RESEARCH PAPER

Developing a Canadian Real-World Evidence Action Plan across the Drug Life Cycle

Développement d'un plan d'action canadien fondé sur les données probantes du monde réel tout au long du cycle de vie des médicaments

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Abstract

Policy makers face challenges with the number of drugs for rare indications and rapidly rising costs. In facing these challenges, decision-makers see real-world evidence (RWE) as an opportunity. Health Canada and the Canadian Agency for Drugs and Technologies in Health (CADTH) recently announced their intent to co-develop an action plan to optimize the process for the systematic use and integration of RWE into both regulatory and reimbursement decision-making in Canada. When implemented, this will have a significant impact on how drugs are approved and paid for in Canada. We highlight the key opportunities, barriers and future directions related to the use of RWE throughout the life cycle of drugs in Canada.

Résumé

Les responsables des politiques sont confrontés au grand nombre de médicaments pour les indications peu fréquentes et à l'accroissement rapide des coûts. Face à ces défis, les décideurs sont conscients des possibilités que peuvent apporter les données probantes du monde réel (DPMR). Santé Canada et l'Agence canadienne des médicaments et des technologies de la santé (ACMTS) ont récemment annoncé leur intention de développer conjointement un plan d'action pour optimiser le processus d'utilisation systématique et d'intégration des DPMR dans la prise de décisions réglementaires et de décisions de remboursement au Canda. Une fois mise en œuvre, cette politique aura un impact significatif sur la façon d'approuver et de rembourser les médicaments. Nous mettons de l'avant les principales occasions, obstacles et directives à venir quant à l'utilisation des DPMR dans le cycle de vie des médicaments au Canada.

Background

Healthcare decision-makers such as drug regulators and payers face challenges in curbing rising drug costs and a rapidly growing number of rare indications (CADTH 2016). These challenges, associated with the advent of technological advances in identifying rare conditions and available treatment options, come at a time when there is a demand for quicker access to novel treatments (CADTH 2016, 2018; Krause and Saver 2018). To address these challenges, decision-makers see the use of real-world evidence (RWE) as an opportunity to make better and more informed decisions related to market access and funding (CADTH 2018). RWE is often defined as clinical evidence derived from sources other than traditional randomized controlled trials (RCTs). RWE leverages data collected in the routine care of patients through mechanisms such as electronic medical records, healthcare claims data or disease registries. Studies leveraging these data can be based on a variety of study designs, including observational studies and pragmatic clinical trials.

The use of and demand for RWE by regulatory, reimbursement and healthcare decision-makers have quickly expanded (CADTH 2018; Krause and Saver 2018). Currently, the use of RWE has largely been limited to the post-marketing safety evaluation of drugs and

supplemental evidence for submissions. In Canada, Health Canada and CADTH held a joint workshop in 2018, launching an initiative to integrate RWE throughout the life cycle of drugs (IHE 2018). At this workshop, they announced the intention to co-develop an action plan to optimize the process for the systematic use and integration of RWE into both regulatory and reimbursement decision-making in Canada. The development of this action plan will aim to outline activities that need to be taken across the drug life cycle to support the optimal use of RWE in Canada. The full integration of RWE will have a significant impact on how drugs are approved and paid for in Canada, but multiple challenges will need to be addressed for RWE's potential to be fulfilled. We aim to highlight the key opportunities, barriers and future directions related to the optimization and integration of the use of RWE throughout the life cycle of drugs in Canada.

Challenges and Opportunities

Currently, drug regulators face challenges in a dynamic ecosystem; these challenges present opportunities for the use of RWE. Specifically, in the past decade, there has been a significant rise in the cost of all new drugs and the number of drug treatments (Mullard 2020). Specific pressure has been added in the area of drugs for rare diseases, as the rise of genetic biomarkers has resulted in further subdivision of populations driving the number of orphan drug indications higher, a form of "high-tech salami slicing." Two significant challenges have accompanied these shifts in drug development: identification of rarer indications and increases in cost of treatments.

