Developing a Patient Group Pathway Model to Accessing Cancer Clinical Trials in Canada

G. Batist MD,*†‡ S. Michaud PhD,§ D. P. Richards PhD,// F. Servidio-Italiano MA,# and B.D. Stein BCL,LLB#.

Author affiliations

* McGill Centre for Translational Research in Cancer
† Segal Cancer Centre at the Jewish General Hospital, Montreal
‡ National Centre of Excellence in Personalized Medicine – Exactis Innovations
§ BioCanRx
// Clinical Trials Ontario
Colorectal Cancer Canada

Running header: PATIENT GROUP PATHWAY MODEL TO ACCESSING CANCER CLINICAL TRIALS

Correspondence to: Filomena Servidio-Italiano, Director of Education and Clinical Information, Colorectal Cancer Canada, Suite 300, 1350 Sherbrooke Street West, Montreal, QC H3G 1J1.
E-mail: filomenas@colorectalcancercanada.com. Telephone: 1-877-502-6566 ext.2632.

Acknowledgements

Support for this initiative was generously provided by BioCanRx: Biotherapeutics for Cancer Treatment, Boehringer Ingelheim, Bristol-Myers Squibb, Canadian Partnership Against Cancer, Coalition Priorité Cancer au Québec, Innovative Medicines Canada, Eli Lilly Canada, Merck Canada, Hoffman-La Roche and Novartis. We thank all the meeting participants and members of the Scientific Advisory Committee for their active and insightful input into the development of the recommendations and for their leadership in promoting the engagement of Canadian patient groups in cancer clinical trials. Also, we are grateful to the Clinical Trials Transformation Initiative for their inspiration in serving as the basis for the Canadian Pathway.

Previous publication:

Word count: 4,035 (text only)

Figures & tables: 5 figures; 1 table

ABSTRACT

Background

A Canadian Patient Group Pathway to Accessing Cancer Clinical Trials (Pathway) is being developed by Colorectal Cancer Canada, in partnership with a Scientific Advisory Committee. A central element of the Pathway is presented here, namely a set of recommendations and tools aimed at each stakeholder group.

Methods

A summary of peer-reviewed and gray literature informed discussions at a meeting, held in June 2017, in which consensus among a cross-section of stakeholders was reached on: potential roles of patient groups in the cancer clinical trials process; barriers to accessing cancer clinical trials; best practice models for patient group integration; and a process for developing the Pathway.

Canadian recommendations and tools were subsequently developed by a small working group and reviewed by the Scientific Advisory Committee.

Results

The major output of the consensus conference was agreement that the Clinical Trials Transformation Initiative (CTTI) model, successfully applied in the United States, could be adapted to create a Canadian Pathway. Two main differences between the Canadian and American cancer clinical research environments were highlighted: the impact of global decision making, and systems of regulatory and funding approvals. The working group modified the CTTI model to incorporate these aspects and to reflect Canadian stakeholder organizations and how they currently interact with patient groups.

Conclusions

Developing and implementing a Canadian Pathway, incorporating the concepts of multi-stakeholder collaboration and the inclusion of patient groups as equal partners, is expected to generate significant benefits for all stakeholders. The next steps to bring forward a proposed Pathway will involve engaging the broader cancer research community. Clinical trial sponsors will be encouraged to adopt a Charter recognizing the importance of including patient groups and to support the training of patient groups through an independent body to ensure quality research partners. Integration of patient groups into the process of developing “real-world” evidence will be advanced by a further consensus meeting being organized by Colorectal Cancer Canada for November 6-7, 2018. [comment 7]

KEYWORDS:

Cancer patient groups, cancer clinical trials, clinical research, patient engagement, advocacy, recruitment, Clinical Trials Transformation Initiative

INTRODUCTION

Colorectal Cancer Canada believes that access to clinical trials of new drugs, medical technologies and other cancer treatments should be a standard of care for all Canadian patients, regardless of their age, where they live and their income. (In this paper, the term "patients" refers to persons who have been diagnosed with cancer and their caregivers.)

Need for improved access to cancer clinical trials

While the positive impacts of cancer clinical trials are widely acknowledged, participation rates of adult cancer patients in Canada remain significantly low. In 2014, less than 7% of adult cancer patients in Canada were enrolled in a clinical trial, compared to fewer than 5% in the United States and 12% in the United Kingdom.[1] Rates of recruitment and retention of patients are unsatisfactory. In the United States, for example, it is estimated that 85% of clinical trials fail to retain enough patients to continue; 80% fail to finish on time; and half of sites enroll one or no patients.[2] Of the overall pharmaceutical clinical trial budget, it has been reported that 40% is spent on recruitment and 30% of patients drop out of a study.[3] These discouraging statistics suggest that opportunities for potentially life-saving improvements in patient outcomes may be missed, leading to a devastating loss of hope for many cancer patients.

Part of the answer to improving the system of cancer clinical research and development lies in reducing barriers that dissuade or prevent patients from participating in studies. For too many patients, these deterrents are significant and have been shown to contribute to low enrollment rates in cancer clinical trials.[4]

