Enabling Efficient Research Through Pragmatism

While randomized clinical trials are key to generating evidence that improves public health, they are often associated with significant challenges such as high costs and lengthy timelines. DCRI faculty and operational experts have successfully implemented a variety of pragmatic approaches to introduce efficiencies while maintaining scientific rigor and data quality. Pragmatic approaches can be used throughout a study’s lifecycle, from recruitment to data collection to dissemination of results.

Pragmatic elements in clinical trials have the potential to alleviate burdens for study sites, but more importantly, they also can help address barriers to research participation, ensuring that DCRI’s pragmatic research is participant-centered research.

“We are uniquely positioned to help our partners utilize the appropriate pragmatic elements in their studies to enable more efficient research with valid results.”

Robert Mentz, MD
“The DCRI faculty and operational team members have deep expertise in determining which pragmatic approaches to use and when to implement them,” said DCRI cardiologist Robert Mentz, MD, the principal investigator of several pragmatic studies, including TRANSFORM-HF and PROVIDE-HF. “We can collaborate to design and conduct trials where nearly every component of the study is fully pragmatic. But we also understand that this isn’t the best fit for all studies. We are uniquely positioned to help our partners utilize the appropriate pragmatic elements in their studies to enable more efficient research with valid results.”

**Planning: Designing Studies that are Efficient and Adaptive**

The DCRI was recognized this year for its expertise in coordinating efficient studies when it received an award to be the U.S. coordinating center for a COVID-19 master protocol study.

The study, ACTIV-1, is part of the National Institutes of Health (NIH)’s Accelerating COVID-19 Therapeutics Interventions and Vaccines (ACTIV) initiative. ACTIV-1 will initially test three immune modulators that may prevent the overactive immune response that occurs in some severe COVID-19 cases. The trial will study how these three drugs impact severity of illness, speed of recovery, mortality, and hospital resource utilization.

“This protocol design is more efficient because it tests all three drugs at once and requires enrollment of fewer patients.”

Danny Benjamin, MD, PhD, MPH

The U.S. coordinating center for ACTIV-1 is being led by DCRI pediatricians Danny Benjamin, MD, PhD, MPH, and Brian Smith, MD, MHS, MPH. Hornik designed the trial’s clinical pharmacology component. Kevin Anstrom, PhD, DCRI therapeutic area lead for Statistics and Data Science, will lead the analysis of results.

“We don’t know if giving any of these immune modulators will work, but we know that several might work,” Benjamin said. “Traditionally, these three drugs would have to be tested in three separate protocols, with 500 patients in each protocol receiving the study drug and 500 receiving a placebo—so 3,000 patients total. This protocol design is more efficient because it tests all three drugs at once and requires enrollment of fewer patients—540 will be assigned to each drug and another 540 will receive placebo, for a total of only 2,160 participants.”

**ACTIV-1**

DCRI investigators are also involved in another component of the ACTIV program, ACTIV-4, which consists of adaptive trials conducted in three different care settings: outpatient, hospitalized patients, and recently discharged patients.

DCRI faculty are involved in all three of these trials, which are examining optimal use of oral anticoagulants to prevent COVID-19-associated blood clots. DCRI cardiologist Tracy Wang, MD, MHS, MSc, who is co-leading the post-discharge trial along with Duke hematologist Thomas Ortel, MD, PhD, explained the benefits of ACTIV-4’s adaptive design.

“The adaptive design enables us to be as efficient and as patient-centered as possible; if the treatment shows early signals of efficacy, patients can switch from placebo to treatment to give them the best chance at positive outcomes,” Wang said. “COVID-19 has been an incentive to accelerate the adoption of adaptive design, and we will now be able to apply this iterative research model to other clinical areas so that we can recycle research infrastructure and find answers faster.”
Recruitment, Enrollment, and Retention: Emphasizing Representative Research

When designing studies, DCRI investigators ensure patients are at the forefront so that research will answer questions that can improve their medical care and quality of life.

One way the DCRI improves care for as many patients as possible is by designing trials with broad eligibility criteria that allow for wider enrollment. One example is CleanUP-IPF, a pulmonary study led by Anstrom.

“By setting broad inclusion criteria and excluding fewer patients, we were able to efficiently enroll a trial population that is representative of patients typically seen in clinical practice.”

Kevin Anstrom, PhD

CleanUP-IPF, which was conducted as part of the Pulmonary Trials Cooperative funded by the NIH, sought to determine whether antimicrobial therapy could reduce risk of respiratory hospitalization or death for patients with idiopathic pulmonary fibrosis (IPF). When setting eligibility criteria, Anstrom and the study team excluded only those patients that had a contraindication to either of the two antibiotics being tested.

“By setting broad inclusion criteria and excluding fewer patients, we were able to efficiently enroll a trial population that is representative of patients typically seen in clinical practice,” Anstrom said. “That means the results from this trial will be easier to implement in clinical care and more likely to work for a wide range of patients.”

DCRI’s expertise in implementing pragmatic approaches has also been beneficial in adapting to challenges introduced by the COVID-19 pandemic.

Wang and DCRI cardiologist John Alexander, MD, MHS, lead PROACT Xa, a cardiology trial testing whether patients with an On-X mechanical aortic valve can safely and effectively take apixaban rather than warfarin. The trial was just beginning enrollment when the pandemic reached the U.S. and curtailed in-person research. Fortunately, the study had already been designed with in-home study drug delivery for all participants. The study team, determined to maintain momentum, was also able to successfully implement remote enrollment—and by four months into enrollment, an unprecedented 14 percent of participants had been enrolled completely remotely in this investigational new drug trial.

