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Red Flags in the Study Office:
Ann Marie Cisneros on the Ketek TREAT Study

By Norman M. Goldfarb

Ann Marie Cisneros was trained in the U.S. Air Force as a medical technologist. She then earned a bachelor's degree in occupational education and worked for about ten years as a medical technician. Pharmaceutical Product Development, Inc. (PPD), a contract research organization (CRO), then hired her as a clinical research associate (CRA), where she conducted hundreds of site monitoring visits. After three years at PPD and a promotion to senior CRA, she was managing about 15 site monitors on Aventis's pivotal Phase III TREAT clinical study of Ketek. The study enrolled over 24,000 subjects at 1,824 sites.[1]

In 2004, FDA approved Ketek (telithromycin) to treat mild-to-moderate community-acquired pneumonia, acute bacterial sinusitis, and acute exacerbation of chronic bronchitis. The FDA later withdrew approval for treatment of acute bacterial sinusitis and acute exacerbation of chronic bronchitis, and added bl~~a~~ack-box safety warnings on possible liver toxicity and certain contraindications.[2]

Dr. Anne Kirkman Campbell, the investigator who enrolled the most subjects in the TREAT study (up to 30 per day[1]), was subsequently sentenced to 57 months in federal prison and fined $557,251 for misconduct during the study.[3] The investigator who signed up the second-highest number of subjects, 251, had never conducted a study before, and was cited by FDA investigators for failing to follow the study plan and report adverse events. The investigator who signed up the third-highest number of subjects, 214, was on probation with the Medical Board of California for gross negligence and failure to keep adequate records. During the study, he apparently was in a chronic state of cocaine addiction; he was arrested and found to have cocaine hidden in his underwear, while holding his wife hostage with a loaded handgun.[1,4]

How did you become involved with Dr. Campbell's site?

Dr. Campbell had been monitored once after she enrolled 50 subjects. No issues had been discovered. But after her enrollment climbed to 407 between November 2001 and February 2002, she was cut off or the study ended. She had enrolled 1% of the population of Gadsden, Alabama, a town in my region.

After her site was closed, an Aventis QA auditor visited the site. He came back and asked me to look at patients that Dr. Campbell had diagnosed with acute exacerbation of chronic bronchitis (AECB). A lot of the patients didn't have a history of bronchitis and didn't meet the definition of AECB. I went out with two of my monitors to review 100 consents and CRFs (case report forms).

There were three indications in the study: acute sinusitis, AECB and community-acquired pneumonia. Aventis wanted enrollments for all three indications. Acute sinusitis was the easiest to enroll, so they cut enrollment off for that indication after a third of the patients enrolled had acute sinusitis. Dr. Campbell had enrolled mostly acute sinusitis patients and then when it was cut off, she suddenly had all of these AECB patients. The QA auditor wanted me to scrutinize those charts because, obviously, that was rather bizarre.

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There were in-house CRAs managing the sites, as well as traveling monitors. I met with the in-house CRA for Dr. Campbell's site. One of the red flags he found was rapid enrollment, many patients a day. Dr. Campbell was enrolling patients on times and days when the office was supposed to be closed. Enrollment was done via an IVRS system (interactive voice response system), so it was easy to track. A lot of times, she called in and enrolled patients when she had no drug on-site. If they really had acute sinusitis, she was sending patients home without any medication and then bringing them back later to give them Ketek or the control, Augmentin. The only conclusion you could reach were that these patients weren't real, weren't sick, or were going home untreated until she got drug on-site. It was happening a lot.

The in-house monitor knew something was going on at the site, so she kept very good records. She created spreadsheets of the oddities. For example, Dr. Campbell reported less than five adverse events for 407 patients.

What happened when you visited Dr. Campbell's site?

We arrived on Monday and stayed for a week. It was a small GP (general practitioner) clinic. When we walked in, she didn't have anybody in the waiting room. It wasn't busy while we were there. She was a sole practitioner. She had three study coordinators. None of the coordinators would talk to us or look at us. If we asked any questions, they would always refer us to Dr. Campbell. That was weird because usually the coordinators are involved and engaged. They obviously seemed very intimidated by Dr. Campbell.

She stuck us in a very small exam room surrounded by hundreds of charts. She made it very uncomfortable for us to work and complained that we were taking up space in her exam room.

The first thing we did was look at informed consents. Right away, we found patient initials that did not look like the signatures. On most consents, the date the patient signed wasn't in the patient's handwriting. I started comparing patient signatures in the medical charts, where they signed a Medicaid form or something, to signatures on the consents. I immediately found one that was a blatant forgery. It looked nothing like the signature in the medical chart; it looked like the study coordinator's signature. A lot of the initials on the consent forms were in the study coordinators' handwriting. The dating of the consents was done by the coordinators as well.