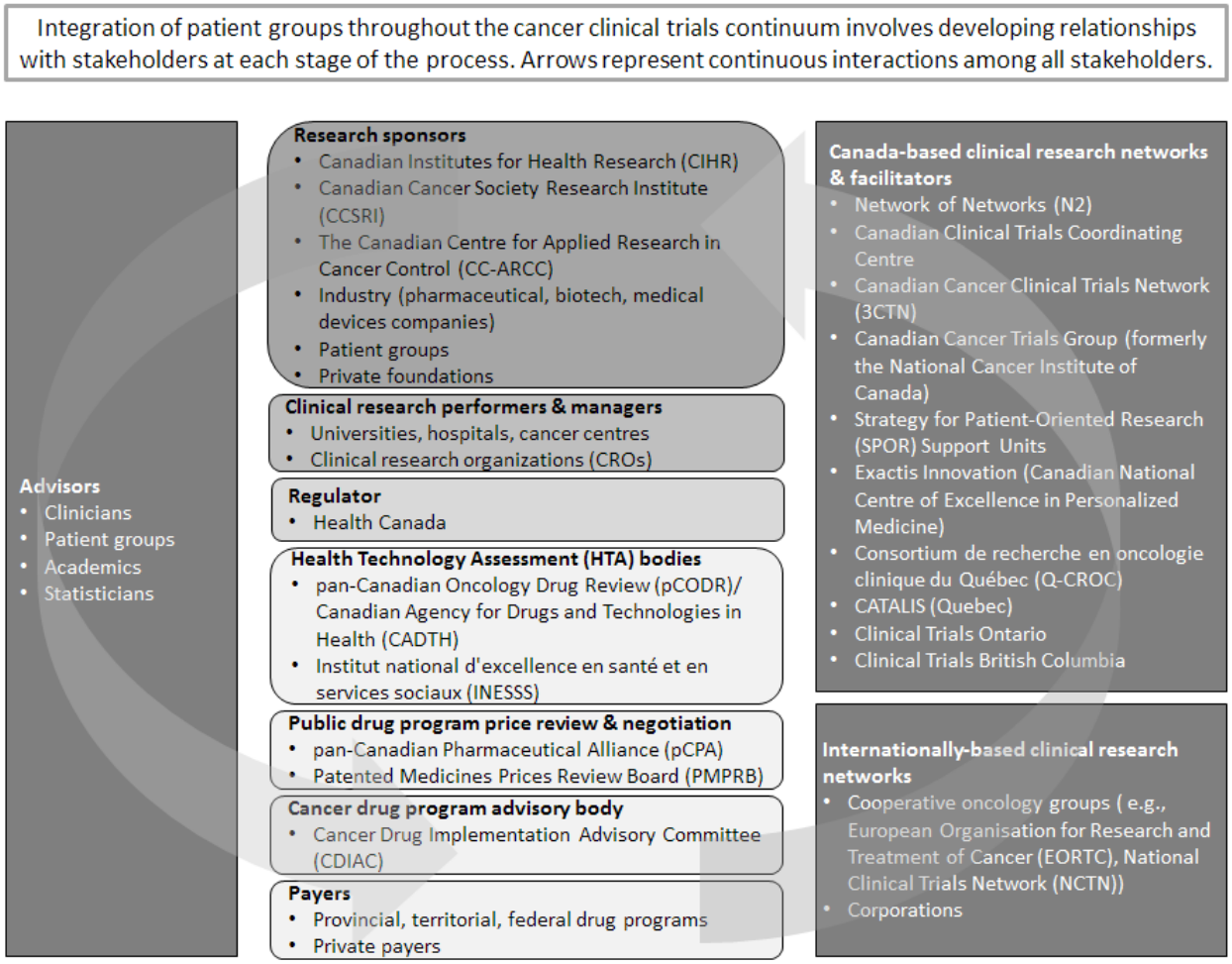
Emerging role of patients in clinical research and development

Patient input has proved effective in identifying and resolving barriers to participation in cancer clinical trials.[5,6] Moreover, the patient voice is of emerging importance across the spectrum of cancer clinical research. For example, patients in many countries now advise on setting research agendas[7] and on the design, planning and implementation of trials.[8-12] Patient-focused strategies such as patient reported outcomes (PROs)[13] have gathered momentum and contribute to "real world evidence" which is increasingly valued by stakeholders. Multi-stakeholder efforts, such as that of the American Society for Clinical Oncology (ASCO), Friends of Cancer Research, and the US Food and Drug Administration, have successfully collaborated with the goal of improving clinical trials accrual rates.[14] [comment 3]

Patient groups (a term encompassing patient advocacy organizations, disease advocacy organizations, voluntary health agencies, health charities, nonprofit research foundations, and public health organizations) can play a critical role by facilitating the patient voice and by organizing the involvement of patients in a systematic way, ensuring consistency and quality throughout the process.

Figure 1, below, illustrates the Canadian cancer clinical trials "ecosystem", including examples of organizations in each stakeholder group. Integration of patient groups across the cancer clinical research and development continuum involves developing relationships with stakeholders at each stage of the process.

Figure 1 **Canadian cancer clinical trials "ecosystem"**



[Heading changed from 'clinical research performers' to 'clinical research performers & managers'] [comment 5]

Value of a systematic framework

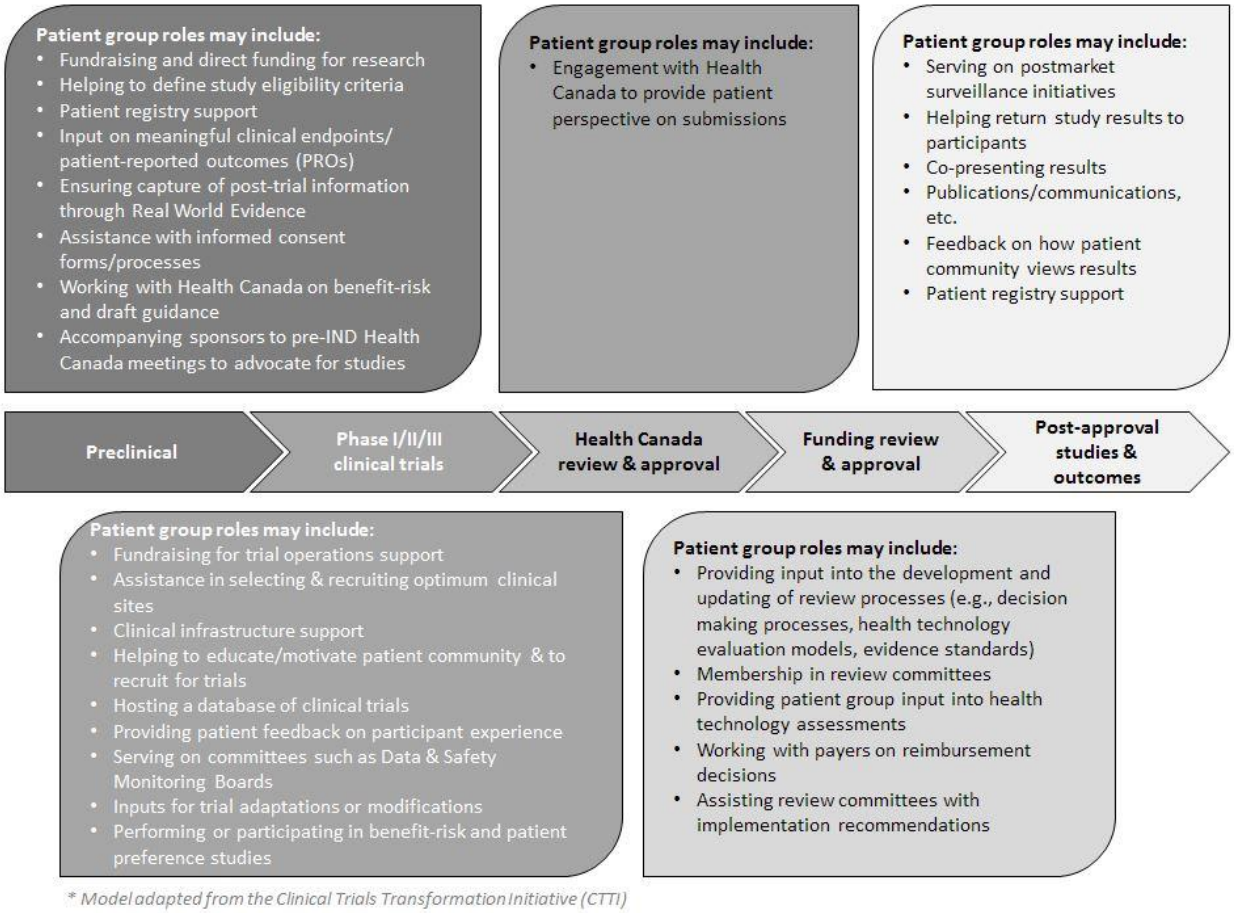
While inclusion of patient groups in cancer clinical research has advanced in recent years, particularly in the area of health technology assessment where formal mechanisms are now well integrated, policies and practices across other aspects of the Canadian cancer clinical trials process remain inconsistent. An evidence-based framework may help to integrate the patient voice in a coherent and meaningful manner.[15]

