CenterWatch Monthly

March 2021 A CenterWatch Publication Volume 28, Issue 03

Translational Research Key to Meeting Real-World Needs During Pandemic

By Mike Ingram

There is an increasing effort in the industry to mesh clinical trials with clinical care and the line between the two must be made more permeable, says Johnathan Casey, an assistant professor of pulmonary critical care at Vanderbilt University Medical Center.

"If you have research that's embedded in clinical care, you're testing treatments in the populations that are most likely to be getting them outside of a trial," he says. A practice-based model also makes recruitment easier, he says, since it's built into established clinical practice, with doctors and other healthcare providers acting as a natural bridge between researchers and study subjects.

Casey notes that traditional trials requiring massive investment in patient recruitment makes sense for certain studies, he says, like first-in-human trials for new drug treatments, where patient safety concerns dictate a tightly controlled study population, rigorous screening and a labor-intensive informed consent process. But for other studies, he argues — comparative effectiveness studies of existing drugs, for instance, or new indications for drugs with established safety protocols —that work can be counterproductive.

Comparative studies, Casey says, are particularly important for effective translation, and they can be carried out relatively inexpensively in a practice setting. As a critical care doctor in the ICU, he says, he regularly faces decisions "for which there is no real data." In many cases, there may be two or more treatment options for a given disease or medical situation, and no good way to decide which would be more effective. "Some doctors will choose one, and some doctors will choose the other. And eventually, if we decide we really need to know which option is best, we'll bring in a research team, totally separate from clinical care, and we'll cherry-pick who to test the drug on."

Other organizations that can provide support for practice-based research include WCG ThreeWire, which helps physician investigators augment their staff resources "to maintain their patients' access to clinical trials as a healthcare option."

—Molly Hair, director of clinical strategic solutions and new product development, ThreeWire

Instead, he suggests it would be better to randomize that treatment decision and then study it, collecting data on the different options. This would require overcoming some patient — and physician — resistance to the idea of randomization, he admits, but he maintains that the resistance is based on a "false confidence" that these physician decisions are based on evidence.

"In the current system, one doctor makes one choice, and I make a different choice, and our patients experience all the benefits and risks of that choice. But we don't learn anything."

Hospitals, he suggests, could be incentivized to improve outcomes through research. But not all hospitals — and few physician practices — are equipped to handle the many tasks trials undertake to ensure data integrity and protect human subjects.

Integrated research organizations like Elligo Health Research can help fill that gap by providing study coordinators and trial infrastructure to physician practices acting as decentralized sites in larger trials.

Elligo COO Eli Alford advocates for pragmatic trials, which study a drug's effectiveness in a real-world setting and produce data that can be crucial for effective translation from research to clinical

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practice. Many such trials have had success with a hybrid model, he says, which incorporates a mix of traditional clinical sites and community health centers.

Other organizations that can provide support for practice-based research include WCG ThreeWire, which helps physician investigators augment their staff resources "to maintain their patients' access to clinical trials as a healthcare option," according to Molly Hair, ThreeWire's director of clinical strategic solutions and new product development.

In another model of practice-based research support, Javara recently inked a deal with Wake Forest Baptist Health in North Carolina to plan and facilitate trials through community healthcare clinics and medical centers, many of them located in rural parts of the state. "We believe the best way to reach patients is to bring the clinical trial to them at the point of care," says Javara CEO Jennifer Byrne.

Still, there can be a bias against practice-based research in the trials industry, Alford says. "One concern I've heard about these decentralized trials is a worry that you're compromising data integrity, but that's simply not true," he says. "If it's designed appropriately and executed appropriately, you can have adequate and well-controlled decentralized trials."

There are cases, of course, where a traditional trial site and careful in-person monitoring is necessary, he says. A dose escalation study, for instance, needs to be performed in a tightly controlled environment with a high level of monitoring to ensure patient safety. But for other trials, remote administration of a study drug actually better matches the conditions in which patients would ordinarily be taking the drug, which facilitates the collection of data that will be important to successful translation.

Casey also believes that the government could do a better job matching regulation to risk. He contrasts two studies, for instance, that he recently played a role in, with two very different risk profiles. The first, on monoclonal antibodies, was a first-in-human trial. "We have no idea if it's safe or effective, so it makes total sense to run a tightly-controlled study, with an hour-long consent conversation and strict enrollment criteria," he says. If a patient wasn't in the study, he or she wouldn't have access to the drug.

The second study, on the other hand, was looking at the possibility of hydroxychloroquine for treatment of COVID-19. In that case, there was an existing safety profile for the drug, even if its effectiveness in treating COVID was unknown. "And, importantly, if a patient wasn't in the study, they were likely able to get the drug anyway, but without any outcomes being collected." In a case like that, he argues, it would make more sense to tie the study to clinical care, so that data could be collected as the drug is being prescribed.

