Remote Monitored Sites Must Maintain Vigilance and Communication, Expert Says

By Bill Myers

Multiple-site trials rely on experienced remote monitors to coordinate their activities and communications, but that doesn’t mean the individual sites can slack off. The absence of face-to-face communication can magnify seemingly simple errors, a veteran trial monitor warns.

Barbara Winter, an independent consultant and remote monitor based in Sacramento, Calif., urges sites to improve their internal communications and training strategies if they don’t have a dedicated monitor on-site to keep a careful eye on things.

Winter, a veteran with more than 33 years of experience, knows of what she speaks. She’s a remote monitor for an ongoing, 13-site trial of a vaccine for children and adults who’ve received bone marrow transplants. One of the sites, at “a prominent research institution” Winter declines to name, has just had to suspend operations so that she can root out problems with the site’s delegation-of-authority logs.

What she discovered, reviewing the scanned, online documents, is that the site appeared to be allowing an unapproved employee to take patients through the informed consent process. The employee wasn’t listed in the site’s delegation-of-authority log but was still performing an essential function.

A delegation-of-authority log is not specifically required by FDA regulations, but is a commonly used method of keeping

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Six Practices of High Performing Clinical Research Sites

By Lindsay McNair, M.D.

Many medical practices and clinicians explore the possibility of participating in clinical research studies, but half of the principal investigators who participate in one study never participate in a second. Meanwhile, other investigators continue to add studies and build successful clinical research teams within their practices. So, what do high-performing clinical research sites do that make sponsors return to them again and again?

1. They invest in infrastructure.

While a medical practice participating in its first clinical trial may be cautious about the number of resources to allocate toward the preparation required to conduct clinical research, it’s essential to recognize that clinical research and medical practice are fundamentally different. True preparation for research requires staff training, a realistic assessment of the tasks and associated human resources necessary to conduct research and the commitment to maintain those resources for the duration of the study.

High-performing sites have staff with time dedicated to research, which in busier sites means full-time research staff.

2. They hire clinical research coordinators with strong management and interpersonal skills.

The clinical research coordinator (CRC) will often make or break a site’s performance. The most successful coordinators are those with strong management skills who thrive in a multitasking environment because they will take

see Six Practices on page 5 »
New Clinical Review Guidance on FDA’s 2019 Agenda, Gottlieb says

For the first time in 20 years, the FDA will update its guidance on how clinical investigators should conduct trials, Commissioner Scott Gottlieb told a key House appropriations subcommittee last week as the lawmakers begin the process of developing next year’s budget.

The revised guidance is part of the FDA’s efforts to modernize the way it looks at clinical evidence of a drug’s effectiveness and safety, Gottlieb said. Much has changed in the science and data in the past 20 years, but the agency’s approval standards remain unchanged, he said.

Now, Gottlieb said, “We have much more opportunity to use a broader array of data as confirmatory evidence to help support product review. This includes real-world evidence and real-world data.”

In addition to the new guidance, Gottlieb said the FDA plans to “update our approach to drug review across every stage in the life cycle of a new innovation, from the time an investigator first asks the FDA for permission to begin the clinical testing of a new drug to how we continue to assess the safety and effectiveness of new medicines after they’re approved by the agency.”

Beginning in the next few months, CDER will adopt new standard templates for its 30-day IND safety reviews and protocol reviews, Gottlieb added. This will better integrate the work of clinical and scientific reviewers and will improve the consistency of the IND reviews. It will also provide greater predictability to product developers, he said.

And the agency will expand its Adverse Event Reporting System to contain premarket safety data, including IND safety reports on serious unexpected adverse reactions in clinical trials and generic bioequivalence trial safety reports.

“The aim is to make the entire process more structured and predictable,” Gottlieb said.

FDA Issues Draft Guidance on Bioavailability Trials

Sponsors may want to think about pilot trials to establish bioavailability or bioequivalence of a proposed treatment to help sponsors gauge appropriate time intervals to collect samples, and to determine the “washout periods” for a proposed treatment, among other things, says a new draft guidance from the FDA.

The agency also recommends that bioavailability trial sponsors only recruit healthy subjects. If there are safety concerns, patients may be enrolled, but only when their “disease is expected to be stable for the duration of the study.”

When finalized, the guidance will replace the FDA’s March 2014 draft guidance on bioavailability and bioequivalence studies submitted in NDAs or INDs.