Of the models that currently exist internationally, the Clinical Trials Transformation Initiative (CTTI) offers the most comprehensive guidelines for patient involvement in cancer clinical trials. CTTI is a public-private partnership co-founded in 2007 by Duke University and the U.S. Food and Drug Administration to the inefficiency and high costs of clinical trials and the need to generate strong evidence to answer therapeutic questions. CTTI employs a collaborative approach to develop and drive adoption of best practices that will increase the quality and efficiency of clinical trials. Since its inception, the initiative has grown to include more than 80 member organizations—representing

academia, clinical investigators, government and regulatory agencies, industry, institutional review boards, patient advocacy groups, and other groups.[16] [comment 1]

Figure 2, below, depicts the potential roles that patient groups could potentially play across the research and development continuum in Canada.

Figure 2 Potential engagement of patient groups in the Canadian cancer clinical trials process



** Model adapted from the Clinical Trials Transformation Initiative (CTTI)*

[Added: 'Hosting a database of clinical trials' to box related to Phase I/II/III clinical trials] [comment 6]

Adoption of a Canadian Patient Group Pathway to Accessing Cancer Clinical Trials (Pathway), incorporating the concepts of multi-stakeholder collaboration and the inclusion of patient groups as equal partners, is expected to generate significant benefits for all stakeholders. For cancer patients it is intended that the outcome will include faster access to innovative treatments and a greater understanding of new cancer therapies, as well as improvements in overall standard of care. Clinical trial sponsors and investigators may see improved cancer research and development strategies, shorter development timelines, lower costs and higher approval rates for new drugs and other treatments. Society at large may eventually benefit from lower costs as treatments are better understood and targetted to patients' needs. An early example of a positive impact in this direction comes from a recent publication by CTTI citing significant cost reductions to clinical trials sponsors as a result of implementing their recommendations.[17] [comment 4]

Those developing new therapies could also gain a better understanding of unmet medical needs and advance their knowledge of real-world outcomes. Health technology assessment bodies and public and private insurers may be able to determine the value of new treatments with increased confidence. (To further advance patient involvement in developing real-world outcome measures, Colorectal Cancer Canada is convening a multi-stakeholder consensus conference on November 6-7 2018 as a next step.) [comment 7] Canada may be better positioned to attract cancer research opportunities, resulting in greater funding flows and increased utilization of this country's research infrastructure. Finally, all participants are expected to benefit from improved relationships among stakeholder groups.

The impact of the Pathway could be measured initially by increased participation rates in cancer clinical trials. Statistics presented in future issues of the Canadian Partnership Against Cancer's *Cancer System Performance Report* could be reported at five-year intervals, for the next twenty years. Further metrics could be developed as implementation of the Pathway progresses. [comment 8]

METHODS

The development and implementation of a Canadian Patient Group Pathway to Accessing Cancer Clinical Trials (Pathway) is an initiative of Colorectal Cancer Canada (formerly the Colorectal Cancer Association of Canada). A cross-sectoral Scientific Advisory Committee continues to provide guidance on all aspects of the Pathway development and is central to its implementation.

The components of the Pathway are: a) a set of recommendations and tools aimed at each stakeholder group; b) a Charter, signed by clinical trials sponsors, which commits them to implementing the recommendations; and c) a guide for operationalizing the recommendations, including training of patient groups through an independent body to ensure quality research partners.

Step 1: Literature review

In advance of the consensus development meeting, a literature review was prepared to inform the discussions. Peer-reviewed publications and the gray literature identified by the Scientific Advisory Committee were examined and summarized. Subject areas were: assessments of cancer clinical trial performance in Canada and internationally; barriers to patient participation in cancer clinical trials; roles of patient groups in cancer clinical research and development; and patient engagement models.

Step 2: Consensus meeting

A meeting was held in June 2017 with a cross-section of stakeholders to develop a consensus on:

- The role of patient groups in cancer clinical trials;
- Barriers related to accessing cancer clinical trials;
- Best practice models;
- Process for developing a Pathway; and
- Identification of relevant stakeholders.

Details of the consensus meeting are available on Colorectal Cancer Canada's website at: https://www.colorectalcancercanada.com/.

Step 3: Canadianizing the model

Following the meeting, the selected international model was "Canadianized" to address key factors that distinguish the Canadian reality from that in the United States.

RESULTS

Meeting participants agreed that the Clinical Trials Transformation Initiative (CTTI)[18] model, which has demonstrated success in the United States, could be adapted for use in Canada. Two major areas of difference between the cancer clinical research and development systems in each jurisdiction were identified for adaptation and are described in detail below: global decision making processes, and systems of approval for new cancer treatments. [comment 2] Also, key Canadian stakeholder organizations were identified and their interactions with patient groups characterized. These inputs were also incorporated into the Canadianized recommendations and tools.

Global decision making processes

Meeting participants heard that pharmaceutical companies' research programs are designed and implemented on a worldwide basis. Also, global and regional academic clinical trials groups may develop their plans centrally.

Unlike their American counterparts, Canadian stakeholders generally are not involved in strategic decisions made at the earliest stages of the research and development process. By focusing the involvement of Canadian patient groups on the later stages of cancer clinical research, the resources of all stakeholders would be optimized.

Therefore, engagement of Canadian patient groups at the "Prediscovery" phase of the CTTI model was removed in the Pathway; patient groups first become involved at the "Preclinical" phase, as described in Figure 2, above.

Systems of approval for new cancer treatments

The approval of new cancer therapies includes both regulatory and funding systems, both of which differ between the United States and Canada. Health Canada is structured differently than the U.S. Food and Drug Administration (FDA) with respect to engagement with patient groups. Legislation and policies have been created to facilitate robust patient group involvement with the FDA[19,20] whereas Health Canada has only one formal opportunity for patient group participation in oncology-related decisions.[21] Since the speed of marketing approvals for new cancer drugs in Canada lags behind that in the United States by approximately six months[22,23] – a delay that is highly significant for cancer patients – the Canadian Pathway emphasizes working collaboratively with Health Canada and with manufacturers of new drugs and other cancer treatments to reduce submission and review timelines.

