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COMMENTARY

Fulfilling the potential of real-world evidence for lung cancer in Canada

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The use of real-world evidence (RWE) through real-world data (RWD) is becoming increasingly prevalent in health care around the globe. The U.K. National Institute for Health and Care Excellence defines RWD as "a term to describe data generated from sources that relate to everyday clinical practice, generally outside the artificial constraints of randomized controlled trials (RCTs)"[1]. Although RCTs pull data from a specific pool of patients in a highly controlled setting, RWD are—exactly as the name suggests—data drawn from patients in routine real-world clinical settings.

The benefits of RWD are far-reaching, with the potential to affect new-drug development and inform health technology assessments (HTAs) that influence regulatory approvals in Canada. Those benefits hold particularly true when it comes to oncology, and to lung cancer specifically. Despite extensive investments of time and money, conventional methods of evidence-generation such as RCTs simply have not kept pace with the rapidity of scientific innovation.

Real-world data can be considered an effective means of supplementing data from RCTs and providing additional context where needed. For example, using RWD, the understanding of treatment options for small subgroups who would not otherwise be studied in the setting of a RCT can be advanced. Consideration can also be given to patients who are commonly excluded from clinical trials but who are routinely encountered in clinical practice—for example, those with mild organ impairment, poor performance status, multiple comorbidities, or brain metastases. Real-world data can also offer insights into disease progression patterns, patient selection criteria, and practice patterns, all of which can inform the design and conduct of RCTs.

The foregoing examples are just the tip of the iceberg in terms of how RWE can be used. Precision medicine is playing an increasingly prominent role in lung cancer treatment. A wide array of patient subgroups with rare oncogenic driver mutations such as *BRAF* and *ROS1* that are treatable with standard-of-care targeted therapies have now been identified[2]. Unfortunately, the populations with those rare mutations are not large enough to be considered on their own in a RCT, and many randomized phase III trials comparing standard-of-care drugs with chemotherapy have become unnecessary because of the overwhelmingly clear response rates from single-arm phase II studies. However, the lack of data beyond phase II trials has created difficulties for regulators.

An example of a situation that could have benefited from RWE comes from the pan-Canadian Oncology Drug Review (pCODR). Despite Health Canada approval of dabrafenib–trametinib for *BRAF*-mutated non-small-cell lung cancer, pCODR recommended against reimbursement because the committee was uncertain about its effectiveness given a shortage of evidence from clinical trials[3].

It is in such situations that RWE has a consequential role in guiding HTAs. If the Canadian Agency for Drugs and Technologies in Health and pCODR had access to a robust set of RWD, they would be better equipped to evaluate the clinical effectiveness of potentially life-saving or life-extending treatments for which a RCT might never be able to provide the necessary evidence or might not be feasible to conduct.

The U.S. Food and Drug Administration and other international regulatory bodies, including the European Medicines Agency and the U.K. National Institute for Health and Care Excellence, have taken the lead by using available RWD to make regulatory decisions or by requesting RWE on new drug indications after approval[4–6]. For example, ASTRIS—a real-world phase III treatment study—was used to evaluate the safety and value of osimertinib for patients with advanced or metastatic *EGFR* T790M–positive non-small-cell lung cancer[7]. In that case, the drug had already been approved, but the U.S. Food and Drug Administration specifically requested RWE of the drug's effectiveness[8].

An example of how regulatory bodies are making use of RWD in Europe is illustrated by the case of the ALK inhibitor alectinib, in which European HTA bodies asked the manufacturer to provide further evidence of its effectiveness compared with the standard of care, ceritinib[8]. To satisfy that request, the electronic health records of patients treated with ceritinib were retrospectively analyzed and compared with the alectinib phase II trial data[8]. The results were submitted to multiple European HTA bodies, and in part because of that RWE, funding for alectinib was approved about a year and a half earlier than if it had awaited presentation of the phase III data[8].

In Canada, strides are being made to usher in the greater use of RWE in various disease areas. As recently as autumn 2018, the Canadian Agency for Drugs and Technologies in Health teamed up with Health Canada to advance the use of RWE. Those organizations established an advisory group to develop a framework for incorporating RWE into Canada's health care decision-making process in a consistent manner[9].

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It is interesting to note that, in addition to health care regulators, health care providers and researchers around the world and pharmaceutical manufacturers are beginning to adopt this form of evidence as a valuable tool to better understand the impact of their treatments and to guide research priorities more efficiently. For example, the RealGiDo study assessed the safety and effectiveness of the EGFR tyrosine kinase inhibitor afatinib in patients with *EGFR* mutation–positive advanced non-small-cell lung cancer in a real-world setting[10]. That retrospective study evaluated patients treated in 13 countries and found that dose adjustment with afatinib lowered the number of adverse drug reactions without hindering effectiveness[10].

It is promising to see various stakeholders along the spectrum of health care delivery putting RWE to good use, but more work remains needs to be done to make such data more easily accessible and broadly accepted in the health care industry. Poor-quality RWD has been a major hindrance to acceptance, and more consistency and rigour in how RWD are collected and recorded are needed, which is where disease registries come into play.

Not only do disease registries provide the opportunity to generate high-quality, transparent, and standardized data for HTAs, but they could also allow groups from various countries to easily collaborate to produce RWE on a global scale—provided that the registries are established with the necessary infrastructure and safeguards.

Canada has already seen the success of national databases for some forms of cancer. The Canadian Kidney Cancer Information System (https://www.kidneycancercanada.ca/for-patients-and-caregivers/clinical-trials/canadian-kidney-cancer-information-system-ckcis) was recently used to measure quality indicators for patients undergoing surgery for renal cell carcinoma[11], and information from the Canadian Melanoma Research Network Patient Registry has been helping researchers to better understand the real-world effects of the introduction of new therapeutics in that disease[12].

It is for that reason that, together with our Canadian peers, we have been discussing a Canadian collaboration in lung cancer. Already in Canada, a few provincial or centre-specific lung cancer databases are in place, and we are now discussing ways to take those efforts to a national level. The goal of a national collaboration is to enable the study of regional and national practice patterns and clinical outcomes, including quality of life and overall survival for patients over time. A national registry would also allow for the development of robust RWE for smaller subgroups of the lung cancer population, the tracking of adverse events, and the collection of epidemiology data, all of which could help guide HTA assessments and health policy priorities.

Given the speed of new insights and discoveries, the variety of newer therapies being tested, and the urgency of access to newer treatments for patients, today is a pivotal time for national health care delivery as a whole. Now that organizations in growing numbers are accepting data outside conventional RCTs as a legitimate source of evidence, the sky is the limit for what the medical community can accomplish in collaboration. More widespread use of RWE through RWD in Canada is imperative, and patients don't have time to wait.

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