Roche Pays $4.8 Billion for Spark, Expands Gene Therapy Portfolio

Roche has agreed to acquire Philadelphia-based gene therapy company Spark Therapeutics, in a deal valued at nearly $4.8 billion, the two companies announced last week.

It’s another sign that the advanced therapy market is maturing: In 2017, Spark, a startup founded just four years previously, won approval for its Luxturna (voretigene neparvovec-rzyl), a treatment for retinal dystrophy. It was the first gene therapy to win approval in the U.S. and Europe for a genetic disease.

Spark has four other therapies in clinical trials. Two of them — SPRK-7001 for Choroideremia and SPK-8016 for hemophilia A with inhibitors — are in early phases and two others — SPK-9001 for Hemophilia B and SPK-8011 for Hemophilia A — are in Phase III. The hemophilia trials are being run in cooperation with Pfizer.

Roche hopes to close the deal by the second quarter.

FDA Revises Guidance on Testing Effect of Food on Drugs

Clinical trial sponsors should assess the effect of food on a new drug before conducting pivotal safety and efficacy trials, the FDA said in a new draft guidance.

The agency calls for preliminary assessments on the effect of food on new drugs during Phase I pilot trials to determine whether the drug should be administered with food in clinical trials until they can identify a to-be-marketed formulation.

Read the full guidance here: https://bit.ly/2SYx1kq.

UK Issues New Guidelines for Trials Transparency

The UK has laid out 10 new regulations to bring needed sunlight to clinical trials.

Last year, it emerged that few clinical
trials in the UK were sharing their data publicly, and the government promised to overhaul the rules. The new report from Undersecretary of State for Health Nicola Blackwood, issued Tuesday, is the first step.

The top recommendation is that the government “explicitly commit” to adopting EU rules, which are scheduled to take effect in Europe shortly after Brexit in March. It also recommends that:

- universities be required to report any trial data from their campuses to the relevant public authorities;
- Public Health England, the government regulatory body, explain why it has failed to report results from trials it had funded or supervised; and

- The government’s top health research agency be given funds for a national audit of trial data sharing, and that the agency be given legal authority to punish trial leaders who flout reporting requirements.

**Pfizer Reduces Xeljanz Doses After Trial Signals Clotting Dangers**

Drug giant Pfizer is reducing Xeljanz doses for patients in an arthritis trial after it was discovered that the higher dose may be causing blood clots in the lungs and even deaths.

Xeljanz (tofacitinib) has been on the market since at least 2012, but the FDA required a clinical trial among rheumatoid arthritis patients to test the risk of heart problems, cancer and opportunistic infections. Patients were given two doses — 10 mg and 5 mg, respectively — in combination with methotrexate.

In a public warning issued Tuesday, the FDA says that an external data safety monitoring committee “found an increased occurrence of blood clots in the lungs and death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a TNF inhibitor.”

Xeljanz has been approved for psoriatic arthritis and ulcerative colitis patients. The safety trial will continue, the FDA says.
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track of staff responsibilities, assignments and qualifications. Delegating authority for essential tasks to staff without appropriate qualifications is a potential federal violation and breach of the trial’s data integrity. FDA data reviewers and inspection teams peruse such documentation very carefully, and any slipup could mean rejection of a new drug application on the basis of suspect data or a warning letter from the agency citing failure to follow good clinical practices.

Sharing data and documentation online is no excuse for experienced trial staff making such errors, Winter says. “They should be paying attention to the same details whether it’s remote or whether it’s on-site.”

The difficulty is that mistakes can be compounded when the monitor isn’t on-site to help catch those problems and rectify them quickly, she says.

“If I was on-site, it wouldn’t have blown up into an issue. Whereas, now we’re going through this back and forth,” she says. “It’s becoming a big whoop-di-doo, and I’m being sent out for a rare on-site visit. I’m having everybody at this site retrain on how to complete regulatory documents.” All of this adds to a trial timeline that already is tight.

Winter admits her own Luddism — “I’m from the old generation where you pick up the telephone. Now people text, and I’m not into texting” — but the fact is that seemingly simple paperwork errors can gum the works quickly no matter how well technology facilitates communication, she says.

“It takes time for me to write a query, it takes time for them to answer the query. It’s the query process that’s expensive,” she says.