Canada and the United States also differ in their funding mechanisms for cancer treatments, in terms of sources of financing and review mechanisms used by public sector payers. A greater proportion of the population in the United States is covered by private health insurance (91%)[24] than is the case in Canada (67%).[25] The greater role played by public sector payers has resulted in a more restrictive environment in Canada. Compared to the United States where, by legislation, all or substantially all new cancer drugs must be made available to patients through Medicare,[26] many fewer are recommended for listing or include restrictions in Canadian public drug programs.[27-30] In the United States, Medicare reviewers are explicitly prohibited by law from considering evidence relating to the cost or cost-effectiveness of technologies when making coverage determinations.[31] In contrast, cost-effectiveness criteria are included as part of the deliberative frameworks of the pan-Canadian Oncology Drug Review[32] and the Institut national d'excellence en santé et en services sociaux[33] (along with evaluations of overall clinical

benefit, alignment with patient values and feasibility of adoption into the health system) and these considerations feature prominently in coverage decisions.[27] Finally, the funding review process for oncology medications takes much longer in the Canadian public sector: more than one year[34] compared to just over a month in the United States.[35] Consequently, the Canadian Pathway recommendations were adapted to include a greater focus on public systems of health technology assessment and reimbursement.

RECOMMENDATIONS

The intent of the following recommendations is to enhance, rather than replace, any existing models of integration of patient groups into the clinical research processes.

Part A. Recommendations for all stakeholders

1. Engage the "patient voice" by establishing partnerships starting at the pre-clinical phase of the research and development program to improve trial design and execution.

Include the perspective of patients in the early stages of disease targeting, making full use of patient group input while clinical trials are still in the planning phase to help shape and refine the study protocol. Soliciting patient group input early in development benefits both sponsors and patients.

Table 1 Sponsor and patient benefits of early patient group inputs

Sponsor benefits	Patient benefits
• Clearer, more focused understanding of unmet need and therapeutic burden • Awareness of opportunities for expanding indications and more appropriate targets • Improved clinical trial design, selection of optimum study participants, endpoints, and clinical sites • Faster trial recruitment and greater patient compliance with the protocol • Fewer costly and time-consuming adjustments during the clinical trial	• Less burdensome study protocols • More meaningful and relevant study endpoints • Increased likelihood of participation and retention in cancer clinical trials • Increased chance of developing an important treatment for their disease

2. From the start, clearly define the expectations, roles and responsibilities of all partners, including the resources being committed, data being shared and objectives of the program.

Patient groups and research sponsors often have different backgrounds and perceptions of the value that patient representatives bring to the clinical trials process, or the tasks that patient groups will be expected to undertake. At the outset of the development program, it is important to clearly delineate the roles of the partnership and to clarify the goals and objectives of the collaboration. Responsibilities and expectations could be outlined in agreements reflecting the resources being committed, data being shared, or overall nature of the program (e.g., early vs. late phase, trial process issues, informed consent forms, patient-reported outcomes vs. clinical endpoints).

While patient group input may be taken into account when determining the objectives of a clinical program or development of a protocol, it is important for research sponsors to balance that input with scientific understanding as well as patient, business and regulatory needs.

3. Build the trust required for successful partnerships by being transparent and trustworthy, following through on commitments and honouring confidentiality.
Building trust requires all stakeholders to be open, transparent and to honour commitments to the development program. Commitments between partners may be pre-specified and documented in an agreement, including how teams will be formed and intellectual property and revenue sharing will be managed. Confidentiality Agreements (CAs) and Non-Disclosure Agreements (NDAs) can be useful tools to allow sharing of sensitive information with patient groups.

4. Involve the expertise of multiple partners for a broader perspective to mitigate risk and enrich pipeline development.
Engaging with as many organizations as possible across the Canadian cancer clinical trials "ecosystem" (illustrated in Figure 1) will encourage a broad scope of inputs into the decision making processes and maximize efforts to recruit and retain patients in clinical trials, ultimately resulting in more and better therapeutic options.

5. Manage real or perceived conflicts of interest by establishing policies that require full disclosure, transparency and accountability.
Restrictions that may limit patient group engagement need to be understood and followed. For example:

- Some industry associations (such as Innovative Medicines Canada[36]) require their members to adhere to codes of ethical practices; and
- Patient groups may adhere to a written code of conduct (such as the *Code of Conduct Governing Corporate Funding* from the Canadian Cancer Action Network[37]).

Contractual rules and parameters may increase transparency and accountability. Some common examples are:

- Patient groups as service providers to the company on a contractual basis:
    - Roles and responsibilities in the contract are clarified
    - If the sponsor is retaining the patient group to do certain work with a tangible end product, the patient group may be compensated at fair market value
- Patient groups as recipients of funding from a company:
    - Providing unrestricted funds increases patient group independence
- Patient groups as non-compensated collaborators:
    - Rules of engagement consider the partners' legal, regulatory and research administration requirements and may include a Non-Disclosure Agreement (NDA).

Part B. Recommendations for research sponsors — industry and academia

1. Integrate into your ongoing research and portfolio planning an assessment of patient group expertise, assets and value to your program.
Research sponsors may benefit from building awareness within their organizations about the impact of early patient group engagement on clinical trial success.

Plans can be created for integrating patient groups into local clinical drug development processes at each phase of the process. The plan may serve to:

- Include and coordinate activities across all relevant departments;
- Outline how the interactions with patient groups will be managed; and

- Allocate appropriate resourcing to support patient group engagement.

2. Match patient group expertise and assets to the specific needs and phases of your research and development programs.
It is important for research sponsors and investigators to recognize differences in the skills, experience and capabilities of patient groups. Ideally the selection criteria for patient groups would include:

- Excellent relationships with patients and families;
- Experience working with patients and caregivers;
- Experience working with patient registries, trial networks, trial design, trial awareness and recruitment, and dissemination of results; and
- Broad communication platforms.

Tools 1 to 3, available in the next Section, can be used to analyze patient group skills and strengths. These tools may also facilitate the assignment of tasks according to the patient group's strengths and limitations.

3. Ensure that patient groups are essential partners throughout the research and development process and not token voices.
Experience has shown that the most successful partnerships with patient groups are those in which both entities are full partners at the outset, working toward the same goals from different perspectives. The patient voice, as communicated by patient groups, is key to understanding the day-to-day effects of the condition and acceptable benefit-risk tradeoffs of treatment.

Patient groups can add value across all phases of the cancer clinical research and development continuum. Figure 2, above, lists some of the potential roles for patient groups at each phase. Engagement with patient groups is optimized when there is a discrete division of labour in which each group contributes its unique area of expertise.

4. For consistency, establish guiding principles and clear lines of communication to facilitate a fit-for-purpose process for collaborating with patient groups.
Having standard work practices may assist the sponsor in ensuring that all elements of the collaborative partnership are met on each project and provide a means of measuring its success. Elements of a work practice may include a database of previous collaborations, required documents and clear lines of communication.