Some of the recently approved drugs are much more likely to include those that are intended for use in much smaller populations, many of which meet the definition of rare disease. The number of "orphan drugs" – a US Food and Drug Administration (FDA) designation for drugs for rare diseases – approvals have increased five-fold from an average of 15 approvals per year in the 1990s to over 80 in 2017 alone (Bagley et al. 2018; CADTH 2016). Given that these drugs target smaller populations, the efficacy and safety evidence for these drugs tends to be developed in relatively smaller studies, which can undermine their reliability. For example, recent Phase III studies studying sebelipase alfa in lysosomal acid lipase deficiency had 36 individuals in the intervention group of the study (Burton et al. 2015). In contrast, a recent Phase III trial of dapagliflozin for the treatment of type 2 diabetes had 695 subjects in the intervention arms (Frías et al. 2016). These smaller studies introduce a higher level of uncertainty related to the efficacy and safety of these products. This uncertainty due to smaller studies for drugs makes regulatory decisions related to both market entry approval and pricing negotiations challenging (Raphael et al. 2020). The integration of RWE would allow the inclusion of further evidence to support RCT evidence and strengthen the reliability of results. Similarly, often RCT evidence does not include evidence to support the use of medication in more vulnerable subpopulations, such as pediatric or older adult population. RWE can serve as a key opportunity to support the expanded use of medications in older adults not currently supported by traditional RCT evidence.

A challenge that the recent shift in the drug development landscape presents is the rising prices associated with new treatments, for both rare and common indications. Strikingly, the number of approved drugs in Canada with price tags over $10,000 annually increased from 20 drugs in 2005 to 124 in 2015 (Government of Canada 2016). The combination of limited evidence and steeper prices has created a need for more information to assess value as drug prices are negotiated. The consideration of incrementally accrued RWE into negotiated flexible pricing arrangements has the potential to reshape how much we pay for drugs in Canada. A broader strategy incorporating RWE would support the need for more progressive listing agreements, such as pay-for-performance and outcome-based reimbursement models, that have the potential to reduce drug prices (Keohane and Petrie 2017; Vlaanderen et al. 2018). These models are not new and have been touted as potential solutions for years but have had low uptake to date owing to the complexity of application for making decisions (Vlaanderen et al. 2018). Both of these highlighted challenges present a timely opportunity for the development of a more coordinated and systematic approach to the generation and the use of RWE that has the potential to reshape the drug regulatory approval and the reimbursement process. Full integration of the use of RWE into the drug-approval life cycle, from pre-market to post-market, may advance our ability to approve drugs earlier for rare diseases, more adequately monitor safety and improve our ability to assess the economic value of therapies. Furthermore, the inclusion of RWE may allow for more robust assessments and reassessments of the effectiveness and impact of drugs.

Barriers

As exciting as the potential impact of RWE implementation may be, there are important barriers to its adoption that must be considered as an action plan is developed. These barriers have been highlighted through early discussions with stakeholders, such as regulators and funders, and include the alignment of stakeholders, development of RWE standards that account for the diversity of RWE use-cases and development of standards that align with international initiatives for high-quality RWE (IHE 2018). Full implementation of RWE must overcome complex and challenging issues that have been cited by stakeholders.

First, the implementation of RWE throughout the drug-approval life cycle will have a significant impact on a large number of stakeholders, including payers, regulators, manufacturers, patients and clinicians, who all have differing interests. As frameworks are developed, it is essential to keep in mind that these various stakeholders have varied but overlapping foci and motives. A successful action plan must aim to balance many of the interests and prioritize transparency where feasible, to develop trust among stakeholders. It is important to recognize that this action plan will not always directly fulfill all interested parties' interests, as some may be opposing; however, a comprehensive action plan that is developed collaboratively will acknowledge these differences in a transparent manner while capitalizing on the benefits of mutual engagement. Developed frameworks must not lower established standards of decision-making structures but will need to define roles and expectations of all parties involved.