“Sites are doing more work for [fewer] people,” she says. “It takes time for me to write a query, it takes time for them to answer the query. It’s the query process that’s expensive,” she says.

Start-up Costs Can Be an Uphill Slog in Need of Change
A host of long-standing expense and inefficiency realities continues to create problems even threaten the viability of the sector. According to some sources, such uphill headwinds for the clinical trial sector are intensifying. These issues range from sluggishness of electronic health records to complications from technology.

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“For example,” she says, “we have very few electronic health records that interface with each other. So if you have a patient who’s on trial and is also in the hospital with a heart condition, you can’t look at his heart info in the electronic health record on your computer and also look at his trial info on the computer.”

By Angela Roberts

FDA Signs Off On Treatment for Rare, Adrenal Gland Tumors
The FDA has approved the investigational drug Atrinco for rare cancers of the adrenal glands — the first ever non-surgical therapy (OS) for these tumors.

Atrinco (mepolizumab) is a radiolabeled drug that attaches itself with a high specificity to tumors. It’s designed to treat adults and children (16 and older) with hyperplasia caused by a genetic defect called phospholipase C Beta.

By Brion Regan

Japanese Greenlights Parkinson’s Trial
In the first trial of its kind, Kyoto University researchers have approved a Japanese protocol to test adult stem cells as a possible treatment for Parkinson’s disease. Induced pluripotent stem cells (iPSCs) are derived from skin or blood cells and induced back into an embryonic-like pluripotent state that can divide into more stem cells or become any type of cell in the body, leading to a potentially unlimited source of any type of human cell needed for therapeutic purposes. They can avoid growing brain or neurological research because they are being different for more cells and also avoid causing any.

All is not lost, though, Winter adds. Sites can make their lives easier by focusing on a top-to-bottom, bottom-to-top training regime, where everyone involved in a trial understands every piece of paper involved.

“They need to know the purpose and the design of each form that’s being requested. Why are we being asked to fill out a Form 1572 [Statement of Investigator]?” Well, it’s a contract between the site and the FDA” that is required by regulation, she says. It’s a commitment that a trial will be conducted in a specific way.

Similarly, sites should focus on that same vertical and horizontal communication (yes, even email) to keep the entire team informed about staff changes.

“The PI has the oversight, but if the PI doesn’t know that so-and-so has been promoted to coordinator,” that communication channel has been blocked, she says.
Six Practices continued from page 1

an active rather than passive role in managing research studies. Sponsors want to work with sites that take an active role in managing the progress of their studies and control timelines whenever possible.

Strong interpersonal skills are critical to providing research participants with a positive experience during their study participation. Effective communication with study team members, including the sponsor and partners providing additional support and services, also leads to the constructive collaboration that is a characteristic of all successful sites.

3. They use data and information to support research activities.

Too often, when asked how many potential subjects they will see who meet study eligibility criteria, sites will make an educated guess based on thinking about who comes to the practice for treatment. Sponsors have learned that these guesses are rarely accurate. Site teams should work within their institution or practice to determine how they will identify and reach out to patients who may be potential research participants well before the enrollment period starts.

Some processes and practices work well and have been honed over time to be efficient and successful. But many practices are ingrained due to habit or ease of use, and it’s time to entertain new ideas to improve and accelerate study enrollment. Sponsors are well positioned to support clinical sites with new ideas for study enrollment. Sites that are open to new ideas and new collaborations take advantage of the resources offered to them. Experienced sites also ask sponsors for what they need — sponsors often are happy to provide additional support to keep a study on track.

5. They don’t overpromise.

Multi-center (and multi-national) clinical trials often involve dozens of research vendors and partners, regulatory agencies and submissions and oversight committees. When sponsors plan study timelines and resource projections across an entire study, they want to base their project plans on assumptions that are as accurate as possible. At the start of a clinical study, sites are asked to estimate how many subjects they will enroll, and 68% of sites fail to meet their projected enrollment target. It’s not solely because sponsors want the highest enrolling sites; it’s also because the inaccuracy of the projections impacts the entire study. To get the necessary sample size, another site will have to enroll even more participants, or the study timeline gets pushed out.

Similar considerations are made for meeting important study deadlines. For example, when study data needs to be entered and cleaned due to a database lock for an interim analysis, one site missing the deadline because the staff doesn’t have time to answer data queries holds up the entire study. A sponsor would rather have a site that makes realistic projections about their ability to enroll participants and meet study timelines (or asks for assistance when necessary), than a site that overpromises and doesn’t deliver, even if both sites end up with the same enrollment and timing.

