EDITORIAL

Reflections on Ethical Medical Research

By Philip A. Baer, MDCM, FRCPC, FACR

"Only one rule in medical ethics need concern you - that action on your part which best conserves the interests of your patient."
— Dr. Martin H. Fischer

I started thinking about this topic recently when two seemingly unrelated events occurred in close proximity: the closure of the only clinical research trial in which I was still actively participating, and my wife and I choosing to see a recently released documentary called "Three Identical Strangers."

For twenty-five years, I was a principal investigator in a variety of Phase 2, 3 and 4 trials and registries. NSAID and COXIB trials were common initially, including SUCCESS-1 (celecoxib vs. naproxen), MORE (meloxicam vs. placebo), a trial of enteric-coated vs. plain naproxen, VIGOR (rofecoxib vs. naproxen), and the pivotal Phase 3 trials for a Canadian-developed topical NSAID, diclofenac in DMSO (Pennsaid). VIGOR provoked anxiety as it was an adverse-event driven trial, which would end when a certain number of patients had experienced upper GI bleeds. One of my twelve VIGOR patients had a fortunately mild bleed event while on naproxen, which fit with the study hypothesis that rofecoxib would be safer. Unfortunately, cardio-vascular events tilted in the other direction, starting the cascade of events which would lead to the withdrawal of rofecoxib and other COX-2 inhibitors and multiple lawsuits. Prominent Canadian rheumatology researchers were ensnared in the resulting publicity, including Dr. Claire Bombardier, VIGOR's lead author. I was a tiny minnow and escaped any attention.

Later, I participated in a variety of trials in rheumatoid arthritis (RA) for agents which failed, as well as early trials of a biologic known then as D2E7, now more familiar to the world as adalimumab. For 15 years, I was an investigator in the Canadian BioTRAC registry following patients with RA, ankylosing spondylitis (AS) and psoriatic arthritis (PsA) on either infliximab, golimumab or ustekinumab. This trial survived through 2 corporate mergers, ultimately enrolling 3,000 Canadian patients and generating multiple poster presentations and 1 ACR podium presentation for me personally, before closing in mid-2018.

Over time, trial participation has become more onerous on patients and investigators, in my opinion. The availability of proven agents in many rheumatic diseases make placebo-controlled trials difficult to justify in the Canadian setting. Consent forms are longer and harder to fully comprehend, adverse event documentation is more exacting, research ethics boards demand greater information, and the requirement for record retention has increased to 25 years. That is a long time to contemplate for someone in mid-career or later, as I find myself now. I don't think I will initiate any new trials at my site going forward.

Why are research requirements so exacting? One has only to look at the historical record of human experimentation to see why so much protection is needed for human research subjects. We recall easily the horrors of Nazi medical experiments, leading to the Nuremberg Code (1947), the Declaration of Geneva (1948) and the more familiar Declaration of Helsinki (1964, last amended in 2013). However, despite these statutes, failures to protect human subjects have occurred more recently, even in countries such as Canada and the United States.

Google "Tuskegee Syphilis Study" for a particularly heinous example. Started in 1932 by the US Public Health Service, poor African-American men in Alabama were offered free medical care in a study designed to determine the natural history of untreated syphilis. The patients were not apprised of their diagnosis. Even after penicillin was known to be an effective treatment, it was not provided. The study carried on until 1972, when a whistleblower came forward and the study ended. The study toll included numerous men who died of syphilis, forty wives who contracted the disease, and 19 children born with congenital syphilis. This study led to the establishment in the US of the Office for Human Research Protections (OHRP) to oversee clinical trials. Familiar study requirements became mandatory, including informed consent, communication of diagnosis, and accurate reporting of test results, as well as institutional review boards (IRBs) including laypeople, which were mandated to review study protocols and protect patient interests, ensuring that study patients are adequately informed.

Closer to home, I remember my psychiatry rotation as a medical student at the Allan Memorial Institute at McGill. The institute was located in Ravenscrag, the former hilltop mansion of Sir Hugh Allan, a Canadian railroad and shipping baron of the 1800s. While we found the place a bit eerie, we did not know at the time that patients hospitalized there in the 1950s and 1960s had been unknowing participants in experiments conducted as part of the CIA's MK Ultra project. This was directed at the Allan by Dr. Donald

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Mentoring Future Leaders in Rheumatology

Over the past nine years, the CRA has nurtured its mentorship program, designed for early career stage rheumatologists who are likely to become leaders in research, education, and/or advocacy in Canada. Dubbed FLIRT, short for Future Leaders in RheumaTology, this program operates in two-year cycles, comprised of various initiatives identified directly with its participants, and in collaboration with Canadian mentors as well as expert advisors. The program teaches its participants valuable leadership skills including peer reviewing, mentor-mentee training, coaching, communication and presentation styles, among other skills. Another focus of FLIRT is important skill-building initiatives such as time management, career progression, interpersonal relations, setting expectations and the importance of managing a practical work-life balance.

FLIRT has involved participants from across the country in both adult and pediatric rheumatology, both those involved in community practice and in academia. Participants include basic scientists, clinical researchers, teachers and those with other roles at their institutions or within their communities. All nomination submissions are peer-reviewed and are accepted to participate in the program based on their CV, letter of intent and reference letter. These groups of participants, including those among the many cycles of graduates, are varied in age and interest with a variety of career pathways. As a result, the program creates outstanding discussion and networking opportunities. which also serve to strengthen the bonds within the rheumatology community. FLIRT participants ultimately represent the future of rheumatology within Canada.

As the program approaches its tenth year of operation, several past graduates have moved on to leadership positions at their institutions and various other establishments, including within the CRA. The current program cycle runs until spring 2020, at which point another call for applications will go out to members of the CRA. If you would like to learn more about the Future Leaders in RheumaTology mentorship program, please visit the Canadian Rheumatology Association's website at *rheum.ca/flirt-mentorship-program/*.

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Ewen Cameron, a prominent psychiatrist and one-time president of both the Canadian and American Psychiatric Associations. Subjects received LSD, high-intensity electroconvulsive therapy and "psychic driving" treatment, often while in drug-induced comas. The MK Ultra project did not end until 1973. Some Canadian victims received compensation in 1992, but many did not.

Which brings me full circle to the movie "Three Identical Strangers." As a father of twins, I have always been interested in stories about twins, triplets and higher-order multiple births. Without spoiling the movie, which I highly recommend, the story revolves around identical triplets, adopted out to 3 different families in New York state in 1961, and unaware of the existence of their siblings until chance intervened in 1980. At that point, they experienced their 15 minutes of fame, but the future featured tragedy, as well as the discovery that their adoption had been part of a scientific study gone rogue, akin in its own way to the studies I outlined above.

Next time you wonder why enrolment of patients in clinical trials has become much more rigorous, the answer lies in the failings of scientific researchers not very far removed from the present.

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