Reviewing best practices for engaging with patient groups may help research sponsors to develop their own processes, such as:

- How to approach patient groups;
- Legal requirements for working with patient groups; and
- A template for master services agreements.

Standard work practices may:

- Support the integration of patient group engagement into clinical program strategies;
- Minimize any perceived burden to incorporating patient perspectives as part of this collaboration;
- Ensure consistency across the clinical teams on the approach to and evolution of the work with patient groups;

- Identify parties responsible for relations with patient groups if there are multiple people making contact with them;
- Drive transparent communication between the research sponsor and patient group; and
- Define and implement contracting and communication plans.

5. Measure the impact of patient group engagement.
Though no standard metrics exist to measure patient group integration with industry or academic research sponsors, it is recommended that expectations are mutually established up front on how to measure the effectiveness of the partnership. As such standards are continually evolving, it is important that sponsors and patient groups agree on critical elements of measurement for each arrangement.

A regular assessment of satisfaction related to objectives, expectations and success of strategies is recommended. For example, metrics reported by the Clinical Trials Transformation Initiative (CTTI) assessed reduction in protocol amendments and recruitment times, increased retention rates, shorter cycle times and longer patent life during product marketing. Additional measures were related to the development and validation of endpoints and patient-reported outcomes.[17] In Canada, an initial measure of success could be clinical trial enrollment, as measured in the Canadian Partnership Against Cancer's annual Cancer System Performance Report, as well as retention. [comment 8]

6. Establish ongoing relationships with patient groups and communicate openly with them on a regular basis.
Early involvement and regular communications by research sponsors throughout the development program would allow sponsors to benefit from mutual education and let patient groups know how their feedback has been incorporated into the program.

Such communications may cover: important study events; study modifications or cancellations; redirection of research priorities; enrollment rates; presentations and publications; and study results. It is also important to maintain regular communication with patient groups even when there is no study news.

Part B. Recommendations for patient groups

1. Proactively identify, engage and bring the patients' voices to stakeholders relevant to your clinical research interests.
It is important that patient groups recognize the limits of what any group can accomplish alone. Development of cancer interventions is a team endeavour and partnerships are founded on the trust you have established with your patient community, families and the clinicians who care for them.

Education, awareness and connections among stakeholders can be strengthened by activities such as:

- Involving partners in workshops and meetings to advance the science and collaboration;
- Matchmaking among different partners such as academic investigators and government programs or industry partners and academic investigators;
- Making presentations to industry, government agencies and academic partners;
- Serving on advisory councils, steering committees or external oversight boards of industry and academia;

- Conducting periodic state-of-the-science meetings with Health Canada and, where appropriate, accompanying research sponsors to Health Canada meetings focused on priority areas of drug development; and
- Establishing collaborative relationships with organizations involved in health technology assessment and drug programs to promote the integration of patient groups into the cancer drug review and funding decision making processes.

2. Promote your value as an essential partner by maximizing and articulating your expertise and assets.

Patient groups are better prepared to enter into partnerships when they understand what they can offer research sponsors and have information and metrics that clearly articulate their value proposition. (Tools 1 to 3, in the next Section, provide a template for collecting this information.) They also benefit from understanding the perspectives of potential partners, such as the economics of drug development and clinical research, as well as the associated regulatory and contracting processes.

Patient groups have important clinical trial assets sought by industry and academic partners. Depending on the patient group, these assets may include:

- A group of educated advocates;
- A base of knowledge and understanding of the disease mechanisms and natural history;
- Housing, maintaining and promoting a clinical trials database which would allow patients and healthcare professionals knowledge of available research options in real-time; [comment 6]
- Financial and organizational support;
- Patient preference or benefit-risk assessments; and
- A willingness and ability to assemble key opinion leaders, patients/advocates familiar with the disease; and
- Translational tools to assist in trial design.

Through active, continuous engagement in the development program, patient groups may demonstrate a unique value to their academic and industry partners. Outcomes of engagement may include:

- De-risking early-stage development with funding and public-private partnerships for early clinical research;
- Reducing uncertainty in the regulatory process by working closely with the regulators throughout the entire research and development process; and
- Helping to develop more effective, efficient trials with a greater chance of success through contributing to better questions and study design, efficient recruitment, improved retention, fewer amendments, procedures that are better-suited to the patient, clinical endpoints that are well grounded in the natural history of the disease, and potential benefits that are most important to the patient.

3. Deliver expertise and assets to sponsors throughout the entire research and development process.

Patient groups are positioned to deliver maximum value when they have opportunities to express the patient perspective as early as possible and throughout the research and development process—during the preclinical, clinical trials, regulatory and post-approval phases. Figure 2, above, summarizes potential patient group activities at each phase.

4. Select sponsors who have a product or program with significant promise for your constituents and who are committed to engaging in a meaningful way.

Patient groups are in a stronger position to contribute when they have a "finger on the pulse" of the preclinical landscape. This enables them to proactively identify opportunities and reinforce that they are viewed as valuable partners for sponsors.

Having a formal, prospective review process in place enables patient groups to independently evaluate and prioritize potential partners and/or projects. Potential partners could be identified, as well as the right points of contact and key decision makers within the organization. Advisory boards can be helpful to assist the patient group in laying out a strategy and action plan for meaningful engagement in the clinical trials process.

5. Manage real or perceived conflicts of interest by establishing policies that require full disclosure, transparency and accountability.

It is important for patient groups to recognize and guard against the dangers of being perceived as marketing instruments and/or as offering exclusive services to a particular organization. At the same time, it behooves patient groups to acknowledge and accept that all trial participants must meet standard eligibility requirements and that their involvement with a sponsor will not result in preferential treatment.

Patient groups should be aware of stakeholders' policies regarding conflicts of interest and may wish to consult guidelines such as those published by the Canadian Cancer Action Network, Innovative Medicines Canada and Imagine Canada[38] to determine how best to manage these situations.

Internal and external conflicts of interest can be managed effectively by:

- Having written policies on activities that might be perceived as generating a conflict, such as accepting funds from industry sponsors and purchasing company stock;
- Fully disclosing relationships with industry sponsors in internal deliberations and external transactions; and
- Being transparent and accountable in publications, communications and reporting.