6. They recognize that they are part of a larger team.

Although some sponsors facilitate and encourage sites to communicate with each other, it’s not uncommon to only have direct communication from the site monitor. This can make it hard to remember that your site is part of the larger effort and part of a giant team that includes study managers, medical monitors, partners who provide study drug and randomization systems, the IRB and safety monitoring committees — all doing their part to keep things running smoothly and provide answers to study questions in a scientifically rigorous and ethical way.

Participating in clinical trials as a research site can be difficult, especially when sites are not prepared for the needs of research studies, research participants or the ways in which research differs from the practice of clinical medicine. But research participation is also a critically important task that allows medical practices to offer investigational options to current patients while contributing to the development of medications that future generations will rely on as well.

Lindsay McNair, M.D., is chief medical officer for WCG Clinical, Inc.

“Experienced sites also ask sponsors for what they need—sponsors often are happy to provide additional support to keep a study on track.”

—Lindsay McNair, M.D., chief medical officer, WCG Clinical, Inc.
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## Drug & Device Pipeline News

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<td>Phoenix Tissue Repair, Inc.</td>
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<td>recessive DEB (RDEB)</td>
<td>Phase I/II trial initiated enrolling 14 subjects</td>
<td>phoenixtissuerepair.com</td>
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<td>Immunic AG</td>
<td>IMU-838</td>
<td>relapsing-remitting multiple sclerosis (RRMS)</td>
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<td>Debiopharm International SA</td>
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<td>staphylococcal bone and joint infections (NCT03723551)</td>
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<td>Mycovia Pharmaceuticals</td>
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<td>recurrent vulvovaginal candidiasis (RVVC)</td>
<td>Phase III trial initiated enrolling 180 subjects in 45 sites in the U.S.</td>
<td>mycovia.com</td>
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<td>Axilum Robotics</td>
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<td>Transcranial Magnetic Stimulation (TMS) for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode</td>
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<td>Heron Therapeutics, Inc.</td>
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<td>Eisai, Inc.</td>
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<td>Taiho Oncology</td>
<td>LONSURF (trifluridine/tipiracil)</td>
<td>adult patients with metastatic gastric or gastrointestinal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neutargeted therapy</td>
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<td>BIOTRONIK</td>
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  NJHOA
  Toms River, NJ
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  Rush University Medical Center
  Chicago, IL
- **Research Coordinator III**
  Cleveland Clinic
  Cleveland, OH

Academic Programs

- **Boston College**
- **Clinical Research Certificate Program**
  Chestnut Hill Campus, Newton, MA
- **Drexel University College of Medicine**
  Master’s/Certificate Programs in Clinical Research Organization and Management
  Online
- **University of North Carolina at Wilmington**
  MS Clinical Research and Product Development
  Online

Upcoming Event Highlights

**Conferences**

- **MARCH 26-27, 2019**
  **Conducting Advanced Root Cause Analysis and CAPA Investigations**
  Raleigh, NC

- **MARCH 27-28, 2019**
  **ICH GCP E6 R2 Meeting CRO-Vendor Oversight Requirements**
  Raleigh, NC

- **APRIL 8-12, 2019**
  **FDA Compliance Boot Camp 2019**
  Frederick, MD

- **APRIL 15-18, 2019**
  **18th Annual Design of Medical Devices Conference**
  Minneapolis, MN

- **APRIL 23-25, 2019**
  **Medical Device Quality Congress**
  Bethesda, MD

- **OCTOBER 23-25, 2019**
  **FDA Inspections Summit**
  Bethesda, MD

**Webinars**

- **MARCH 20, 2019**
  **Best Practices for Facilitating Pediatric Clinical Trials: How to Recruit and Retain Patients**
  1:30 p.m. – 3:00 p.m. EST

- **MARCH 21, 2019**
  **FDA’s 2019 Medical Device Regulation Agenda**
  1:30 p.m. – 3:00 p.m. EST

- **MARCH 22, 2019**
  **REMS Regulatory Developments and Best Practices**
  1:30 p.m. – 3:00 p.m. EST

- **MARCH 26, 2019**
  **Data Integrity in Clinical Trials**
  1:30 p.m. – 3:00 p.m. EST