DESCRIBING SOURCES OF UNCERTAINTY IN CANCER DRUG FORMULARY PRIORITY SETTING ACROSS CANADIAN PROVINCES

by

Kristina Jenei

BSN, Vancouver Community College, 2016

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

December 2020

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

DESCRIBING SOURCES OF UNCERTAINTY IN CANCER DRUG FORMULARY PRIORITY SETTING ACROSS CANADIAN PROVINCES

submitted by Kristina Jenei in partial fulfillment of the requirements for

the degree of Master of Science

in Population and Public Health

Examining Committee:

Craig Mitton PhD, Professor, Department of Medicine, UBC
Co-Supervisor

Michael Burgess PhD, Professor, Department of Medicine, UBC
Co-Supervisor

Stuart Peacock PhD, Professor, Department of Health Sciences, SFU
Supervisory Committee member

Arminee Kazanjian PhD, Professor, Department of Medicine, UBC
Additional Examiner

Abstract

Introduction: Over the years, there have been significant advances in oncology. However, the rate that therapeutics come to market have increased while the strength of evidence has decreased - leaving decision makers with more uncertainty than ever before. Currently, there is limited understanding about how this uncertainty is understood and managed in provincial funding decisions for cancer therapeutics.

Methods: A qualitative, two-phase study approach was employed. Phase I comprised of semi-structured key-informant interviews (n=6) with senior officials from four Canadian provinces (BC, AB, QC and ON). In part II, a document review of the uncertainties found in clinical evidence in the pan-Canadian Oncology Drug Review (pCODR) assessments was conducted. Interviews in part I were audio-recorded and transcribed verbatim.

Results: Participants included stakeholders from British Columbia (BC) (n=1), Alberta (AB) (n=1), Quebec (QC) (n=3) and Ontario (ON) (n=1) whom held a variety of roles in ministries of health, cancer agencies and national health technology assessment (HTA) organizations that evaluate evidence and make funding recommendations. Participants reported considerable uncertainty related to a lack of solid clinical evidence (early-phase clinical trials: generalizability, immature data and the use of unvalidated surrogate outcomes). Clinical uncertainty was exacerbated with high costs and accelerated approvals. Other sources of uncertainty were related to external influences. Proposed strategies to deal with the uncertainty included risk-sharing agreements, collection of real-world evidence (RWE) and ongoing collaboration between federal groups and provinces. The document review added to the reported uncertainties by classifying them into five main categories: trial validity, population, comparators, outcomes and intervention.

Conclusion: This study highlights that decision makers have to deal with more uncertainty in funding decisions for cancer drugs than ever before and that this uncertainty generally stems from clinical trials. Since only one decision maker could identify a deliberative priority setting process and cancer drugs are rarely reassessed, this situation might leave ineffective drugs in the health system. These drugs can incur opportunity costs. There is a critical need for transparent priority

setting processes and mechanisms to reevaluate drugs to ensure benefit given the high level of uncertainty of novel therapeutics.

Lay Summary

Decision making for funding cancer drugs – also known as priority setting - has become complex in recent years. Further, the introduction of targeted therapies come at high costs to the public system while challenging traditional methods to evaluate benefit. Current challenges create many uncertainties for provincial decision makers tasked with deciding which therapeutics to fund. In this study, qualitative methods were employed to understand the sources of uncertainty with provincial decision makers across Canada. Additionally, a document review of the uncertainties found in pCODR assessments was conducted to add more depth. The overall results from the interviews indicated that methodological limitations from clinical trials create the main sources of uncertainty. Further there were no consistent mechanisms for priority setting in cancer care across provinces. The document review added to this finding by classifying clinical uncertainty into five main categories; trial validity, population, comparators, outcomes and intervention. This study adds new knowledge about current challenges for decision makers and raises important concerns about fair and equitable priority setting in Canadian cancer care.

Preface

The topic of exploring areas of uncertainty in drug formulary funding decisions arose after I participated in public deliberations about funding costly, experimental gene therapies in cancer care. The deliberations highlighted numerous ethical challenges decision makers face when equitably allocating resources across a publicly funded system. This study was designed, implemented and analyzed by me under the supervision and guidance of co-supervisors Drs. Michael Burgess and Craig Mitton. Dr. Stuart Peacock, committee member, provided feedback to improve the clarity of the content and practical relevance to current practices and concerns in oncology. Originally, the second phase of this study was a survey instrument to explore uncertainties with a larger number of decision makers across Canada. However, the COVID-19 pandemic introduced challenges that decreased the feasibility of this design. Therefore, with support from the supervisory committee, the second phase was changed to a document review. This change enabled me to maintain timelines while offering new knowledge about current uncertainties in clinical evidence in health-technology assessments (HTA).

