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What's New in GCP?
CTTI Develops Analysis Dataset to Examine Trials

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The Clinical Trials Transformation Initiative (CTTI) is developing a publicly accessible, user-friendly analysis dataset of ClinicalTrials.gov content that will be updated quarterly.

"The problem we had in CTTI was that we were trying to make clinical trials better, but we didn't have any sort of measurement of the status of clinical trials," said Robert Califf, vice chancellor for clinical research at Duke University, who is heading the project with Deborah Zarin, who is director of ClinicalTrials.gov.

Speaking to the Friends of the National Library of Medicine's Clinical Trials Conference June 6, Califf said he and Zarin realized ClinicalTrials.gov "is the closest thing to a measurement of where we are today and is constantly being updated so that we can keep track of where we are in the future." He added that "ClinicalTrials.gov gives us a public scorecard of pretty much everything that is happening relative to the United States in the field of clinical trials all in one place."

Can ClinicalTrials.gov Data Be Used To Assess the State of Clinical Trials?

"We said 'let's see if we can measure what is going on and let's make it publicly accessible in a database that is relatively easy to interrogate, and then let's begin to get more people involved in thinking about the aggregate portfolios at ClinicalTrials.gov," Califf said.

"Our clinical trials system is falling behind the needs of society," he noted. "Trials need to be constructed differently and run differently because we are trying to answer very different kinds of questions that require that different measurements be made. The unmet need is growing faster than our ability to do the trials and the trials that are being done are not optimal in science or budget to address the health needs of society."

He added the clinical research enterprise needs "to open up innovation and encourage [its use]. We have gotten to a place where people are afraid to try new things because they will get punished if they try something new and it doesn't work."

"Once we shine sunlight on clinical trials, we will find that it is not being done very efficiently and a lot of energy is being wasted. There are going to be better ways to do it," Califf said. "If we don't seriously look at the whole enterprise and understand it, we are going to put ourselves out of business."

He said that he does not think the system can be fixed "incrementally. We need a transformative, revolutionary change in the way clinical trials are done, if we are really going to meet the needs that society has and answer the questions about treatment." He noted that "in clinical trials and human experimentation in particular, we have made it nearly impossible to get the work done inside the United States."

14 Specialties Detailed

Although the overall snapshot of clinical trials in the CTTI quarterly dataset will be informative, "I think the real action is going to be at the level of specific specialties," Califf

said. “What does cardiology think? What does oncology think? What do patient advocacy groups think about the portfolio?” The CTTI aggregate dataset will break out 14 specialties.

Califf noted preliminary data pulled out of the dataset indicates that “there is a two-fold variation in the average size of trials according to specialty. This probably has a lot to do with cultural habits of the specialties.”

But one of the overall preliminary results that “totally floored” Califf was that 96% of the trials in ClinicalTrials.gov have fewer than 1,000 subjects and 62% have less than 100. “The median number is only 58,” he said. “Obviously, most of those trials cannot answer a question about which treatment to use.”

One reason may be that large trials cost a lot of money, need to go through numerous approval processes and are heavily scrutinized. But “if you want to do a 25-patient study at a university, people think ‘it is not going to cost much, let’s let them do it,” Califf said. However, the “amount of energy put into the study and not answering questions relevant to the public health” raises questions about “our priorities and where we are putting our energy. ClinicalTrials.gov is going to be a wonderful way to look at this.”

Califf added that the number and size of trials needs to increase not decrease. “Most medical and health interventions only have modest effects. There is really no substitute for a proper clinical trial,” he said. “No matter how many times we try to circumvent or get around it with other methods, they are not going to work and eventually we are going to learn that.”

In addition, “the concept of personalized medicine, which I think has been largely mistakenly thought to be a way to reduce the number of trials, is going to increase them because there is such a risk of false positives and random error,” he said. “Sample sizes need to be increased by 100-fold and the reason is that there is so much variation in the human genome and human biology that to understand which people benefit from a treatment and which don’t is going to take a much larger sample size.”

Specialty Differences Noted

In terms of specialties, oncology represented the largest proportion of ongoing and newly registered trials in ClinicalTrials.gov and those trials are most likely treatment oriented. “Relative to the two other largest areas — cardiovascular and mental health — oncology has approximately twice as many studies as the other two combined,” he said. However, the oncology trials are very focused on Phase 0-II. “A lot of little tiny things are going on and the good news is that the National Cancer Institute has become a very active partner” and the project has created a number of databases to specifically examine oncology trial efficiency and other issues.

Cardiovascular trials are most likely to involve prevention and assess devices. They are also most likely to be conducted outside of the United States. The number of subjects in cardiovascular trials is twice as large as the oncology trials, and mental health studies fall between the two. Califf noted, “mental health trials are enrolling a lot of children” and are most likely to exclude seniors.

In addition, the number of women-only trials is twice as many as men-only trials.

Less than half of the trials have data monitoring committees. “Whether that is good or not is a matter for further debate,” Califf said, adding “advocates should know about this and should think about what the right monitoring of a clinical trial should be.” He added that, on average, NIH-sponsored trials had data monitoring committees, and Phase III trials had more data monitoring committees, as did more recent trials.

Registries Proliferate Around the Globe

"Globalization is a huge issue [and] we need to understand it," he said, noting many trials conducted outside of the United States do not have to be registered at ClinicalTrials.gov. "For us to really understand globalization, we've got to develop a network of registries that work together." He noted that there is "a proliferation of registries but I'm hopeful that we will get the main registries in the world to agree to a common set of terms" beyond the 20 established by the World Health Organization.

"To make this work, we need a lot of work done on terminology. Just take a simple phrase like 'interventional clinical trial.' Most people get the clinical part but for interventional and trial, you'd be amazed at the different views people have about defining those two terms, and that has an impact on what they enter into the registry.

"There are also legal issues for the dataset. We have to be really careful as we develop derivative datasets" because, by law, trial sponsors have to enter data into ClinicalTrials.gov and be responsible for it. "What if someone on the outside has a different interpretation of what you entered or you made an error. The outside person can't change it — you've got to change it yourself. So we are going to have derivative datasets that will need to be very carefully labeled and measures taken to make sure people don't attribute changes in the database that don't come in the original database and don't come from the sponsor."

Califf noted a "move toward the democratization of data... It is just a matter of time until there will be requirements to post the protocols, to put in trials of unapproved products and summaries. It is now required for some trials in Europe but there are many issues because of the interpretation of the trials."

To Find Out More

For more on the CTTI project go to https://www.trial-stransformation.org/projects/clinicaltrials.gov.

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