An internationally renowned rheumatologist, Dr Claire Bombardier has been the recipient of a number of distinctions for her research in the field. Here, she discusses her recent work towards ensuring the real-world potential of drugs through longitudinal studies.

Initially, the OBRI was predominantly focused on pharmacotherapy research, specifically looking at recently approved drugs and how they performed in real-world settings. This meant we would be able to study the effectiveness of these drugs in all patients with comorbidities – who are nearly always excluded from clinical trials. Effectiveness and sustainability, as well as tolerability profiles were all measured. As the OBRI evolved, we developed evidence-based guidelines and quality care indicators for rheumatology. Now we are expanding our research focus beyond pharmacotherapy and looking at clinical practice and quality of care provided.

By embedding the guidelines and quality indicators in data collection we can measure variations and look at best practices across the province. To build on this, we are also looking at healthcare efficiencies – we can map out the epidemiology of disease, the representation of patients and doctors, appropriateness of care and healthcare cost implications downstream.

There is an ongoing global effort to reduce fraudulent claims and issues pertaining to publication bias. In what capacity do you address this?

My motivation to develop real-world data collection was very much stimulated by the withdrawals of drugs, because in rheumatology a lot of drugs have been withdrawn due to adverse events once they were used by the general public, so when the biologics were approved in Canada, our community was very concerned. Not only are biologics very expensive, but they are a new class of drugs and their long-term safety and effectiveness were initially unknown.

Is it hard to manage all of these data? How can you guarantee that you have a useful repository that can be accessed by anyone?

We have built a very strong infrastructure by leveraging peer review, public and industry funding. The challenge is to maintain this very successful infrastructure over the long-term.

Could you explain the information system for evidence implementation you developed? What are the shortcomings in the current management and delivery of care?

Physicians have to fill in forms, and when you imagine a busy clinician in a private practice in the community, not only do they have to write something in their charts, they also have to fill in forms. We’re spending a lot of time working with the Ontario Ministry of Health and Long Term Care. They are encouraging the adoption of Electronic Medical Records (EMRs) by providing finances to physicians. The first funding priority was focused on primary care, but they are now helping specialists. To this end, specialty specific clinical data collection tools are embedded in their EMRs.

These tools are not the same as ones employed for primary care physicians. EMR vendors that embed these specialty tools will eventually become preferred providers for rheumatologists. For example, we use a homunculus – a little sketch of a skeleton – with joints, and we circle joints that are painful or swollen. But if we switch from paper to electronic medical records, you have to embed the homunculus, which is an image not text, into the EMR. It is not something a primary care physician would want, because they wouldn’t examine and/or document all the 66 joints in the body – but a rheumatologist does. So, we are working with the EMR Committee of the Ontario Rheumatology Association and eHealth Ontario to help EMR providers support their users by developing and embedding the necessary speciality specific clinical tools within their platforms. Those EMR vendors who are able to embed these clinical tools will eventually become preferred providers for our specialty.

In late 2013, British scientists found that the human protein BiP could act as a potent treatment for rheumatoid arthritis. Could a cure be in sight?

It has a very interesting hypothesis, and was demonstrated in rats to start with. Now, Arthritis Research UK is funding a trial in humans, and we have to see what the trial shows. If the trial is positive, it could lead to quite a striking change in the way we treat our patients, but there are a lot more steps to take before we reach that stage; many promising drugs didn’t meet their promises, even before marketing, and this is very much at the development stage. We’re following developments but it’s not my research expertise; my expertise lies in studies conducted once drugs have been tested in humans, either pre- or now post-marketing.
For a number of years the Ontario Best Practices Research Initiative has been collecting data on the treatment of rheumatoid arthritis patients in Canada’s largest province, in the hope of revealing the effectiveness and safety of current drugs in a real-world observational cohort.

PHARMACEUTICAL RESEARCH IS a good example of where science and industry work well to promote research and quicken the pace of discovery. A pharmaceutical company provides financial support to a research team that develops and tests a drug that the company then markets commercially to make a return on its investment. Everyone involved achieves the financial input they require, research is performed to advance human knowledge of health and a new clinical solution becomes available to patients. It seems like a functioning model but, unfortunately, there is a flaw in the system.

Under this framework, researchers are only involved up until the point where the drug is made commercially available. When the drug is available for use in the general population, studies will either cease to exist or remain in a limited capacity, consisting of a few, short-term observations. The importance of animal trials and pre-clinical studies in gaining information on a potential therapy cannot be overstated, but nonetheless, the studies performed on a drug prior to its approval and marketing are not representative of its real-world impact, but off its compatibility with approval criteria. Very strict inclusion criteria for patients mean that the participants in clinical trials only partially represent patients who will receive the drugs in the real world.

LIMITATIONS OF CLINICAL TRIALS

In Canada, an increasing number of researchers and clinicians are becoming concerned by the apparent disparity between the testing process for drugs and the course over which these drugs will actually be used in the clinic as most patients with complex chronic diseases require treatment for many years. What is more, clinical studies often exclude subjects with common comorbidities such as previous heart attacks and liver abnormalities. The problem is not that researchers make false claims about drugs entering the market, but simply that the trials being performed are not comprehensive enough to reflect real-world scenarios.