A version of Chapter 1 (sub section 1.5) and Chapter 5 stem from material I wrote in a manuscript. Raymakers, AJN., Jenei KM., Regier DA., Burgess, M., Peacock SJ., Early phase clinical trials and reimbursement submissions to the pan-Canadian Oncology Drug Review. I was responsible for data collection and drafting the introduction and parts of the discussion in the manuscript (where a version of this content can be found). Only content that I wrote was paraphrased and included in this thesis.

Ethics approval for this study was secured from the UBC Behavioural Research Ethics Board – Certificate # H19-03646.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AB	Alberta
BC	British Columbia
CADTH	Canadian Agency for Drugs and Technology in Health
CDIAC	Canadian Drug Implementation Advisory Committee
FDA	Food and drug administration (US)
HTA	Health Technology Assessment
INESSS	Institute national d'excellence en sante et en services (Quebec HTA)
MCDA	Multi-Criteria Decision Analysis
NICE	National Institute for Health and Care Excellence
ON	Ontario
OBR	Outcome-based reimbursement
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
QC	Quebec
RWE	Real-world evidence

Acknowledgements

"I view writing as kind of like running the 800 – torture in the middle, but if you PR [personal record] or give a supreme effort, pretty soon you look back and say, 'Well, that wasn't so bad.' It was, but you should still do it again." – David Epstein in Range

All things worthwhile are hard. This process was no exception. However, there were many remarkable things that transpired during my graduate studies. Mainly, as a nurse, I learned a great deal about the system I worked in. Also, I believe that being surrounded by the sheer excellence of research, mentorship and opportunities at the School of Population and Public Health has propelled me further in my academic and professional career than I believed was possible.

It's true what they say – that big things are seldom accomplished alone. There are too many people for me to thank but a few stand out. Thank you, first, to my committee members Drs. Craig Mitton, Michael Burgess and Stuart Peacock. You all provided me with hands-on opportunities, a team to learn from and endless references (thank you!) Your responsiveness, kindness and humor made this process so much more enjoyable. Your support to pivot this research during COVID-19 was instrumental in my success.

Second, thank you to my friends – the ones that meet me at ridiculous hours in the morning to run endless miles on the Vancouver seawall – Alex, Mary and Sabrina. To my partner-in-academia Monica, who was so generous with her time, giving me feedback on applications and presentations, along with being a good friend when times were tough. It has been fun planning our applications (and lives!) together. Thank you to Neelam and Danielle, who constantly remind me of the frontline and patient implications for system-level policy decisions. And lastly, thank you to my family. Who might not always know exactly what I am doing, or how this whole grad school thing works, but were nevertheless my biggest fans. I owe a dept of gratitude to my husband Nic, who, over the past two years, has spent an unsettling number of hours talking through health policy issues with me and could probably write a thesis of his own by now.

I am grateful to the Canadian Institute of Health Research for the Frederick Banting and Charles Best Masters Scholarship that I received during my studies. Also, for financial support from the Faculty of Medicine and the Registered Nurses Foundation. As a first-generation

Canadian and college student, these awards are more than financial support, they are boosts in confidence that allow me to dream bigger and reach further than I ever imagined before.

Dedication

For Nic,

For Jessica and Matt,

For my parents, with love

Chapter 1: Introduction

1.1 Background

Decision making for funding cancer drugs – also known as priority setting - has become increasingly complex in recent years. This is partly due to an increase in cancer incidence, rising drug costs and an increased proportion of individuals living into survivorship. In Canada, expenditure in cancer care more than doubled from $2.9 billion to $7.5 billion between 2005 and 2012 (Bach, 2009; de Oliveira et al., 2018; Kantarjian, 2014). Further, the introduction of precision medicine and novel therapies have pushed cost-effectiveness thresholds well beyond traditional boundaries and there is a concern that these new therapeutics might not be as beneficial as described by the manufacturers. These novel therapies often come to market with limited long-term evidence through accelerated pathways. The concern is without a solid evidence base, patients can be exposed to unforeseen risks or receive treatments that are not as effective as they seem. The trend in cancer expenditure, limited evidence and patient risks create uncertainties for decision makers tasked with funding services and therapies and threatens the sustainability of publicly funded systems around the world (Cressman et al., 2015).

The following chapter explores prominent areas of uncertainty in cancer care. The chapter begins with uncertainty about clinical benefit and how this might challenge traditional economic evaluation methods. Further, external factors such as influence from patients, clinicians and politics. An overview of the federal approval and reimbursement process is discussed. Since reimbursement decisions are ultimately made at the provincial level, the chapter concludes with a brief discussion of what is known about the priority setting in cancer care.

