

# Oncology Trial Comparator Drug Reimbursement: A Canadian Perspective

Denise Deakin

Examining a region's comparator reimbursement climate to better inform trial expansion decisions.



When evaluating regions in which to expand clinical trials, oncology drug developers must take many factors into consideration, including patient enrollment potential, the region's standard of care, and a myriad of other direct and indirect costs that affect feasibility. Comparator arm drug access and reimbursement policies are other key components that pose a distinct set of challenges to sponsors and which are becoming increasingly important to consider as part of early clinical development planning. Between 2002 and 2007, 41% of all clinical trial sites used by U.S. companies were located outside the United States, so weighing these considerations has become a mainstay in the daily routine of clinical operations professionals.<sup>1</sup>

Due to the limited amount of published data on clinical trial comparator arm reimbursement in Canada, the purpose of this article is to shed some light on the topic so that sponsors can make more informed decisions when evaluating the region as a possible option for geographic expansion.

## Comparators critical in cancer trials

Once an oncology clinical investigative compound progresses beyond the Phase I setting, it is subjected to a study design that includes its application either in combination with or compared to a drug that is deemed, by clinical guidelines, to be the safest and most effective in treating a particular cancer indication.

These comparator drugs, or standard of care, are the benchmark against which new experimental drugs are evaluated. The FDA has published guidelines to support the choice of comparator arm drugs for clinical trials, but this does not address the sponsor's responsibility in assessing a drug's availability, establishing a procurement mechanism, and managing its cost.<sup>2</sup> These issues, although administrative in nature, are critical steps that must be skillfully executed to ensure timely execution and return on investment of any clinical drug development program.

## Expensive proposition

While there appears to be a wide variation from one year to the next in terms of the industry's average annual spend on comparator arm drugs, 11 large pharmaceutical companies reported that their average spend between 2009-2011 represented half of their overall clinical supply budget, or \$25 million USD.<sup>3</sup> In an attempt to contain these costs, sponsors have traditionally adhered to a strategy of maintaining their early phase trials within the United States whenever feasible, and the reason is clear.<sup>4</sup>

With 85% of Americans having private health-care insurance to help reimburse the cost of comparator arm drugs, this was once an effective cost containment strategy<sup>5</sup>; however, it's a different reality today. The Personalized Medicine Coalition reports that 60% of early phase trials now use de-

financed biomarkers and are, thereby, classified as personalized medicine. This distinction has changed the drug development landscape significantly.<sup>6</sup> Under this classification, the inclusion criteria for these trials are extremely selective, leading to a low incidence of a specific patient population and, hence, the need to look abroad for patients. This challenge, coupled with the fact that today's costly breakthrough biomarker-enabled medicines will be tomorrow's comparator drugs, means that the cost of conducting oncology trials is set to skyrocket. Sponsors will be under even greater pressure to execute a well thought-out international site selection strategy.

### Prime destination for oncology trials?

Canada has some strong cards to play as a prospective region for the expansion of both early and late phase oncology trials. Cancer treatments tend to vary widely from one region to the next, as well as within any one particular region, making it difficult for sponsors to implement a U.S. protocol in other countries.<sup>7</sup> In Canada, however, the standard of care for cancer patients is somewhat consistent across the country due to its universal healthcare system. In terms of clinical guidelines and best practices, Canada's approaches to cancer treatment are often similar to those in the United States. Therefore, a protocol designed to reflect treatment standards in North America would likely be a good fit for Canada.

A combination of the universal healthcare system and the fact that Canada's population is located predominately around urban centers, means most Canadian patients are treated in publicly funded teaching institutions located in large metropolitan cities. This trait facilitates rapid site selection and may result in enhanced patient enrollment. Finally, coupled with its geographic proximity to the United States, Canada boasts excellent clinical data quality and a standardized clinical trial agreement (CTA) designed to accelerate the study start-up process. Despite the potential advantages, U.S. sponsors, especially smaller biotechnology companies, may have reservations about coming to Canada simply because they are unfamiliar with the region's drug availability and reimbursement landscape.