In addition, to help patient groups navigate the complex web of decisions and opportunities, it is recommended that they prospectively develop a "Guiding Principles" document which defines how and with whom they will collaborate. The following topics may be covered:

- Confidentiality
- Working with competitors
- Data sharing
- Expectations for communication
- Working with regulators (e.g., will you advocate for specific treatments/approvals or will you advocate only for general principles?)
- Compensation policy for consulting
- Expectations for expanded or continued access to research treatments
- Ethical treatment of research participants

Tools

Figure 3

Tool 1. Patient group organizational expertise and assets evaluation tool

	Preclinical	Phase I/II/III clinical trials	Health Canada review & approval	Funding review & approval	Post-approval studies / outcomes
Input with respect to interest of research question to patient community					
Providing data on unmet need and burden of current therapies					
Facilitating collaboration with CIHR and other funding agencies					
Characterizing the disease & relevant mechanisms of action					
Helping to define a study's eligibility criteria					
Patient registry support					
Input on meaningful clinical endpoints and/or patient-reported outcomes					
Assistance with respect to the relevance and wording of an informed consent form					
Working with Health Canada on benefit-risk and draft guidance					
Accompanying sponsor to pre-submission meetings with Health Canada to present the patient perspective for the study					
Fundraising and direct funding for research and trial operations support					
Assistance in selecting and recruiting optimum clinical sites					
Clinical infrastructure support					
Helping to educate and motivate the patient community about research; providing information to community about participating in clinical trials					
Providing patient feedback on participant experience					
Serving on Data & Safety Monitoring Board					
Input for any trial adaptations or modifications					
Accompanying sponsor to milestone meetings with Health Canada					
Serving on post-market surveillance initiatives					
Helping to return study results to participants					
Co-presenting scientific findings and results					
Publications/communications of results					
Providing feedback on how the patient community views study results					
Input to health technology assessment bodies on the patient experience					
Working with payers (private and public) with respect to understanding a need for reimbursement					

Figure 4

Tool 2. Assessment of patient group internal aspects: Focus

Assessment of patient group internal aspects	Yes	No	N/A	Notes
Vision/Areas of Focus: Are the patient group's vision, mission, goals, and areas of focus clearly stated and reasonable?				
Do these statements seem to reflect sound judgment regarding the disease space and state of the science?				
Is commitment to these statements demonstrated in the patient group's activities and performance?				
Operations: Are the patient group's operational programs well structured, performing well, and demonstrating measurable impact?				
If the patient group awards grants, are awards made via a credible application and peer review process and do the awards reflect the vision, mission, goals and areas of focus?				
Does the patient group have and make good use of solid scientific/medical professional staff and/or advisors?				
Does the patient group have an effective fundraising and budgeting process adequate to its vision, mission, goals and areas of focus?				
Does the patient group receive good ratings from charity monitors such as Imagine Canada?				
Does the patient group's collaborative model include partnering options for sponsors outside of grant-based options?				
Budget and Fundraising: Do the patient group's budget and fundraising programs seem adequate to its needs or show signs of being able to become so?				
Are the sources of the patient groups fundraising transparently disclosed (donors, industry, government grants, etc.)?				
Has the patient group been able to marshal the resources required to establish important assets for development (e.g., patient registry, clinical network)?				
Does the patient group devote a healthy percentage of its budget to its operational program vs. its overhead (e.g., administrative and fundraising costs)?				
Does the patient group's budget over the last 5 years demonstrate a fundraising capacity that is steady or growing and diverse in sources?				
Communications: Does the patient group have the communications systems needed to facilitate development across the full continuum?				
Does the patient group have sufficient online presence, including social media?				
Does the patient group issue a variety of publications to various audiences?				
Does the patient group use these communications effectively to educate, motivate and engage its patient community, medical, scientific, industry and government partners?				
Does the patient group use these communications effectively across all phases of clinical development in which it is engaged?				

Figure 5

Tool 3. Assessment of patient group external relationships

Assessment of patient group external relationships	Yes	No	N/A	Notes
Relationships with other patient groups: Does the patient group engage collaboratively with other patient groups of interest?				
Does the patient group collaborate with other patient groups in advocating for policy and budget initiatives beneficial for their public and private partners [patients, CIHR, CADTH, INESSS, Health Canada, payers (private and public), academia, industry]?				
Does the patient group collaborate with other patient groups in co-funding research of mutual interest?				
Does the patient group collaborate with other patient groups in organizing or participating in meetings/conferences focused on best practices, lessons learned, and insights gained in areas of mutual interest?				
Relationships with academia: Does the patient group engage collaboratively with academic and other research institutions, centres of excellence, etc.?				
Does the patient group collaborate with such institutions in funding research projects supportive of the patient group mission?				
Does the patient group maintain two-way communication between CIHR and the patient group's other stakeholders (e.g., keeping CIHR staff informed of the status of research and needs of the disease community, keeping the patient group's academic and industry partners aware of CIHR opportunities, submitting letters of support for CIHR applications, participating as co-applicant for CIHR programs when appropriate)? Does the patient group participate in the functions of the Institute Advisory Boards of the CIHR?				
Does the patient group collaborate with such institutions in keeping academic investigators informed of funding opportunities of government agencies and other patient groups?				
Does the patient group collaborate with such institutions in supporting academic investigators' grant applications to these other funding sources?				
Does the patient group collaborate with such institutions in encouraging and facilitating scientific collaborations?				
Relationships with Industry: Does the patient group accept funding from industry to conduct its business?				
Does the patient group follow a written code of conduct governing its relationships with industry partners?				
Does the patient group engage collaboratively with industry partners?				
Does the patient group facilitate discussions between industry and academic "discovery" scientists?				
Does the patient group have and make available resources needed to assist industry partners throughout the development cycle (e.g., patient registry, translational tools, key opinion leaders)?				
Does the patient group help de-risk early-stage development by funding or co-funding discovery, translational and clinical work?				
Does the patient group educate, motivate and inform patients about clinical trials so they can make informed decisions about their potential enrollment, compliance and staying in the study?				

Relationships with patients: Does the patient group's relationship with patients and their families enable the patient group to:				
Communicate effectively with the patient and caregiver population?				
Obtain robust registration in a patient registry, in compliance with applicable privacy regulations?				
Motivate patients to understand the potential importance of participation in a natural history study?				
Assist in post-market surveillance?				
Relationships with drug plan sponsors: Does the patient group engage collaboratively with private payers, governments and government agencies that influence access to cancer therapies?				
Relationship with private payers: Does the patient group engage with private payer organizations?				
Relationships with governments and government agencies: Does the patient group maintain dialogue with public drug program officers and appropriate offices of special interest at the provincial and federal levels (e.g., Chief Health Innovation Officers, translational or clinical staff)? Does the patient group participate in advisory boards to provincial and/or federal drug programs? Does the patient group have patient representatives designated as liaisons with governments and/or government agencies?				
Relationships with HTA review bodies: Does the patient group provide patient input to HTA reviews related to their specific disease area(s) or generally to calls for input (e.g. to general patient input submission templates, etc.)? Does the patient group respond to calls for input on strategic or operational issues (e.g., patient input submission templates)? Does the patient group attend and participate in symposia or forums organized by HTA bodies?				
Relationship with Health Canada: Does the patient group engage collaboratively with the appropriate centres and offices of Health Canada (e.g., Health Products and Food Branch, Therapeutic Products Directorate)? Does the patient group help educate Health Canada personnel regarding the disease, its unmet medical needs, benefit-risk evaluations, etc. (e.g., include Health Canada personnel in the patient group's scientific conferences, brief Health Canada personnel at Health Canada workshops and events)? Does the patient group work with its academic and industry partners in preparing IND (investigational new drug) submissions, participating in pre-IND and other milestone meetings?				
Relationship with elected representatives: Does the patient group encourage its community members to engage their elected representatives in support of legislation beneficial to them? Does the patient group collaborate with other patient groups in organizations aimed at concerted efforts to work with government in support of beneficial budgets and policies?				