As another example, Casey contrasts two recent COVID-related studies with two very different designs, both looking to study the effectiveness of existing therapies to treat this new virus. The first, run in the U.S. through the Mayo Clinic, was studying convalescent plasma, a treatment that had shown some early promise in treating COVID patients. The study included 2,762 participating sites and nearly 15,000 physicians, who ultimately infused about 82,000 patients. Data on baseline variables and clinical outcomes were collected in a web-based database. "Essentially, it was a single-arm clinical trial of convalescent plasma," he says. The study cost nearly $49 million, money which came from an HHS grant.

"At the end, they published what data they had, which was limited, because there was no control group," Casey says. There was no consensus reached on how best to deliver the plasma or the proper dosage or even overall effectiveness. "After this huge investment of money and resources, the most important questions about convalescent plasma went unanswered," he says.

Contrast that with a UK study of dexamethasone, a corticosteroid, which was run through the National Health Service's (NHS) network of hospitals. That study enrolled around 13,000 patients randomized from 176 hospitals. During the peak of the COVID crisis in the UK, some hospitals were reportedly enrolling 60 percent of hospitalized patients. It was incredibly easy for physicians to participate, Casey says, as some of the usual qualification requirements were waived, including good clinical practice training. Any physician could act as a site principal investigator, and training was limited to a 30-minute self-directed webinar. Informed consent could be obtained quickly, via a two-page form and two-minute conversation.

Importantly, the dexamethasone study protocols limited data collection, so the necessary data could be collected in only a few minutes, and that data focused specifically on the drug's effectiveness. The study employed an adaptive design that included interim analyses and adjustments, so that the trial could continue until effectiveness was definitively proven or disproven.

Within 100 days of its launch, the UK study had managed to present definitive data on not only corticosteroids — which the study showed, against expectations, to have a mortality benefit in COVID patients — but also on hydroxychloroquine and lopinavir-ritonavir, both of which were shown to be ineffective.

"Importantly, instead of enrolling the bare minimum number of patients to demonstrate effectiveness," as would

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typically be done in a traditional clinical trial, "they enrolled enough patients to let them study outcome differences by subgroup," Casey says. As it turned out, the sickest patients were the ones who reaped the greatest benefit from dexamethasone, while patients who were only mildly ill actually showed some harm from the drug.

Also, the UK study was far less expensive: $2.8 million to the coordinating center, plus the cost of the drugs themselves and the labor of the enrolling physicians, but those costs were already covered by the NHS.

The key difference between these two studies, Casey says, was that the UK trial built itself on an existing network of care, making use of resources that were already being outlayed to treat COVID patients. Randomization was built into clinical care, which saved time and money. Also, the study design was a pragmatic one, focusing on the most important — and most urgent — questions. Another key difference: in the UK, patients were discouraged from being prescribed dexamethasone unless they were participating in the study, which helped incentivize that participation. In the U.S., on the other hand, hydroxychloroquine was, for a time, being readily prescribed to COVID patients, but data were being collected on only a relatively narrow slice of that population.

Even within a more traditional clinical trial, experts say, there are steps sponsors and sites can take to make for better translation between research and practice. One is to recruit study participants who better mirror the populations who will eventually be prescribed a given drug.

The University of New Mexico (UNM) Health Sciences Center recently made changes to its recruitment efforts so that participants in its clinical trials better matched the demographics of people in the state as a whole. The academic medical center won a Clinical and Translational Science Award (CTSA) from the NIH to help them carry out the work, which they documented in a 2018 paper published in the *Journal of Clinical and Translational Science*.

UNM took a three-pronged approach. The first focused on the university health system itself, with new methods of screening the electronic health records of existing patients to identify those who may qualify for various trials. To comply with HIPAA regulations, researchers used what they called an "honest contractor" system, which was given the green light by the university's IRB. Under the plan, the staff of the medical center — the "honest contractors" — represent the institution, but they are independent of the specific investigations for which they're recruiting.

The second prong focused on connecting the academic medical center to community health centers around the state, particularly in rural areas with large numbers of Native American residents. The effort wasn't simply about recruiting a more diverse population for studies, but actually working with these health centers to design studies that would target the medical needs of different communities in the state. These kinds of partnerships help ensure that sponsors and sites are running studies that will actually translate into real-world clinical care.

Finally, the third prong was to step up efforts to recruit patients from outside the UNM system. The university set up a voluntary statewide registry where individuals could provide health information, via a web portal, so they could be matched to relevant studies.

While the examples of practice-based research Casey cites have been borne out of the COVID-19 pandemic, he emphasizes that the lessons of those studies are not COVID-specific. Rather, the pandemic has forced researchers to rethink how they conduct clinical trials and exposed a number of inefficiencies in the existing system.

Raymond Panettieri, vice chancellor of the Rutgers University Institute for Translational Medicine and Science, agrees, saying that changes to how studies are conducted under COVID-19 represent a "paradigm shift" for the industry. "The pandemic has made many of us rethink clinical trials, and we've realized that in a lot of cases they might be unnecessarily cumbersome and time-consuming," Panettieri says.