### Many complexities to navigate

A brief explanation of the process may be helpful in better understanding a dynamic and sometimes complex regulatory environment. First, the Therapeutic Drug Directorate at Health Canada must approve the drug's use based on its safety and efficacy profile. Next, the Patented Medicine Prices Review Board, an independent, federally funded agency, decides whether the drug's proposed pricing is reasonable when compared to other benchmark countries. Finally, the decision to fund a drug on provincial formularies falls within the jurisdiction of each of the 10 provinces and three territories after receiving a recommendation from the Pan-Canadian Oncology Drug Review (pCODR).

Created in 2007, the pCODR operates as a collaborative health technology review and advisory body, acting on behalf of all participating provincial and territorial jurisdictions, except Quebec, which has its own oncology review agency. With the intent to ensure that public funds are invested wisely, pCODR accomplishes its mandate to support sound reimbursement decision-making based on rigorous review of clinical and economic evidence leading to the most beneficial patient outcomes. While taking the pCODR's recommendations into consideration, each member province also reviews drug reimbursement applications according to its own policies and formulary practices before rendering a final decision

**In Canada, the standard of care for cancer patients is somewhat consistent across the country due to its universal healthcare system.**

on reimbursement listing and scope of coverage. In essence, pCODR provides a strong influence in creating uniformity of cancer care treatments across all Canadian jurisdictions.

With respect to trial comparator arm reimbursement of formulary drugs, the landscape is also changing. Canadian provinces were once very lenient in issuing reimbursement in support of clinical research. While there is still a strong commitment to advance these efforts for improved health outcomes, provinces have adopted a more stringent reimbursement approach to contain rising healthcare costs. This includes an initiative to publish guidelines on the subject. To date, only two provinces have an official policy, while the province of Ontario has one that is currently in draft format. The policies outline the principles, criteria, and process related to the reimbursement of publicly funded cancer drugs when patients participate in trials as part of their therapy.

As per Ontario's draft policy, The Ontario Public Drug Programs and Cancer Care Ontario will consider all requests for the reimbursement of publicly funded cancer drugs within the context of trials where the drug is being used within the approved indication.<sup>8</sup> While meeting other select criteria that run parallel to GCP/ICH guidelines, the study must not incur any deferred or incremental costs to the provincial public health system. Although the remaining provinces do not have an official policy, they regulate reimbursement activities according to a similar set of unofficial guidelines. Exceptions may apply to protocols bearing a particularly compelling scientific hypothesis. Since oncology is a highly dynamic therapeutic area, it is plausible that a study design may include a comparator arm drug that has only recently been approved by the FDA, but that has not yet been reviewed by Health Canada or listed on the provincial formulary for an approved indication. In such a case, the provincial policies do not apply.

It is also possible that the comparator arm drug is not a newly approved drug by the FDA, but rather a drug that has never been filed and approved in Canada. In either case, sponsors may file a Clinical Trial Application with Health Canada, the equivalent of a U.S. investigational new drug (IND) application, but they must obtain comparator arm information submitted to the FDA. If the comparator arm is part of a head-to-head study design, then obtaining the required information will likely be difficult due to competitive concerns of the comparator drug manufacturer. On the other hand, if the drug is used in combination with the research compound, then the process of obtaining the required information should be fairly easy since there are no real competitive concerns. Clearly, in either case, the sponsor would be obliged to obtain the drug from a U.S. source, such as a drug wholesaler, or from a collaborative non-profit organization, such as TransCelerate BioPharma Inc. TransCelerate's Clinical Trial Comparator Network has created a new model for comparator drug distribution by enabling direct shipment between participating companies.

