The Role of Expert Committees and the Regulatory Landscape

In conversation with... Dr. Jonathan Seltzer

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What's the role of expert committees today? What's happening on the regulatory side?

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Stedman: Dr. Seltzer, tell us a bit about your background and the founding of ACI Clinical

Dr. Seltzer: ACI Clinical was founded officially in 2001. I was an academic cardiologist; I came out of training in the late '90s when the issue of cardiac safety reared its ugly head in drug development. Drug developers put together committees, consisting of expert cardiologists, to oversee their clinical trial work and make sure there was no danger to the patients.

One thing led to another, and over time I was asked to serve on a number of these committees, with different sponsors. I noticed they were done very, very differently. Some were better, some worse, and there were really no best-practice standards, or anything like that. At the time, I thought it was a good idea to try to put that together, and these expert committees became the focus of ACI Clinical.

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Stedman: As a leader in this area, can you highlight the scientific and regulatory benefits of convening such groups as endpoint adjudication and data-monitoring committees?

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Dr. Seltzer: What we try to do for any expert committee is harness the world's best thinking in a way that is understandable and helpful to regulators across the globe. You could ask a friend who's a cardiologist for an opinion. That's great and the information is often correct, but it's not something that the regulators accept. Regulators, whether here or in Europe or Japan or Australia, require very rigorous and transparent standards in order to accept information.

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***Dr. Seltzer**, president and founder of ACI Clinical, and chief scientific officer of WCG Clinical, shared his insights on expert committees during a recent conversation with Bill Stedman, manager, member services, ACI Clinical.*

The interview has been edited for clarity and length.

In fact, you almost need to make the opinion like a piece of data. For instance, saying that an expert panel believes "this event is acute renal failure" is an opinion. To make it more "data–like," you would say the expert panel believes this is an event of acute renal failure based on a) pre–specified criteria such as laboratory values, concomitant medications, procedures, etc.; b) the methodology by which the experts arrived at the opinion, and c) the information the committee examines.

One type of expert committee is the data monitoring committee (DMC), also known as a data safety monitoring board, a data safety board–there are lots of names for it; that might be one of the problems. There is specific guidance, both from the FDA and the European regulatory bodies, about what they expect a safety committee to look like. (All clinical trials require safety monitoring, but not all require a DMC.)

The DMC is a group of experts that sits arm's length from a clinical trial. Unlike the sponsor, they're actually allowed to look at unblinded data.

The DMC looks at the entire trial as it's unfolding in case there's something wrong with one of the study arms. For instance, let's say you're doing a trial of an antibiotic and you see that, in one arm of the trial, the new drug is causing all sorts of negative side effects and it's not really working much better than the old drug. It's unethical to let that trial continue. In that case, the data monitoring committee would recommend the sponsor end the trial.

On the other hand, let's say the DMC looked at the data and the new drug was curing the disease at a much higher rate than the old drug. Well, in that case, it's unethical to leave people on the old drug, so the DMC may recommend stopping the trial.

Regulators require sponsors to have these types of committees in certain type of circumstances--for instance, if you are studying vulnerable populations, such as children, the elderly, those who cannot understand consent, etc.

If you have a drug with a known toxicity, for instance if you're doing a drug trial and you know that it might cause blood problems, you should probably have a DMC that includes a hematologist.

If the drug is brand new–a new molecular entity–anything could happen, so you need to pay special attention to it. Likewise, if there's a really long trial, people working on the trial, including the investigators, switch in and out. It's important to have a committee that has a stable view of the safety of the compound.

Those are some of the indications for which safety committees are required. Even when it isn't required, sponsors often choose to have one because they believe it's the best practice to have additional oversight on a clinical trial.

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Stedman: How about endpoint adjudication committees?

Dr. Seltzer: They are a little different. I think we've all been in–or at least heard of--situations when everyone in a family has the same symptoms. One person's doctor says it's a cold. Another person's doctor calls it the flu.