1.1.1 Uncertainty about the magnitude of benefit of new cancer therapeutics

The rise in incidence, survivorship, drug costs and subsequent health system expenditure are coupled with the concern that many novel therapies are associated with considerable uncertainty. Clinical trials often form the evidence base that informs drug approvals and reimbursement decisions. Frequently, especially in oncology, these studies introduce a significant amount of uncertainty into the health care system due to methodological limitations. One example of a limitation includes the increasing use of surrogate endpoints. Surrogate endpoints are designed

to be substitutes for more meaningful patient-centered outcomes such as overall survival and quality of life. They are often used because they tend to be easier and faster to measure. However, the evidence supporting their use is limited. A systematic review found that more than half of the surrogate measures (52%) had low correlation to many different tumor types (Prasad, Kim, Burotto, & Vandross, 2015). This means that their use ought to be highly specific. However, this is counter to the current trend where they might be invoked too often (Kemp & Prasad, 2017). For example, a recent study in Canada demonstrated that almost all trials (93%) submitted to the Canadian Agency for Drugs and Technology in Health (CADTH) reported a surrogate measure (progression-free survival (PFS)) as a primary or secondary outcome (Pinto, Naci, Neez, & Mossialos, 2020). Since the strength of correlation between PFS and overall survival highly variable upon the setting it is used, it is likely that its widespread use in these submissions is not validated. Other current methodological limitations in clinical trials include the absence of blinding and randomization, the use of crossover designs, recruitment based on positive performance status and gender inequities (Booth & Tannock, 2008; Lexchin, 2018).

1.1.2 **Uncertainty in economic evaluations**

The uncertainty resulting from methodological limitations in clinical studies flow into economic evaluations and introduce additional challenges in priority setting decisions. Economic evaluations also form part of the evidence base for drug reimbursement decisions and offer a variety of methods to determine value by comparing health benefits with associated costs. While economic evaluations can incorporate uncertainty into models with various methodological techniques, the rapidly increasing numbers of experimental and costly drugs in oncology in particular, introduce new complexities that challenge traditional methods (Love-Koh, Peel, Juan, et al., 2018). Due to changes in study design, use of surrogate endpoints, and limited long-term evidence, economic evaluations must be made on a number of assumptions related to long-term effectiveness, adoption feasibilities and quality of life. Further, health technology assessments (HTA), such as the approach used by pCODR, rely partly on economic evaluations submitted by manufacturers. These evaluations can have a high degree of uncertainty due to selective reporting or lack of data pertaining to patient-centered outcomes such as health-related quality of life (Raymakers, Regier, & Peacock, 2019).

1.1.3 **Uncertainty from external factors**

The uncertainty of the magnitude of benefit of new therapeutics that filters into economic evaluations can be exacerbated by 'external factors' such as political priorities and pressure from media, industry, patients and clinicians. In policymaking, there is often an appeal to make decisions solely on quantifiable clinical and economic evidence (Stone, 1997). However, in practice, this might be unrealistic. External factors have been shown to influence priority setting processes. A Canadian study demonstrated that media coverage had significant effects on generating positive and faster funding decisions when compared to other drugs with similar benefit that received less media coverage (Booth et al., 2007).

Further, the concern about confounded benefit is compounded by widespread concern about the financial conflicts between clinicians (and, at times, patient representatives) and pharmaceutical companies. In Canada, 66.3% of all submissions to pCODR reported some kind of financial conflict (Lexchin, 2019). Half of these were directly with the drug under review. Further, a study from the United States demonstrated that financial conflicts of interest might also extend to patient representatives and advocacy groups (Abola & Prasad, 2016). These challenges, among others, translate into a growing skepticism for the benefit of new cancer drugs (Ahn, Herrera-Perez, & Prasad, 2019; Lexchin, 2019)

1.2 **Overview of the approval and reimbursement pathway for cancer drugs in Canada**

For a drug to come to market, it must be approved by Health Canada, evaluated by the pCODR and funded for reimbursement at the provincial level. While Health Canada, CADTH and Institute National d'Excellence en Sante et en Services (INESSS) review similar evidence, their goals vary slightly.

Health Canada focuses primarily on safety and efficacy whereas CADTH and INESSS evaluate therapeutics for value based on specified criteria. An overview of the process is represented below (see Figure 1).