Abbreviations:

CIHR = Canadian Institutes for Health Research
CADTH = Canadian Agency for Drugs and Technologies in Health
INESSS = Institut national d'excellence en santé et en services sociaux
pCPA = pan-Canadian Pharmaceutical Alliance
CAPCA = Canadian Association of Provincial Cancer Agencies
HTA = health technology assessment
IND = Investigational New Drug

CONCLUSIONS

Developing and implementing a Canadian Patient Group Pathway to Accessing Cancer Clinical Trials (Pathway), incorporating the concepts of multi-stakeholder collaboration and the inclusion of patient groups as equal partners, is expected to generate significant benefits for all stakeholders. Through a consensus meeting, stakeholders from across the cancer clinical research and development continuum concluded that the Clinical Trials Transformation Initiative (CTTI) model, employed successfully in the United States, could be adapted for use in Canada as the basis for a comprehensive framework for patient group engagement. Canadianization of the CTTI recommendations and tools involved adapting them to the Canadian cancer clinical research and development landscape, identifying the relevant stakeholder organizations and processes, and modifying engagement approaches to suit the Canadian context.

Recommendations are presented for each broad stakeholder group, accompanied by a set of tools for clinical research sponsors to utilize to assess patient groups' readiness and capacity to engage with them.

Further steps in the development of the Pathway will be undertaken. The broader cancer research community will be invited to participate in the process. A Charter, in which clinical trials sponsors commit to involving patient groups in all stages of cancer clinical research, will be developed collaboratively. As part of an operationalization plan, clinical research sponsors will be encouraged to support training of patient groups so that they are able to participate as equal partners. The integration of patient groups into the development of "real-world" evidence will be advanced through a further consensus meeting being organized by Colorectal Cancer Canada on November 6-7, 2018, in Montreal.

ACKNOWLEDGEMENTS

Support for the consensus meeting was generously provided by: BioCanRx: Biotherapeutics for Cancer Treatment, Boehringer Ingelheim, Bristol-Myers Squibb, Canadian Partnership Against Cancer, Coalition Priorité Cancer au Québec, Innovative Medicines Canada, Eli Lilly Canada, Merck Canada, Hoffman-La Roche and Novartis. We thank all the meeting participants and the Scientific Advisory Committee for their active and insightful input into the meeting and for their leadership in promoting the engagement of Canadian patient groups in the cancer clinical trials. Also, we are grateful to the Clinical Trials Transformation Initiative for their inspiration in serving as the basis for the Canadian Pathway.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest and declare the following interests:

Colorectal Cancer Canada has received support from the following organizations: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim Canada Ltd., BMS, Eli Lilly Canada Inc., Hoffmann-La Roche Ltd., Janssen Inc., Merck Frosst Canada & Co., Novartis Pharma Canada Inc., Pfizer Canada, Pharmascience.

G. Batist has contracted with multiple biopharma companies in clinical research programs, and has collaborated with many of these in matching funds for major peer-reviewed grants. These include Hoffman-LaRoche, Merck, Pfizer, BMS, Lilly, Esperas, Chorus, AstraZeneca, Novartis, Amgen.

D. Richards has accepted consulting fees, speaker fees, and honoraria from multiple biopharma companies. These companies include AbbVie, Amgen, Janssen, Lilly, Merck, Novartis, Novo-Nordisk, Pfizer, and Hoffman-LaRoche.

BioCanRx has received support from the following organizations: Turnstone Biologics, Merck, EMD Serono, Roche Pharma, GE, Peprotech, Immudex, Immunovaccine, Pall, Zymeworks, Beckman Coulter, AstraZeneca, Roche Diagnostics, GSK, Affymetrix, BlueLine Bioscience, Caprion, Perkin Elmer, BioLegend, PeproTech and Nanostring.

REFERENCES

1. Canadian Partnership Against Cancer. *The 2017 Cancer System Performance Report*. Toronto, ON: Canadian Partnership Against Cancer; 2017.

2. Hargreaves B. Clinical trials and their patients: The rising costs and how to stem the loss. *Pharmafocus* 2016; November:18-20. [Available at: http://edition.pagesuite-professional.co.uk/html5/reader/production/default.aspx?pubname=&edid=c64556ab-bf8d-4389-82d1-3006925cdb70&pnum=18; cited February 8, 2018]

3. Nuttall A. Considerations for improving patient recruitment into clinical trials. *Clin Leader Newsletter* 2012. [Available at: https://www.clinicalleader.com/doc/newsletterarchive/ac74d6cb-75c0-4e4f-8d9c-a2120062dcd0; cited Nov. 9, 2017]

4. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book* 2016;35:185-98.

5. Swartz LJ, Callahan KA, Butz AM, *et al*. Methods and issues in conducting a community-based environmental randomized trial. *Environ Res* 2004;95:156–165.

6. Shah SG, Robinson I. Benefits of and barriers to involving users in medical device technology development and evaluation. *Int J Technol Assess Health Care* 2007;23:131–137.

7. Oliver S, Clarke-Jones L, Rees R, *et al*. Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach. *Health Technol Assess* 2004; 8:1–148.

8. Brett J, Staniszewska S, Mockford C, *et al*. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Health Expect* 2014;17:637–650.

9. National Institute for Health Research (UK). The James Lind Alliance [Web page]. London, UK: National Health Service; n.d. [Available at: https://www.nihr.ac.uk/research-and-impact/research/the-james-lind-alliance; cited November 9, 2017]

10. Crowe S, Fenton M, Hall M, Cowan K, Chalmers I. Patients', clinicians' and the research communities' priorities for treatment research: there is an important mismatch. *Res Inv and Eng* 2015;1:2.

11. Esmail L, Moore E, Rein A. Evaluating patient and stakeholder engagement in research: moving from theory to practice. *J Comp Eff Res* 2015;4:133–145.

12. Domecq JP, Prutsky G, Elraiyah T, *et al*. Patient engagement in research: a systematic review. *BMC Health Serv Res* 2014;14:89.

13. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). *Guideline on the evaluation of anticancer medicinal products in man. The use of patient-reported outcome (PRO) measures in oncology studies*. Appendix 2. London, UK: European Medicines Agency; 2016.