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Another one says it's a viral syndrome and maybe somebody has a walking pneumonia thrown in, or allergies. But everybody looks the same.

This happens also in clinical medicine. Different people in different parts of the world may have different definitions for the same event.

Endpoint adjudication makes trials more scientifically rigorous and more efficient. Again, we get a roving band of expert doctors who create standard definitions for endpoints. Let's take that example where one person says you have a cold, one says you have the flu; the endpoint adjudication committee develops precise definitions for "cold" and "flu." Then they look at the incoming data from the trial and they classify patients very specifically. This lends great precision to the study endpoints, making regulators quite comfortable and potentially shrinking the size of the study.

We're seeing something interesting in the marketplace. Adjudication used to be for really big trials, big cardiovascular trials–they are big and expensive, and they absolutely require adjudication. What we're seeing now is a move toward much smaller numbers of events, but in a much broader range of therapeutic areas. So if we look across our roster of clients now, we'd certainly see 10s, if not scores, of different therapeutic areas for which we are performing adjudication.

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Stedman: Now that we're part of the WCG family of companies, can you talk a bit about the synergy of services that are available to prospective clients?

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Dr. Seltzer: I think what WCG represents are the services CROs don't really specialize in. A CRO generally helps study enrollment, they get patients in the study, they get their data in and they do some of the calculations for your NDA submission or clinical study report. The CRO sort of works for the sponsor: Whatever the sponsor tells them to do, they do. But they don't really specialize in arm's length services.

Whereas with WCG, we specialize in maintaining our independence, which is actually what the regulators want. So, for instance, in our IRB services it's obviously very independent. Likewise, in our group, we specialize at independent expert thinking. So the advice we sometimes have to give is things that would be very detrimental to the business of the CRO. We like to maintain that separation along with many, many other services that the WCG family of companies provides.

Because all these companies are under the WCG umbrella, many clients feel it's very convenient to work with us exclusively because it's one contract. WCG can cover all the services. You don't have to buy them all at once; you can really have a chance to pick from a palette of services.

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Stedman: Given your strong relationship with and understanding of the ever–emerging regulatory landscape, can you give us an outlook on the future of the way the expert committee is used?

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Dr. Seltzer: Expert committees are really relatively new. The first guidance was finalized in 2007 in the regulatory space. Endpoint adjudication is really beginning to filter its way through. The Europeans are increasing reliance on expert opinion to advise on how to think about things.

We're seeing it also spread across very, very different areas. In phase 2 and 3 interventional industry–sponsored trials, approximately 24% report using a DMC. The FDA has draft guidance that expands the use of what they call "safety assessment committees," which are a form of data monitoring committee. In the draft guidance, they recommend them for every single clinical trial.

I think you're seeing acceptance of independent oversight doing some of the work to help advise the regulators and give them perspective.

In terms of adjudication, as I mentioned, there's nothing published from regulators. However, over the last few years we have seen an increase in publication around best practices in adjudication. We were fortunate to be asked to author a paper both with the FDA Center for Drugs as well as Center for Devices on best practices in endpoint adjudication.

Interviewee

Dr. Seltzer Chief Scientific Officer of WCG and Founder of WCG's ACI Clinical, is a recognized leader in the area of cardiac safety, Endpoint Adjudication Committees and Data and Safety Monitoring Committees. He has chaired and served as a committee member for scores of protocols, and has functioned as an advisor for dozens more. He is actively publishing in these areas and participating in thought leadership efforts focused on defining best practices. Currently, Dr. Seltzer is on the scientific programs committee for the Cardiac Safety Research Consortium (CSRC) and the steering committee for the Clinical Trials Transformation Initiative (CTTI).

Interviewer

Bill Stedman is the manager of member services at WCG's ACI Clinical. He is a dedicated professional with 15 years of clinical research and trial experience who provides management and oversight of the recruitment, contracting, relationship building of expert physicians who serve on adjudication and data monitoring committees.