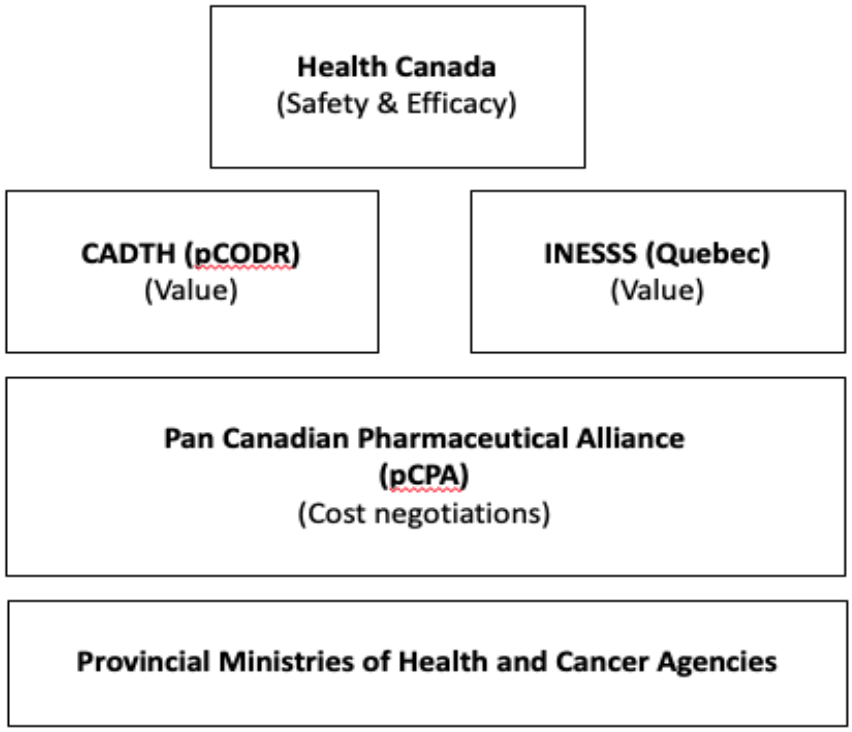

Figure 1. An Overview of the Canadian Approval and Reimbursement Process (adapted from CAPCA, 2020)

1.2.1 Health Canada

The Health Products and Food Branch (HPFB) at Health Canada undergoes a drug review process that focuses on safety, efficacy and quality which relies on data from clinical studies submitted by the pharmaceutical manufacturer (Health Canada, 2020b). A drug can be approved either on an accelerated or standard pathway, with or without conditions. Accelerated approval is reserved for promising new drugs or products developed to treat severe conditions. When a drug is approved, it is issued a Notice of Compliance (NOC) and the pharmaceutical company can begin marketing the product. A conditional approval is specified when data are immature, and signals post-market studies must be conducted to confirm clinical benefit. However, this requirement is not legally binding and has been found to not affect market use (Andersen et al., 2019). Further,

previous research into FDA practices suggests that accelerated pathways designed for rare or orphan diseases might be used too often for cancer therapies (Vokinger & Kesselheim, 2019). While accelerated pathways enable access to new therapeutics that might be beneficial, they add uncertainty about the effectiveness of the treatment. Since clinical benefit of new therapeutics is rarely reassessed post-approval, this means ineffective drugs can remain in the clinical space for extended periods of time or indefinitely, incurring opportunity costs such as not funding other more effective treatments.

1.2.2 **CADTH**

After receiving Health Canada approval, cancer drugs are evaluated by CADTH, specifically the pCODR program. pCODR assesses the value of a new therapeutics through a deliberative framework which includes clinical and economic evidence, patient input and adoption feasibility. The submissions are evaluated by pCODR and then reviewed by the pCODR Expert Review Committee (pERC). Once a submission is reviewed, pERC provides provincial and territorial decision makers with recommendations regarding whether a drug should be reimbursed. pERC membership includes professionals from economics, medicine, pharmacy and ethics has up to 17 voting members including three patient representatives.[1] Once a therapeutic has received a reimbursement recommendation from pERC, the pricing is negotiated by the pan-Canadian Pharmaceutical Alliance (pCPA) – a joint provincial pricing collaborative. Each province or territory is then responsible for the ultimate funding decision.

CADTH has recently expanded to include the Canadian Drug Implementation Committee (CDIAC). Originally, CDIAC was housed under the Canadian Association for Provincial Cancer Agencies (CAPCA). CDIAC allowed stakeholders from each province to address common challenges in drug reimbursement process to ensure sustainability of cancer care in Canada with a focus on implementation issues such as how drugs can fit into existing treatment regimens. (Canadian Association for Provincial Cancer Agencies, 2020). This guidance occurred at the end of the pCODR submission evaluation process. However, the recent expansion of the CADTH

[1] A full list of the membership can be found on the pERC website: https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/pcodr-expert-review-committee-perc

submission process has shifted the role of CDIAC much earlier, beginning with pre-submission. Given the current challenges for integrating highly expensive and burdensome drugs into the health system, this expansion to include CDIAC to CADTH is seen as a positive shift.

1.2.3 **Provincial priority setting processes for formulary decisions with cancer drugs**

Health care financing and delivery is primarily the responsibility of provincial governments. This means that provinces independently decide which drugs are eligible for public coverage. This, along with different public coverage structures, allows for considerable variability across provinces. Dependent on the jurisdiction, one drug might be covered under a public plan, whereas not in in another. For example, oral cancer drugs receive universal coverage in Saskatchewan. This differs from Newfoundland where patients must qualify for a provincial assistance to access the same drugs. This variation can lead to significant financial implications for patients and raise ethical concerns about differential access within the same country (Chafe et al., 2011).