In most of the patient charts, the acute sinusitis diagnosis appeared to be backdated. There would be a notation that the patient came in for diet clinic and, in different ink next to the chart note, she wrote "ASx3 enrolled in TREAT study." Her patients came in for something like back pain and then, next to it in different-colored ink, she would write "acute sinusitis x3."

On her sign-in log, there were six sets of patients with the same last name. It looked like a husband and a wife were both coming in with acute sinusitis and being enrolled on the same day. According to the CRFs, most of the patients, if not all, were 100% compliant with study meds. They all came back within window, which just doesn't happen. None of the 407 dropped out of the study. None of them were lost to follow up.

As luck would have it, the copy machine broke. I asked Dr. Campbell if I could take some documents to a local copy store and she agreed. She asked me if I could make a copy for her of an informed consent for a different study. She didn't care that it was another sponsor's study.

She expected us to take her and her staff out to lunch every day. The coordinators would never say anything to us if she was around. She didn't mind if they were there with us as

long as she was there. They closed every day two hours for lunch and we were not allowed to stay in the office to monitor, even if the coordinators were there. That really slowed us down. There were several occasions when I had to take Dr. Campbell out to dinner. She would order take-out dinner for her husband and her daughter, who weren't even there. I had to pay for that too.

It was so obvious that many of the study subjects weren't true subjects. I didn't know if she was giving them drug, or keeping it, or throwing it away. We never did find out what she did with the drugs. The suspicion was that she was selling it. She had all that Augmentin.

I called my managers and told them what we were finding. They just said bring back as much documentation as you can. I called the IRB, Copernicus, on Wednesday, because I was so upset about what I was seeing. I wanted Copernicus to call some of the patients. I said, "We need to know what is going on at this site." The IRB person said that they wanted to wait to see what the sponsor did.

There were three or four visits in the study, with lab tests at each visit. The levels were so completely different at each visit that it looked like she was collecting blood on any patient that walked in the door and sending it in as a sample for patient XYZ.

What happened when you returned to PPD?

When I came back from the site, I met with the head of QA at PPD and told him our findings. I wrote a report. We set up a conference call with the project manager, the QA department, some of our statisticians, and Aventis. Aventis pretty much whitewashed everything, like enrolling subjects without drug. I remember walking away from that teleconference being aghast at what I was hearing. Most sponsors would say, "this site is shut down yesterday, we are throwing out all of her data." They didn't see that as necessary at all.

Shortly after that, I left PPD for a better opportunity; it had nothing to do with the Ketek study. At the time, I thought things were going to be handled properly. About six months later, I found out that the FDA was going to inspect Dr. Campbell's site. I called the FDA to ask if I could provide any information. The reviewer told me the investigation was because she enrolled so many patients, not because of any call from the sponsor or allegation of misconduct.

Were you the only one at PPD or Aventis who seemed concerned?

The CRAs that went on the visit with me, the in-house CRA, and the lab reviewer were all concerned, but we were low-level. Aventis's QA auditor, who I knew when he was at PPD, seemed concerned, but he was newly hired at Aventis, and didn't say much, at least to me. Nobody senior seemed concerned or came to talk to me. When you are working on such a huge clinical trial, there are so many things going on and this was just one of them. But, it was probably the biggest money-making trial that PPD had ever done, so I assume everyone in management knew about it. Obviously, PPD is a CRO that doesn't want to bite the hand that feeds it.

What did the FDA investigator find?

The FDA's regulatory auditor went out there and, within a matter of days, realized what was going on and turned the investigation over to the criminal department. They interviewed 200 or 300 patients. Only 50 were valid subjects.

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What happened to the data eventually?

The FDA knew that there were data integrity issues with the study but approved the drug anyway. Dr. David Ross, the lead FDA reviewer for Ketek didn't want to approve the drug, but he was forced to change his review. The drug caused several deaths and liver failures. That's in the black-box warning now. The head of FDA testified before Congress and said that they didn't use the TREAT data to approve Ketek. But, according to the FDA website, they did. FDA said that they used European data for approval.

What lessons did you learn?

Don't always count on the sponsor doing the right thing. I don't want to encourage CRAs to call the IRB, but if they feel like their concerns aren't being heard, or if they are not being taken seriously, reach out to somebody. Certainly, don't be afraid to call the FDA as a confidential informant. You can do that.

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