Second, the implementation of RWE will have a wide array of clinical areas, drugs and gaps in evidence that will require varying methods, designs and data. For example, study designs and data needed for a rare cancer treatment to gain market approval will differ from those that are developed to support an outcome-based reimbursement model for a new asthma inhaler. Importantly, recent work has highlighted the need to more greatly improve real-world data to allow the potential alignment and replication of clinical trials (Bartlett et al. 2019). Potential improvements cited include expansion to include patient-reported outcomes, clinical insights using natural language processing and linking to medical devices. No action plan can or should aim to be prescriptive or attempt to define all available permutations. Rather, a successful action plan should aim to describe and advise on potential actions to address and handle the diversity of applications, allowing flexibility in the adoption of RWE while ensuring the development of the highest quality decision-grade evidence. Importantly, ensuring evidence quality should leverage decades of methodological development in observational research and be informed by the understanding of limitations of this type of research. The action plan developed must balance risk and benefits to patients and not be seen as a means to rapidly allow access to the market and reduce the evidence threshold. RWE must and should be used as a tool to augment current evidence regulatory standards and not a process to bypass them. Important lessons can be learned from the current use of RWE in both the US and Europe (Avorn and Kesselheim 2015; Davis et al. 2016; Fralick et al. 2018). For example, recent oncology drug approvals by the US FDA have highlighted the benefit of expedited approval but increased uncertainty around clinical benefits (Raphael et al. 2020).

Finally, drug development and pharmaceutical policy is a global issue, and thus, the action plan should be developed with an eye toward the ongoing international initiatives in other major jurisdictions, such as those at the European Medicines Agency and the US FDA (Krause and Saver 2018; Plueschke et al. 2018). The Canadian action plan should consider the current and ongoing initiatives. For example, when considering the development of data collection and analysis standards, it is important to align with market standards and leverage ongoing international standards. This will also be an opportunity to learn from other jurisdictions such as those that leveraged RWE to conduct performance-based pricing (Wenzl and Chapman 2019). Not aligning with international standards will lower the potential for uptake and engagement by stakeholders that operate across jurisdictions, specifically manufacturers.

What the Future Holds

Leveraging Canada's growing national pharmaceutical enterprises, such as the pan-Canadian pharmaceutical alliance, and growing data infrastructure is a crucial opportunity for the Canadian healthcare system to be a world leader in the integration of RWE in decision-making throughout the life cycle of drugs. Canada is uniquely situated to have a robust and unified drug life-cycle process with access to rich data sources and capacity. Various

international jurisdictions have aimed toward the implementation of RWE in specific points of the drug life cycle, mainly focusing at the point of market entry. Canada aims to be one of the first jurisdictions to implement RWE throughout the life cycle of the drug. This is illustrated by the fact that the action plan is being co-developed by Health Canada, CADTH and National Institute of Excellence in Health and Social Services (IHE 2018). In addition, the current focus of health technology assessment and price negotiation at a national level allows a potential broader inclusion of RWE. To our knowledge, no other jurisdiction has developed any initiatives that leverage both health technology assessment and regulators to develop a robust set of activities that spans the entirety of the drug life cycle. This presents a key opportunity to leverage RWE to inform market entry as well as reimbursement models such as conditional and performance-based reimbursement models. This important initiative will help to reframe the way we think about how drugs exist in the healthcare ecosystem. Importantly, this signals a shift in the classic siloed approach to drug policy and a shift toward a more integrated approach that will reduce duplication and capitalize on the strengths of the stakeholders involved. Expanding our focus from market entry to ongoing monitoring of agents in the healthcare environment will allow RWE to develop ongoing evidence. This reframing will allow the integration of current evidence that will help improve how we use and pay for medications in Canada.

We aim to develop an action plan for the use of RWE that will help Canada take advantage of the opportunity to optimize our $30-billion national investment on drugs. Importantly, this initiative comes at a time of an active national discourse on the potential implementation of a national pharmacare strategy. The stakes could not be higher for us to develop a novel, Canadian-style framework that balances the needs of stakeholders, ensures quality of RWE, leverages capacity and improves access and value of medications. We are confident that the challenges decision-makers face will allow for a key opportunity for the success of RWE integration through the maturation of drugs and reshaping the life cycle of drugs in Canada.

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