The decision making process for which cancer therapeutics receive public coverage also varies considerably across provinces (Srikanthan, Penner, Chan, Sabharwal, & Grill, 2018). Dependent on the structure of the provincial health system, cancer agencies or Ministries of Health are responsible for reimbursement decisions. For cancer care, provinces generally rely on the assessment and recommendations from pCODR. However, some provinces have also established their own review boards such as the Priorities Evaluation Committee in BC and the Ontario Steering Committee on Cancer Drugs in ON (Peacock, Regier, Raymakers, & Chan, 2019). However, it is also known that resource allocation occurs differently across provinces. For example, some provinces closely follow pCODR recommendations while others use deliberative frameworks for decision making such as multi-criteria decision analysis (MCDA). Since each province is responsible for its own decision, coverage for the same drug can differ province to province and has led to some concern about “fragmentation" of the cancer system across Canada (Srikanthan et al., 2018).

The growth in expenditure for cancer care and methodological limitations from clinical trials, coupled with increased utilization of accelerated approval pathways means that decision makers may be forced to make reimbursement decisions on the basis of immature evidence. This

situation introduces uncertainty into the health care system and has significant implications for how to distribute resources equitably across a population (Andersen et al., 2019). This, coupled with inefficient and non-transparent decisions, means that resources might be allocated inefficiently. There is little knowledge as to how provincial decision makers reconcile and manage these challenges uncertainties in cancer drug reimbursement decisions. As oncology enters into an era of precision medicine - where evidence becomes more complex – it is important to understand current challenges of decision makers in cancer care.

In the next chapter, the study objectives are presented along with the research questions and overall aim.

Chapter 2: Study Objectives and Research Questions

2.1 Research Aim

The overarching aim of this study is to describe common sources of uncertainty in oncology and how decision makers understand and manage this uncertainty in the context of priority setting decisions in Canadian provinces. The knowledge from this study will contribute to a better understanding of current challenges in decision making and priority setting in cancer care and suggest potential solutions.

2.2 Research Questions

1. What are the sources of uncertainty when funding cancer drugs in Canada?
2. How, if at all, is this uncertainty managed in priority setting processes?
3. From the perspective of the policy maker, what is required for minimizing uncertainty when funding cancer drugs?

2.3 Study Objectives

- Document the sources of uncertainty related to funding cancer drugs through interviews with decision makers and a pCODR document review
- Document current strategies for managing this uncertainty employed by decision makers
- Describe elements (from the perspective of the decision-maker) that might decrease uncertainty and contribute to equitable priority setting for cancer drugs.

2.4 Summary

Currently, there is little known about the main sources of uncertainty decision makers face in oncology and how these challenges are managed. Despite numerous sources identified through the literature, this study adds new knowledge as it focuses on the perspective of the decision maker. As oncology enters the era of precision medicine, where evidence becomes more complex, it is important to describe the current landscape to ensure future policies are pragmatic and transition into practice.

To do this, this study is divided into two phases; phase I and phase II. In phase I, senior decision makers in oncology across four Canadian provinces were interviewed. To supplement these interviews, a document review was conducted of pCODR submissions to categorize current uncertainties in clinical evidence. The following chapter provides details about the methods for each phase of this study.

Chapter 3: Methods

3.1 Research Design

To describe existing sources of uncertainty related to decision making for funding cancer drugs and propose specific elements for future priority setting practices, a two-phase qualitative design was employed that combined key informant interviews with a document review of submissions to pCODR. The document review served to triangulate qualitative data obtained during the interviews and add an additional perspective and comparison between federal and provincial bodies. The following section describes the overall methodological approach, along with the data collection and analysis for each phase of the study

3.1.1 Methodological approach

The research follows a qualitative descriptive methodological approach. Developed by Sandelowski (2000), qualitative description is an approach to study design, data collection and analysis and has been used successfully in similar studies (Driedger, Cooper, Annable, & Brouwers, 2018). Qualitative descriptive studies are the least "theoretical" of all qualitative designs and are amenable to the "who, what, and where" research questions about policy processes. This method is distinct form other qualitative approaches such as grounded theory or phenomenology, as it does not seek to describe results through conceptual or philosophical frameworks but rather as an interpretation of the "facts" using common language (Sandelowski, 2000). As Sandelowski (2000) describes; "there is nothing trivial or easy about getting the facts, and the meanings participants give to those facts, right and then conveying them in a coherent and useful manner" (p. 336).

3.1.2 Positionality

Despite the low-inference interpretation of qualitative description, every researcher still must make choices about what to describe from their observations (Sandelowski, 2000). The themes researchers identify are always "filtered through (human) perceptions" (Wolcott, 1994, p. 13, cited in Sandelowski, 2000, p. 336). For these reasons, it is important to describe the ways in which my training as a Registered Nurse and graduate experiences (facilitator of public

deliberations and Methods Lead at CADTH have influenced the study design. I reflected on two conflicting perspectives; one at the policy level and another at the bedside. As a clinician, I have witnessed emotional and physical pain from undergoing cancer treatments and appreciate the desire for hope offered by experimental drugs. However, at the policy level, I also understand the ethical and fiscal challenges for equitably distributing scare resources across the population. Throughout this study, I reflected on the ways these experiences might influence the study design and introduce biases. One concern was interpreting the data in ways that support a preconceived hypothesis (confirmation bias). To avoid this, I tried to remain objective and considered data in its entirety while questioning my conclusions throughout the interview, analysis and writing process.