In cases where the comparator arm is not reimbursed by public healthcare but the drug is licensed for use and is available within Canada, the sponsor may direct the institution to procure the drug from a local wholesaler or directly from a drug manufacturer and then invoice them. Comparatively, patented drug prices in Canada average between 35% and 45% lower than those in the United States.<sup>9</sup> As such, although the sponsor would have to assume the comparator drug cost, it would be less than the U.S. market price. Over time, the Pan-Canadian Pricing Alliance (PCPA), established in 2010, may further mitigate the impact of patented drug prices. PCPA is a purchasing-oriented collaborative with the goal of achieving economies of scale and lowering drug acquisition costs by facilitating the centralized buying of drugs in bulk by provincial governments.<sup>10</sup> By contrast, U.S. laws still prohibit Medicare or Medicaid from negotiating drug prices.

Finally, and perhaps of greatest importance, one must consider the institution's individual needs and preferences. Having a sponsor cover the cost of the comparator arm provides great value to the institutions because it presents an opportunity for them to investigate and advance standard of care for their patients in a safe and cost-neutral manner regardless of the formulary or reimbursement environment.<sup>11</sup>

### New expansion approaches necessary

One thing is certain, the rise of personalized medicine will force sponsors to start thinking about regional expansion much earlier than was previously required. Once clinical trial development is expanded beyond the United States, sponsors should evaluate whether it makes economic sense to absorb the costs of the comparator arm drug when weighing the risks versus the benefits of a particular region.

Opportunities for reimbursement do exist in Canada, but the environment is much more restrictive today than in the past due to sustained public policy on implementing provincial healthcare cost containment measures. But even if a comparator arm drug will not be covered, there are other factors to consider, such as accessibility of patients and investigator interest, which may outweigh the drug costs.

Regardless of drug reimbursement potential, the cardinal rule for successful patient recruitment continues to be focusing on opening trials at the right institutions, because high recruitment and quick study start-up often trump the costs associated with paying for the comparator arm drug. To get this right requires a strategic and careful case-by-case analysis of all country-specific issues that could either derail or speed up enrollment for a particular trial.

### References

1. Tufts Center for the Study of Drug Development, 2007 Report.
2. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>.
3. M.J. Lamberti, T. Walsh, and K. Getz, "Tracking Trial Cost Drivers: The Impact of Comparator Arm Drugs and Co-Therapies," *Pharmaceutical Executive*, 33 (5) 34-37 (2013).
4. C. Bredin, M. Eliasziw, and R. Syme, "Drug Cost Avoidance Resulting from Cancer Clinical Trials," *Contemporary Clinical Trials*, 31, 524-529 (2010).
5. Obamacare Facts, Where Americans Get Health Coverage, <http://obamacarefacts.com/howdoes-obamacare-work.php>.
6. Personalized Medicine Coalition, [http://www.personalizedmedicinecoalition.org/sites/default/files/files/PM\\_by\\_the\\_Numbers.pdf](http://www.personalizedmedicinecoalition.org/sites/default/files/files/PM_by_the_Numbers.pdf).
7. L. Aberg, B. Albrecht, and T. Rudolph, "How Health Systems Can Improve Value in Cancer Care," McKinsey Healthcare Systems and Services, 12, 43, (2012), <http://www.mckinsey.com/Search.aspx?q=How%20health%20systems%20can%20improve%20value%20in%20cancer%20care>.
8. Cancer Care Ontario/Action Cancer Ontario, "Policy On Cancer Drug Reimbursement Within the Context of Clinical Trials," draft for consultation purposes (2013).
9. V. Paris and E. Docteur, "Pharmaceutical Pricing and Reimbursement Policies in Canada," OECD Health Working Papers, 52, (2007), <http://www.oecd.org/canada/37868186.pdf>.
10. W. Dempster, A. Blanchard, and J. Chambers, "Will a Pan-Canadian Approach to Drug Purchasing Save the Provinces Money?," *Inside Policy*, 14-19 (2012).
11. J.S. Hoch and M. Sabharwal, "Informing Canada's Cancer Drug Funding Decisions With Scientific Evidence and Patient Perspectives: The Pan-Canadian Oncology Drug Review," *Curr Oncol*, 20 (2) 121-124 (2013).

**Denise Deakin** is President and Co-Founder of Scimega Research Inc. She can be reached at [ddeakin@scimega.com](mailto:ddeakin@scimega.com).