EMBEDDED
Leveraging real-world data to align research with patient care

This year, the DCRI completed the first randomized controlled trial that fully leveraged a new real-world data system from the U.S. Food and Drug Administration (FDA).

Researchers built the IMPACT-AFib trial entirely on data from the FDA-Catalyst System and Sentinel System network of electronic health records (EHRs), as well as insurance claims data from a diverse group of data partners. The trial randomized 80,000 patients with atrial fibrillation to test whether an intervention would improve use of anticoagulants. Results were presented in late summer 2020 at the European Society of Cardiology Congress. IMPACT-AFib, which was led by DCRI’s Sean Pokorney, MD, MBA, lays the groundwork for future clinical trials that are embedded in clinical care by using real-world data collected during the course of care.

“The trial itself was a success, as it demonstrated that it is possible to conduct a clinical trial entirely using embedded real-world data.”

Sean Pokorney, MD, MBA

“The effort was truly a collaboration, with the Clinical Trials Transformation Initiative, Harvard, DCRI, a patient representative, the FDA, and the data partners (insurance companies) working together closely in order to successfully complete the trial,” Pokorney said. “The actual intervention the trial was testing was not found to be effective—we found out that educational mailers sent to people with atrial fibrillation did not increase usage rates of stroke-preventing oral anticoagulants. However, the trial itself was a success, as it demonstrated that it is possible to conduct a clinical trial entirely using embedded real-world data.”

Enabling Use of Real-World Data

Most of DCRI’s investigators are also clinicians who care for patients. Finding ways to embed research into care helps them to align their research questions with their experience in the clinic, resulting in questions that are more clinically relevant and results that can be implemented into patient care more quickly. Embedded research also has other advantages; for example, it may alleviate participation burden for both patients and sites. In particular, leveraging data that have already been collected reduces data collection burden for research purposes.

Real-world data can be drawn from many different sources, including claims data that document patients’ clinical encounters, EHRs used within hospitals and clinics, and wearable devices and apps that allow people to track or enter their own data. And as real-world data becomes recognized as increasingly important—
for example, the FDA has issued guidance on its use—it becomes even more critical to select the right data sources.

“One of the things that’s unique to the DCRI is that we have our finger on the pulse of the landscape of data opportunities,” said Tracy Wang, MD, MHS, MSc, director of DCRI Health Services Research. “We have the expertise to match-make, to pick and choose the best data sources that are fit-for-purpose to answer a specific research question.”

Creating Data Repositories

The DCRI is known for its expertise in conducting randomized controlled trials, but many of its investigators also engage in another major form of evidence generation by designing and overseeing clinical registries.

“The benefit of registries is that they are embedded in patient care as closely as possible,” said Beth Fraulo, RN, BSN, director of operations for DCRI Health Services Research. “Once patients sign up to be part of a registry, cross-sectional or longitudinal data are collected from their routine clinical care without requiring extra site visits. Registries also allow us to examine a wider, more representative section of the patient population than clinical trials.”

“We have the expertise to match-make, to pick and choose the best data sources that are fit-for-purpose to answer a specific research question.”

Tracy Wang, MD, MHS, MSc

One longstanding registry coordinated by the DCRI is the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, created in 2015 to fill a gap in research on pediatric rheumatic diseases. The registry, led by DCRI pediatric rheumatologist Laura Schanberg, MD, since its inception, has enrolled over 10,500 children and adolescents to date—and continues to grow. This year, the registry further embedded into patients’ lives by enabling telehealth follow-up visits when COVID-19 restrictions limited the viability of in-person clinic visits.

The CARRA Registry serves as a data and biological sample repository, providing opportunities for a variety of research projects, identifying participants eligible for future studies, and continuing to collect data into adulthood. This year, the registry helped identify patients with lupus for enrollment in the DCRI-led iPERSOnal study, DCRI’s first direct-to-family trial, which aims to study dosing and medication adherence for teenagers with lupus.

Enrolled over 10,500 children and adolescents to date

The infrastructure of the registry also enables the DCRI-led LIMIT-JIA trial, which is investigating a potential treatment for juvenile idiopathic arthritis, to be fully embedded within the registry. This benefits the team behind the trial, as they can access data already collected by the registry via regular patient visits. The trial team also benefits from working with existing registry infrastructure, such as clinical sites, investigators, and research coordinators who are already accustomed to conducting research because of their involvement in the registry. Most importantly, follow up of the patients in the trial will continue long term, well after the LIMIT-JIA trial protocol-specified follow-up is complete.

“The benefit of registries is that they are embedded in patient care as closely as possible.”

Beth Fraulo, RN, BSN
Creating a platform to ease the burden of conducting clinical trials was also the goal behind the creation of the Pediatric Migraine Registry, which is led by DCRI pediatrician Christoph Hornik, MD, PhD, MPH.