3.2 **Phase I: Key informant interviews**

To understand the various sources of uncertainty relevant to decision makers in oncology, a group of key-informants from four different provinces (BC, AB, ON, QC were interviewed over the telephone. A semi-structured interview guide (see Appendix A) was developed to assess priority setting processes, the nature and weight of various sources of evidence (clinical, economic, public or patient input), and the role of federal bodies such as pCODR and the pan-Canadian Pharmaceutical Alliance. Key-informant interviews were conducted until multiple participants referred to a similar phenomenon within a given scenario (data saturation).

3.2.1 **Sample**

Key-informants from four different provinces (BC, AB, ON, QC) were purposively selected through the supervisory committee and recruited via an email-invitation outlining the nature of the project. These provinces were chosen as they represent a variation in cancer care delivery across Canada. The diversity of provincial health systems is supported by qualitative descriptive methodology which encourages maximal heterogeneity (Sandelowski, 2000). All respondents shared characteristics of being either a ‘decision-maker’ or someone “involved in decisions for funding cancer drugs” within their jurisdiction.

3.2.2 **Analysis**

Qualitative content analysis was chosen given the considerable amount of previous knowledge about elements for high performance priority setting and decision making (for example,

disinvestment, the use of public engagement and decision frameworks) (Costa et al., 2019; Smith et al., 2016). Further, this method is the strategy of choice for descriptive studies (Sandelowski, 2000). The analysis began with deductive codes from the literature. These categories were also used to structure the interview to ensure that the participants would address each topic to some degree. Inductive themes were identified upon subsequent analysis of the interviews. Inductive and deductive codes were compiled into broad themes.

Data analysis occurred simultaneously with the interview process. Since data collection and analysis are not separate entities but reflexive, interdependent and interconnected, ongoing analysis enabled themes to be discussed and built on throughout the interview process. The emergent themes were amended into the interview guide as additional probes to allow participants to address each topic until convergence occurred. All interviews were audio-recorded with permission and transcribed verbatim afterward. Transcripts were analyzed using NVivo qualitative software. 12.6.0.

3.2.3 **Ethical considerations**

Ethics approval for this study was secured from the UBC Behavioral Research Ethics Board:

- Certificate #H19-03646

3.3 **Part II: Summary of uncertainties in submissions to the pan-Canadian Oncology Review**

The objective of the second part of the study was to summarize common sources of uncertainty in clinical evidence outlined in pCODR documents. This part of the study aided to triangulate the results from the key-informant interviews and add depth by providing an overview of current uncertainties in clinical evidence. Similar studies have been done in Europe and the United States but not Canada (Vreman et al., 2020).

3.3.1 **Sample of cancer drugs reviewed**

Submissions to the pCODR between January 1st, 2015 to December 31st, 2019 were reviewed. This time frame was selected as it represents submissions from the past five years. The search was restricted to completed evaluations for solid tumors that received a final funding

recommendation (i.e. incomplete, withdrawn or submissions pending decision were not included). Drugs that were reviewed for multiple tumor types were included as distinct entries for the analysis. One report per tumor type was included in this analysis. For example, if one drug was submitted twice for two different tumor types, the most recent report was included. The reason for this was to ensure a manageable sample for qualitative analysis while ensuring each drug was at least included once. This type of inclusion and exclusion criteria has been applied in prior studies that have analyzed pCODR submission documents (Raymakers et al., 2019). However, it is acknowledged that this choice might add an additional limitation to the study in the form of selection bias. This is further discussion in section 5.1 Limitations.

3.3.2 **Analysis**

The documents included in this part of the study were the recommendation from pERC and the Clinical Guidance Report. These documents were chosen as they provide overviews of the clinical evidence at the time of a reimbursement decision. First, the pERC document was analyzed and if any questions remained, the Clinical Guidance Report was included. For example, the pERC[2] document might not discuss aspects of a clinical trial as they need to summarize the entirety of the evidence (clinical and economic evidence, patient and clinician input). Therefore, in this case, trial characteristics were included from the Clinical Guidance Report.

In the context of this analysis, uncertainty means "an unresolved issue, limitation or methodological deficiency"(Vreman et al., 2020). Due to prior knowledge from the literature review and key informant interviews, a table was constructed a priori with specific variables (deductive coding). Some examples of initial codes were categories such as "drug costs" and "study design". As the analysis continued, further codes and categories were added (inductive coding). Under "drug costs" I added "implementation burden", "cost-effectiveness". Under "study design" I added categories such as "surrogate endpoints", "sample size" and "randomized controlled trial". Following qualitative descriptive methodology, codes were reviewed and

[2] pERC membership includes a variety of professionals from medicine, pharmacy, pharmacology, or health economics, along with a patient representative. https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/pcodr-expert-review-committee-perc

compiled in broad categories (Sandelowski, 2000). NVivo qualitative software 12.6.0 was used to organize the coding process during analysis.