This dilemma is best demonstrated in figures on rheumatoid arthritis drugs entering the market. Dr Claire Bombardier and her colleagues who work on the Ontario Best Practices Research Initiative (OBRI) showed that the effectiveness and safety demonstrated in clinical trials are not always sustained when they are used in the real world. They found 40 percent of patients stopped taking the drugs prescribed in the second, third or fourth year of treatment; although these solutions performed well in clinical trials, they either caused adverse effects on patients, or they simply lost their efficacy after a certain period of time. The OBRI has piloted the surveillance of rheumatoid arthritis on their innovative research infrastructure and are now adding other conditions such as spondyloarthritis, pregnancy outcomes, paediatric rheumatologic conditions and common conditions in complex chronic diseases (eg, sleep). This longitudinal, prospective observational research platform has been developed with a wide range of stakeholders.

AGGREGATING ARTHRITIS

The objective of the OBRI, which was established in 2005, is to collect comprehensive patient data on rheumatoid arthritis sufferers through the 60 rheumatologists involved in the initiative. To date, 3,000 patients have been recruited from across Ontario. Patients and their rheumatologists complete assessments on a regular schedule.

The clinical dataset, however, is only one of several platforms from which the OBRI derives its data; the Canadian researchers also have access to an administrative dataset collected through collaboration with the Institute for Clinical Evaluative Sciences (ICES – www.ices.on.ca). With this dataset OBRI can link its clinical data to these administrative billing data for the province. It is the final dataset that really puts the clinical data into a national context; the OBRI researchers have been able to identify that there are currently 100,000 Ontarians living with a diagnosis of rheumatoid arthritis. This administrative dataset also captures healthcare utilisation including drug use (in Ontarians over the age of 65), physician and emergency room visits, hospitalisation and mortality data, cancer registry data, and figures on tuberculosis and non-tuberculosis cultures. The power of this linkage is quite unique to Ontario. Through the linked clinical administrative data set, OBRI researchers can now evaluate how patients living

“I want to make sure arthritis sufferers get the best care possible. My relatives were bedridden and told nothing could be done. That was true then, but I’m determined that should never happen again.”

Catherine Hofstetter,
Consumer Advisory Committee Chair and third generation rheumatoid arthritis sufferer
"We need to invest in and support the collection of patient and system outcome data to demonstrate the value of treatments and medications. OBRI is a unique research platform that can deliver this to all of its stakeholder groups."

Sandra Couto, Director of Partnership and Stakeholder Relations

with arthritis who receive various treatment modalities access the healthcare system and their overall impact on healthcare utilisation and optimal patient outcomes.

INFORMED ACTION

In the capable hands of the OBRI, these data will serve to further progress towards four important goals. The first of these is to determine, in a real-world setting, the long-term value and health impacts of current rheumatoid arthritis treatments, to inform future treatment practices that may lead to improved patient outcomes and provide insight into treatment patterns in usual care that may exist regionally. It is also a priority for the OBRI to provide meaningful information for Canadian policy makers. Ultimately, in identifying gaps and barriers to healthcare access, especially in provincial areas, better payment decisions can be made about these drugs to more effectively manage limited resources.

Through the pursuit of these goals, the OBRI aims to affect change in the system, and in order to meet national and consumer priorities, they work closely with a number of rheumatology associations including The Arthritis Society, the Arthritis Alliance of Canada, the Canadian Rheumatology Association and the Canadian Rheumatology Research Consortium and other stakeholders. Sharing their results with these organisations as well as policy makers, drug reimbursement agents and private insurance companies, Bombardier and her collaborators ensure that their voices, and the voices of individual clinicians and patients in the field, are heard.

CREATING CHANGE FOR REAL WORLD RESEARCH

In addition to carrying out this research, a large part of the scientists’ work is concerned with improving the framework for conducting the longitudinal, long-term studies OBRI represents. Traditional randomised trials and individual research projects are time-limited, yet these are the sort of projects that funders and research ethics boards are geared to accommodate. Longer studies, however, which aim to survey pharmaceutical and clinical performance over a number of years run into complications as most funders cannot cater to the initial investment or infrastructure required. As a consequence, work must be divided into several shorter projects, each funded by a different grant that requires ethics approval – a repetitious process incurring great cost to the researchers.

Despite this preferred, albeit inefficient, system, Bombardier’s team has confirmed opinion held by the research community that drugs cannot be properly evaluated in the short term, or through spontaneous reporting from patients, which can lead to bias. Further longitudinal studies are needed to provide more reliable data for future drug development and delivery. Unfortunately, many institutional research ethics boards still require the re-consent of thousands of patients across different locations with different ethical constraints periodically, which is neither practical nor cost-effective. Working with Canada Research in Law and Medicine, as well as the McGill University legal and ethics group and other Canadian ethics experts, Bombardier is ardently trying to bring some clarity to the methods ethics committees use to deal with these projects, and to resolve ethical issues surrounding electronic consent and data collection.

LOOKING AHEAD

In the years ahead, the OBRI’s goals will focus on publicising the importance of real-world drug monitoring, especially for expensive drugs, as well as providing help, where possible, to rheumatology associations attempting to move practice towards an integrated model of care. The population-based analyses using ICES administrative data demonstrate that the number of rheumatoid arthritis patients has doubled in the last 10 years to 100,000, while the number of rheumatologists in the province went from 160 to 162. The OBRI was the first body to observe this trend, and is therefore dedicated to aiding in the changes needed to maintain a high standard of care. Bombardier’s own focus, similarly, is on the future: “The challenge now is to attract young researchers,” she reflects. “It is a big task, and this is not something I can accomplish on my own.”