14. Kim ES, Bruinooge SS, Roberts S, *et al*. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *JCO* 2017; 35:3737-44.

15. Hoos A, Anderson J, Boutin M, *et al.* Partnering with patients in the development and lifecycle of medicines: A call for action. *Ther Innov & Reg Sci* 2015;49:929-939.

16. Clinical Trials Transformation Initiative. *2017 Annual Report*. Durham, NC: Clinical Trials Transformation Initiative; 2017. [Available online at: https://www.ctti-clinicaltrials.org/annual-reports/2017-annual-report; cited July 26, 2018.]

17. Levitan B, Getz K, Eisenstein EL, *et al*. Assessing the financial value of patient engagement. A quantitative approach from CTTI's Patient Groups and Clinical Trials Project. *Ther Innov Regul Sci* 2017; 1-10.

18. Clinical Trials Transformation Initiative. [Web page]. Durham, NC: CTTI; n.d. [Available at: https://www.ctti-clinicaltrials.org; cited November 9, 2017.]

19. U.S. Food & Drug Administration. Enhancing Benefit-Risk Assessment in Regulatory Decision-Making [Web page]. Silver Spring, MD: U.S. Food & Drug Administration; 2017. [Available at: https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm; cited March 8, 2018]

20. U.S. Food & Drug Administration. FDA and European Medicines Agency Patient Engagement Cluster [Web page]. Silver Spring, MD: U.S. Food & Drug Administration; 2017. [Available at: https://www.fda.gov/ForPatients/PatientEngagement/ucm507907.htm; cited March 8, 2018]

21. Health Canada. [Web page]. Scientific Advisory Committee on Oncology Therapies - Summary of Expertise, Experience and Affiliations and Interest. Ottawa, Ontario: August 5, 2010. [Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/scientific-expert-advisory-committees/oncology-therapies/summary-expertise-experience-affiliations-interest.html; cited February 11, 2018.]

22. Samuel N, Verma S. Cross-comparison of cancer drug approvals among international regulatory bodies. *Ann Oncol* 2014;25:v1-v41.

23. Rawson NSB. *Access to new oncology drugs in Canada compared with the United States and Europe*. Vancouver, BC: Fraser Institute; 2012. [Available online at: https://www.fraserinstitute.org/sites/default/files/access-to-new-oncology-drugs-in-canada-rev.pdf; cited March 9, 2018]

24. Barnett JC, Berchick ER. *Current Population Reports, P60-260.Health Insurance Coverage in the United States: 2016.* Washington, DC: U.S. Government Printing Office; 2017. [Available online at: https://www.census.gov/content/dam/Census/library/publications/2017/demo/p60-260.pdf; cited March 12, 2018]

25. Canadian Life and Health Insurance Association. *Canadian Life and Health Insurance Facts, 2016 Edition*. Toronto, ON: Canadian Life and Health Insurance Association; 2016. [Available online at: https://www.clhia.ca/domino/html/clhia/CLHIA_LP4W_LND_Webstation.nsf/resources/Factbook_2/$file/2016+CLHIA+Factbook+ENG.pdf; cited March 8, 2018]

26. National Council on Aging Center for Benefits Access. Medicare Part D Drug Plans: What They Must, May, and Cannot Cover [Web page]. Arlington, VA: National Council on Aging; 2017. [Available at: https://www.ncoa.org/wp-content/uploads/part-d-drug-coverage-rules.pdf; cited March 9, 2018]

27. Rawson N. *Has pCODR improved access to oncology drugs? Timeliness and provincial acceptance of pan-Canadian Oncology Drug Review recommendations*. Vancouver, BC: Fraser Institute; 2014. [Available online at: https://www.fraserinstitute.org/sites/default/files/has-pCODR-improved-access-to-oncology-drugs-rev.pdf; cited March 9, 2018]

28. QuintilesIMS Institute. *Global Oncology Trends 2017*. Parsippany, NJ: QuintilesIMS Institute; 2017. [Available online at: https://morningconsult.com/wp-content/uploads/2017/06/QuintilesIMS-Institute-Oncology-Report.pdf; cited March 9, 2018]

29. IMS Institute for Healthcare Informatics. *Global Oncology Trend Report. A Review of 2015 and Outlook to 2020*. Parsippany, NJ: IMS Institute for Healthcare Informatics; 2016. [Available online at: https://morningconsult.com/wp-content/uploads/2016/06/IMS-Institute-Global-Oncology-Report-05.31.16.pdf; cited March 8, 2018]

30. Millson B, Thiele S, Zhang Y, Dobson-Belaire W, Skinner B. *Access to New Medicines in Public Drug Plans: Canada and Comparable Countries. 2016 Annual Report.* Ottawa, ON: Innovative Medicines Canada; 2016. [Available online at: http://innovativemedicines.ca/wp-content/uploads/2016/05/20160524_Access_to_Medicines_Report_EN_Web.pdf; cited March 9, 2018]

31. Sullivan SD, Watkins J, Sweet B, Ramsey SD. Health technology assessment in health-care decisions in the United States. *Val Health* 2009; 12(S2):S39-S44.

32. CADTH/pCODR. *pCODR Expert Review Committee Deliberative Framework*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2016. [Available online at: https://www.cadth.ca/sites/default/files/pcodr/The%20pCODR%20Expert%20Review%20Committee%20%28pERC%29/pcodr_perc_deliberative_frame.pdf; cited March 13, 2018]

33. INESSS. Médicaments d'exception [Web page]. Quebec, QC: Gouvernement du Québec; 2018. [Available at: https://www.inesss.qc.ca/index.php?id=41; cited March 13, 2018]

34. Srikanthan A, Mai H, Penner N, *et al*. Impact of the pan-Canadian Oncology Drug Review on provincial concordance with respect to cancer drug funding decisions and time to funding. *Curr Oncol* 2017;24:295-301.

35. Mycka J, Dellamano R, Lobb W, *et al*. Regulatory approval to patient access: an evaluation of EU5 and US national timing differences - An update (2009–2015) [abstract PHP139]. *Val Health* 2016;19:A281.

36. Innovative Medicines Canada. *Code of Ethical Practices*. Ottawa, ON: Innovative Medicines Canada; 2016. [Available online at: http://innovativemedicines.ca/wp-content/uploads/2015/06/IMC_Code_EN.pdf; cited March 13, 2018]

37. Canadian Cancer Action Network. *CCAN Code of Conduct Governing Corporate Funding*. Toronto, ON: Canadian Cancer Action Network; 2012. [Available online at: http://www.ccanceraction.ca/wp-content/uploads/2014/12/CCAN-Code-of-Conduct_2012_EN.pdf; cited March 13, 2018]

38. Imagine Canada. Standards Program. [Web page] [Ottawa, ON: Imagine Canada; n.d. [Available at: http://www.imaginecanada.ca/our-programs/standards-program; cited March 13, 2018]