Further, quantitative content analysis was used to add the frequency at which the categories occurred. This portion of the analysis followed the same approach as before. The first pERC document was analysed first and the Clinical Guidance Report second. Categories were established prior to the analysis. For example, categories included “trial validity”, “population”, “comparators”, and “outcomes”. Each review comment that indicated a form of uncertainty was counted once. For example, if there were multiple indications of bias mentioned in the submission document, one point would be counted in the “trial validity” category.

3.3.3 **Ethical considerations**

Submission data are publicly available online, therefore no institutional ethics approval was required for this part of the study.

Chapter 4: Results

4.1 Phase I: Key informant interviews

4.1.1 Sample

Overall, 10 individuals were contacted via email between February and March 2020. As outlined in Figure 3., a total of 6 individuals were interviewed for this study. Among the six participants, four provinces across Canada were represented (BC (1), AB (1), QC (3) and ON (1)).

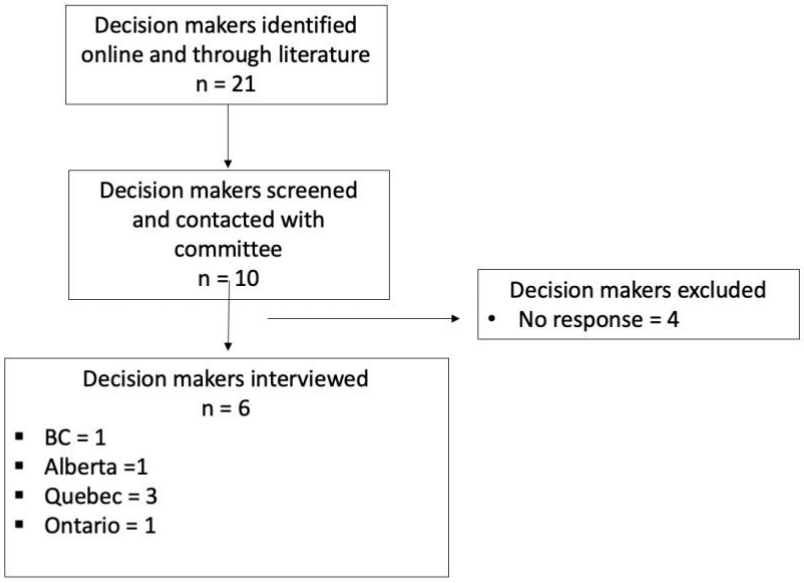

Figure 2 Participants included in the study

4.1.2 Participant Characteristics

Participants were from provincial cancer agencies (n=2), ministries of health (n=1) and national or provincial HTA organizations (n=3). Their roles included senior management, directors of oncology programs, methodologies and members of drug review or advisory committees. Due to the cross-collaboration of agencies across Canada, participants held multiple roles in various provincial and federal organizations. For example, one participant was a clinician and held senior roles in provincial and federal HTA agencies.

Participants	N=6	100%
Role		
Executive Director	3	67.0
Clinician	2	16.5
Scientist (methods)	1	16.5
Organization		
Ministry of Health	1	16.5
Cancer Agency	2	33.0
Federal HTA	1	16.5
Provincial HTA	2	33.0
Provinces		
BC	1	16.5
AB	1	16.5
Quebec	3	50.0
Ontario	1	16.5

Table 1 Participant characteristics

4.1.3 Processes for priority setting

Participants noted systemic challenges, such as a lack of formal priority setting mechanisms, that exacerbates uncertainty in provincial funding decisions. Only one decision maker confirmed that their province undergoes a deliberative priority setting framework (MCDA). Many decision makers said that they could identify the pieces of evidence in the decision (e.g. pCODR recommendation and the negotiated price) but did not know how each one is weighed in the final decision. Further, participants noted the "one-off" nature of funding decisions and the lack of health technology management.

> *And it's a little bit artificial, we make decisions based on one at a time if we fund a drug because we can fund it, not necessarily because that's the best drug program to fund at any particular time. Has it gone through this process? Has it been recommended? Do we have an acceptable negotiated price? Do we have the letter of intent, all of the kind of pieces that we need in order to actually list it? And that determines when we list a drug, not necessarily any ability to prioritize according to the value that it brings. So, I think that's one of the challenges with not only Canadian, but any kind of health technology*

review, decision making process, particularly in cancer, is nobody really seems willing to or able to prioritize or make trade-offs. – Participant 1 (Senior Executive)

"If you are spending an ordinate amount of money and find if you look at your patient outcomes, you are not getting what you thought you were getting, that opportunity cost lost patients who would get a benefit on another drug is kind of unsettling. So that's what I think is kind of flying around right now, trying to figure out that uncertainty."- Participant 2 (Senior Executive)

4.1.4 **Uncertainty**

Participants noted that uncertainty always exists – it is impossible to know everything at the time a decision occurs.