Data Collection and Integration: Leveraging Real-World Environments for Real-World Applications

Because research often requires data from multiple disparate sources, the DCRI has created and incorporated mechanisms for making data collection and integration more efficient.

One study launched this year, EMPACT-MI, is introducing efficiencies by collecting the data needed for the trial through a patient portal. The study, led by DCRI Executive Director Adrian Hernandez, MD, MHS, is exploring whether empagliflozin can prevent heart failure in people who have had a heart attack. The study team, determined to maintain momentum, was also able to successfully implement remote enrollment—and by four months into enrollment, an unprecedented 14 percent of participants had been enrolled completely remotely in this investigational new drug trial.
Another way the DCRI is incorporating efficiencies in data collection is through the DCRI Master Data Management Repository (MDMR) program, which DCRI’s Technology and Data Solutions group has created as a way to integrate and harmonize data into research and analysis datasets.

“The DCRI has been able to lead in this space and define the ideal implementation to make working in this new data environment as efficient as possible.”

Andrew MacKelfresh, MBA

A pragmatic trial called HiLo, led by DCRI nephrologist Myles Wolf, MD, MMSc, was the first to use the MDMR program. HiLo seeks to determine whether a higher versus a lower blood phosphate level alters clinical outcomes in patients who are receiving dialysis for end-stage renal disease. Study data are drawn from each dialysis center’s electronic health record (EHR) system and, through the MDMR, are harmonized at the DCRI in preparation for statistical analysis and reporting.

“With trends in the industry like the use of telemedicine and direct access to data, there are more sources of data and models to support in every research project,” said Andrew MacKelfresh, MBA, a DCRI clinical research informatics project leader. “The DCRI has been able to lead in this space and define the ideal implementation to make working in this new data environment as efficient as possible.”

The DCRI also introduces efficient methods of data collection through its work on collaboratives such as the Lung Transplant Clinical Trials Network (LT-CTN), a group of five adult lung transplant programs (Duke University, Cleveland Clinic, Johns Hopkins University, UCLA, and the University of Toronto).

The LT-CTN, which is supported by the National Institute of Allergy and Infectious Disease, was formed to address the important problem of chronic lung allograft dysfunction (CLAD), the leading cause of death after lung transplant.

The CTOT-20 study, which was developed by the LT-CTN, employs innovative and pragmatic approaches to data collection by enabling patients to enter their own outcome data directly into an online portal. The study team also interfaces directly with sites’ local pulmonary function testing (PFT) laboratories to gather PFT test results obtained during routine clinical care.

The study also uses a novel approach to identify CLAD development through an objective CLAD calculator. Sites perform the final adjudication, ensuring objective and reproducible identification of the condition in real time as it develops. Analysis of these CLAD cases, coupled with translational analysis of biological samples, are providing new insights into the mechanisms that lead to CLAD.

Another collaborative and efficient study overseen by the DCRI is made possible through a partnership with the U.S. Department of Veterans Affairs (VA). The study team of AIM-Back, a pragmatic trial co-led by DCRI physical therapist and musculoskeletal expert Steven George, PhD, PT, and S. Nicole Hastings, MD, MHS, will be conducting the trial at 16 VA sites.

In an effort to improve lower back pain, the trial will randomize the VA sites to one of two clinical pathways: either guideline adherent care coordinated by a pain navigator or sequenced care combining short-term physical therapy on-site at the local VA with
centralized telehealth administered to VA sites across the country by physical therapists in Durham, North Carolina.

“In previous studies, gathering the data from the EHR was time- and resource-intensive. This process is not only more efficient, but it also allows the study team to view data captured in real time.”

Leo Brothers, MPH

Because the VA only uses one EHR, data collection is much more efficient than in a multi-site study that would require harmonization of data across multiple systems, said DCRI project leader Leo Brothers, MPH. In addition, in lieu of a research coordinator manually filling out a data collection form, AIM-Back incorporates a study note into the EHR so that providers can fill it out during a patient’s routine care.

“In previous studies, gathering the data from the EHR was time- and resource-intensive,” Brothers said. “This process is not only more efficient, but it also allows the study team to view data captured in real time.”

Dissemination and Implementation: Sharing Knowledge to Improve Patients’ Lives

The most important part of the research process is disseminating and implementing study results. Not only is DCRI’s mission centered on sharing knowledge, but doing so helps implement research findings more quickly into clinical practice.

The Environmental influences on Child Health Outcomes (ECHO) program coordinated by the DCRI disseminates results by creating plain-language summaries for many of the studies it conducts.

“By asking investigators to pull out the high-level information about their study results, we are helping them to efficiently share with other researchers and parents important research that is being done around the country.”

Adair Brown

The plain-language summaries, a relatively novel approach, are one- to two-page reports that share results of a study in a clear and concise way that patients and their families can understand. The summaries also focus on the study’s impact and next steps related to its findings.

“By asking investigators to pull out the high-level information about their study results, we are helping them to efficiently share with other researchers and parents important research that is being done around the country,” said Adair Brown, a member of DCRI’s Research and Communications Engagement group who helps to edit and produce the summaries.