hill say.

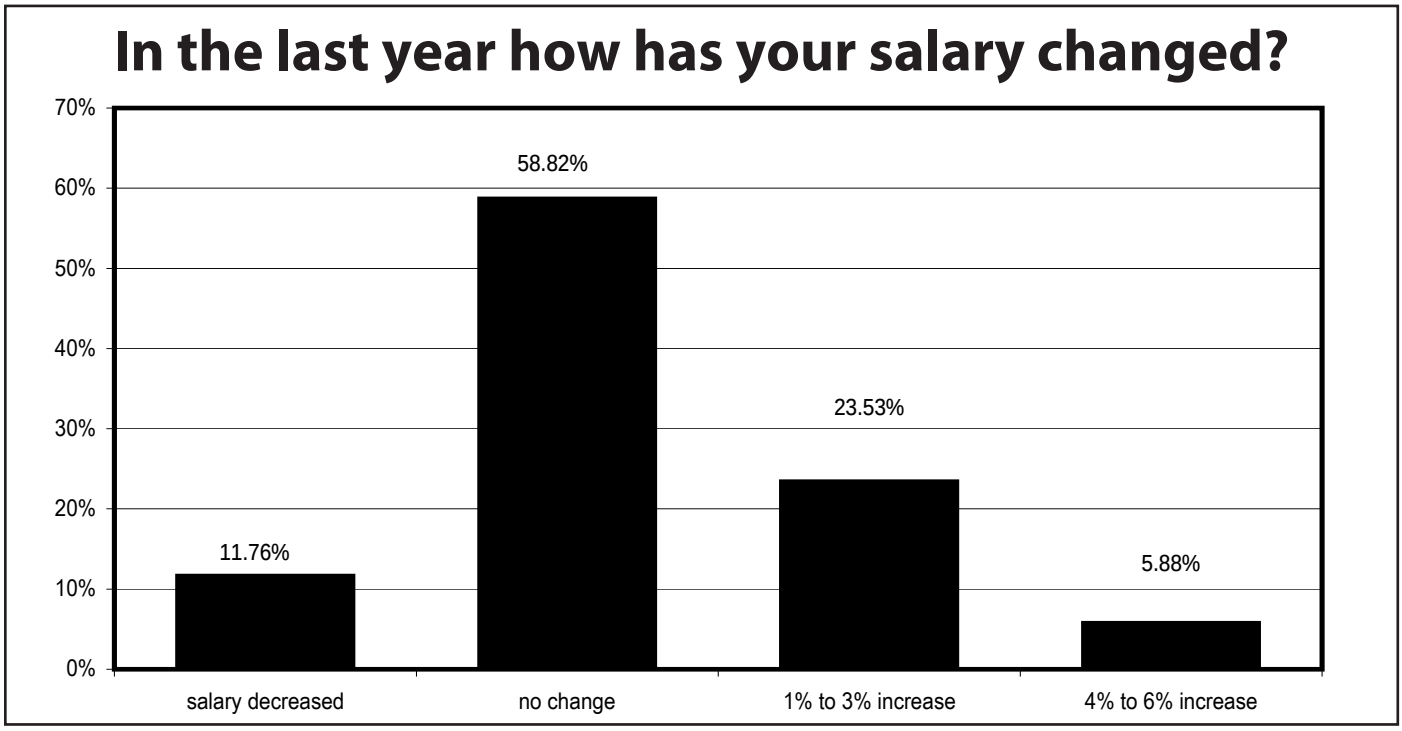
"It's a tight market for finding experienced staff, and there are fewer and fewer experienced coordinators out there," Anderson says.

This is true particularly as salaries are frozen at many institutional research sites.

Clinical Trials Administrator's annual salary survey reflected this trend as about 59% of people

Where is your facility located?





responding to the survey said their salary has not changed in the past year. Another 12% said their salary decreased, and nearly 24% saw a 1% to 3% increase. While many clinical research professionals had received 4% to 6% increases in previous years, there was only one such report this year.

A number of states, including Virginia, have frozen all salaries, including those in state universities.

Also, in November, 2010, President Barack Obama announced freezing federal salaries, including those at VA hospitals.

"I can find people, but I have a hard time finding people with the experience I'd like them to have," Hill says. "It's still a fairly tight job market, and the pay freeze will have an impact on recruitment."

CR sites can improve their staffing situation by using their staff more efficiently, Anderson suggests.

One strategy is to use a team approach that puts the most experienced and highest pay grade employees in jobs that use their skills, while leaving administrative tasks and other lower-level work to less experienced staff, she says.

Sites that do this might find they attract a greater proportion of that small pool of experienced research coordinators.

"I am constantly being emailed and contacted by experienced coordinators and staff wanting to know when we will have positions open," Anderson says. "They like the idea and concept of being part of a team and having support staff."

Everyone is struggling to find qualified coordinators, Anderson notes.

Statistics show many coordinators leave for other types of research work within a few years of starting their first CR job, she adds.

The *CTA* salary survey results indicate that finding and retaining qualified staff is one of the biggest personnel issues facing clinical research sites. Respondents report having problems with coordinator turnover and these other issues:

- Hiring enough people to help the CR program grow.
- Filling management and upper management positions.
- Finding people who are able to produce high quality work and who are self-motivated, highly organized, and internally driven to be excellent.
- Retaining staff.
- Managing workload.
- Finding qualified staff with a commitment to quality and not just a pay check.
- Salary/retention.
- Managing personalities.

The CT office at Virginia Commonwealth University has a strategy for attracting and retaining experienced staff.

"We use more of a coordinator career track, so as employees gain additional experience, they can still get raises and have additional duties and responsibilities as their roles change," Anderson says.

For directors, managers, and other leaders of CR programs, salaries remain competitive with more than 65% earning $70,000 or more, according to the 2010

salary survey. Nearly 30% earn $100,000 or more per year, and about 18% have salaries of $130,000-plus per year. *(See salary survey chart, p. 3.)*

Profil Institute for Clinical Research Inc. in Chula Vista, CA, also has bucked the economic trend in the past year as the institute has had a 20% increase in employees, says **Susan Penn,** director of human resources.

As a private institution, the research organization has not had to deal with hiring or salary freezes, and that has helped with recruitment, she notes.

Also, the organization has found many of its new employees through a successful employee referral plan in which current employees receive incentives to refer new people to the organization.

"We've had maybe 10 people referred by employees over the past year," Penn says.

The organization also has used online resources and local networking services to help find experienced and qualified new staff, she adds.

The recession's impact also can be seen in the length of time CR professionals are spending at their jobs. During recessionary periods, people change jobs less, and the salary survey seems to support that trend. More than 70% of respondents said their staff has remained stable this past year. About 17% reported gaining staff, and fewer than 12% said they'd lost staff.

The stability also extends to the length of time survey respondents reported having worked in their present field. Nearly all respondents had been in the field for four or more years, with close to 60% having been in the field for 10 years or longer. In fact, over 29% of respondents had worked in their current field for 19 or more years.

This trend has negatively impacted new graduates who seek work in clinical research. It's even caused new nursing school graduates to go jobless far longer than they might have anticipated, and when they do get a job, they might find no room for advancement.

The housing market crash has contributed to the trend of less job mobility, Hill notes.

CR leaders and staff might think they'll never be able to sell their houses, so they'll stay at the job even if it means their salary is frozen and their career mobility is limited, she says.

The housing crash has hit Nevada hard, and its impact is continuing. Previous recessions had a much more limited impact on job mobility because they didn't last as long, Hill says. ■