“We initially decided to create the Pediatric Migraine Registry because we thought a real-world registry would be a good way to address challenges we were seeing in pediatric migraine drug development,” Hornik said. “The registry, which collects regulatory-compliant data, provides an ideal platform to support embedded trials in this space.”

This year, registry leaders rapidly met their goal of enrolling 200 patients nationwide between the ages of 4 and 17, and the team is now examining opportunities for further expansion. The registry will collect and analyze two forms of real-world data: any data collected during patients’ normal care delivery, plus patient-reported data submitted by patients and their caregivers through a “headache diary” on a mobile health app. The team is also transitioning the registry from site-based research visits to a fully decentralized, direct-to-participant model, which will allow patients to enroll and complete study visits remotely, further embedding research participation into patients’ lives.

Another DCRI registry has seen such rapid success that it expanded into another registry this year. DCRI pulmonologist Scott Palmer, MD, MHS, and his team have begun enrollment for the Interstitial Lung Disease-Prospective Outcomes (ILD-PRO) Registry.

“Because the IPF-PRO Registry has been a proven success, our partners in this project, Boehringer Ingelheim, were confident that this model would also be effective in studying interstitial lung diseases.”

This registry is modeled after the Idiopathic Pulmonary Fibrosis-Prospective Outcomes (IPF-PRO) Registry, which, since its inception in 2014, has resulted in eight published manuscripts, at least 40 poster or abstract presentations, and a range of new discoveries about IPF, from potential biomarkers to contributing factors that make the lung disease difficult to diagnose. The ILD-PRO Registry uses much of the same infrastructure as IPF-PRO, including many of the same sites.

“Because the IPF-PRO Registry has been a proven success, our partners in this project, Boehringer Ingelheim, were confident that this model would also be effective in studying interstitial lung diseases,” said Palmer, who is the principal investigator for both registries and DCRI therapeutic area lead for Medicine Plus. “We look forward to collecting a new repository of data to help us make new discoveries in an equally challenging lung disease.”

Using the EHR to Expand Registries’ Power

Some registry teams also pull data from the EHR to add more power to their insights. cvMOBIUS, a large-scale cardiovascular registry operationalized by the DCRI, seeks to determine the benefits of PCSK9 inhibitors, a lipid-lowering therapy. The registry team will enroll 8,500 patients, and they will also utilize the Cerner network and PCORnet®, the National Patient-Centered Clinical Research Network, to access EHR data, enabling the study to include an even wider population of patients. This work will help them better understand widespread patterns pertaining to PCSK9 inhibitor prescribing rates, adherence, and outcomes.

“Although data from clinical trials have shown that these therapies are effective in lowering lipid levels, we don’t yet have the real-world evidence to support how they are being used in clinical practice,” said Linda Davidson-Ray, MA, the project leader for cvMOBIUS. “By embedding this registry into regular practice, and by pulling EHR data alongside our registry data, we’ll be able to evaluate the real-world impact of new therapies, as well as where
we still face gaps in improving secondary prevention in cardiovascular disease.”

Studying Implementation via Registry-Based Trials

Traditionally, clinical trials have been conducted to determine the effectiveness of a medication, or to find out whether one medication is superior to another. At the DCRI, clinical trials are also utilized to study implementation.

“Often, the field has proven treatments or strategies that we know should be used, but on average, it takes 15 to 20 years for this evidence to be implemented into practice across the board,” Fraulo said. “That’s where implementation trials come in. We look at the best way to implement evidence and consider a number of different stakeholders, from the health system to the clinician to the patient.”

“One example of an implementation trial is RACE-CARS, a study funded by the National Institutes of Health (NIH) that will test the implementation of community interventions designed to improve survival for people who experience cardiac arrest.

Fifty counties across North Carolina, encompassing over 80 percent of the state’s population, will be enrolled into RACE-CARS. Because RACE-CARS is designed to be a cluster randomized study, participating counties will then be randomized to either a multifaceted intervention or to usual care.

“By embedding this registry into regular practice, and by pulling EHR data alongside our registry data, we’ll be able to evaluate the real-world impact of new therapies.”

Linda Davidson-Ray, MA

One example of an implementation trial is RACE-CARS, a study funded by the National Institutes of Health (NIH) that will test the implementation of community interventions designed to improve survival for people who experience cardiac arrest.

Fifty counties across North Carolina, encompassing over 80 percent of the state’s population, will be enrolled into RACE-CARS. Because RACE-CARS is designed to be a cluster randomized study, participating counties will then be randomized to either a multifaceted intervention or to usual care.

“RACE-CARS will create high-quality evidence about how to implement guidelines at the community level to improve survival from cardiac arrest, one of the top causes of death,” said DCRI cardiologist Christopher Granger, MD, co-principal investigator of the study. “Because we’ve designed the study to be embedded within the day-to-day operations of each community and its health systems, it will not only be easier for counties to participate in the study, but it will ensure that study results are highly relevant to similar communities around the U.S.”