"The thing about uncertainty - there is uncertainty because nobody knows. And once you've explored whether there is any additional information that can help you decide; you may still be left with a situation where there is nothing to inform you to be able to make that decision. And so, that's quite a common scenario where you still must make decisions in the face of just an absence of knowledge."- Participant 1

4.1.5 **Sources of uncertainty**

The main sources of uncertainty fell into four main categories; clinical evidence, costs, external influences and adoption feasibilities.

4.1.5.1 **Clinical evidence**

The most common source of uncertainty identified was uncertainty about the clinical evidence. Participants discussed these challenges in the context of clinical trials which has historically been used as the foundation for the risk benefit threshold. Challenges included the lack of evidence to establish long term effectiveness and immature data that make it challenging for decision makers to determine the value of a new therapeutic. Specific concerns about immature data ranged from the selective recruitment of trial participants, novel trial designs (e.g. basket

trials), submissions based on early phase trials and the increasing use of surrogate endpoints (for example, progression-free disease). Participants noted this as a "culture" of low-level evidence that seems to exist in oncology.

> *"We do see requests for drugs on the basis of what traditionally would be described as low-level evidence. And that seems to be the culture."- Participant 1*

Clinical trials will often enroll patients with good performance status that enable them to withstand treatment and even ensure efficacy. The advancements in cancer research mean that new therapeutics are designed to treat end stage disease, therefore participants often endure many lines of treatment prior to enrolling in a trial. Patient performance status is central in cancer treatment. The ability for a patient to perform activities of daily living (for example, walking, working or dressing) with or without help, informs prognosis and care plans. Performance status also provides information to decision makers about where the drug might fit within different lines of cancer treatment. Concerns about selective recruitment based on favorable performance status make it difficult to generalize the effectiveness of a therapeutic to the provincial population based on trial participants that are heavily treated or selectively enrolled. Further, once a drug is approved for a certain demographic, there is considerable pressure to expand its use to patients with poor performance status, in which the evidence is more uncertain.

> *"It's the patient population, the previous treatment, make that uncertainty."- Participant 6 (Clinician)*

> *"So, there may be a very, very good randomized Phase 3 study that shows benefit in a very tightly controlled population. A common one is good performance status patient. Most clinical trials restrict patients to good performance status. But there is considerable pressure then once you've got the drug, particularly if they don't have too many side effects, is to just expand the population and use it with patients with poor performance status. We just don't know whether it's going to be beneficial in that situation. But there is considerable pressure to fund it."- Participant 4 (Senior Executive)*

Pharmaceutical companies frequently submit evidence for drug approval from early phase clinical trials which are often based on surrogate endpoints. Early phase trials are often non-comparative and their purpose is to often to solely demonstrate safety while establishing a therapeutic dosing regimen. Participants noted increased uncertainty when new therapeutics do not demonstrate improvements in patient-centered outcomes such as overall survival and quality of life. Further, it is hard to fund a drug that has not been compared to the current standard of care.

> *"I think [it's] the clinical evidence and then just more and more pressure to fund drugs based on more limited or limited evidence. So randomized Phase 2's, response rates from phase 1 [trials] and more."- Participant 4 (Senior Executive)*

> *"We are trying - as payers - to buy better patient outcomes."- Participant 2*

The concerns related to clinical evidence were exacerbated by the increasing pace of drug approvals at the federal level which translates into a faster flow to provincial decision makers.

> *"I think the earlier and earlier release of these drugs can be considered. Health Canada is now accepting phase two. So is pCODR and it's getting to be a faster flow through to the payers. And without a follow up loop."- Participant 6*

These methodological limitations make it challenging for decision makers to evaluate the value of a new therapeutic as it is difficult to generalize to the wider patient population.

4.1.5.2 **Drug costs and adoption feasibilities**

Every participant acknowledged the rising cost of oncology drugs as a major source of uncertainty; however, they were hesitant to acknowledge that this factor alone would affect the outcome of the funding decision. Two participants from QC explicitly stated that efficacy is the first criteria for a drug funding recommendation, even if it means funding a drug based on small incremental benefit and significantly higher costs.

"We take into account the efficacy as number one and then look at other criteria, whereas other HTA bodies will amalgamate multiple different criteria, including the economic cost considerations with efficacy. So, you have that weight on both of them, which I thought was really interesting about our process because we seem very explicit in the therapeutic value is number one."- Participant 5 (Methodologist)

Further, all participants noted that the budget impact is often underestimated, and the adoption feasibilities are becoming difficult to manage, especially with new targeted therapies which add significant burdens in their adoption within health care systems.

"So, the budget impact is so huge on that because I mean, what I've read with CAR-T is that it's not just the $450,000 infusion or process, but it's also the side effects. It's the rooms that you need, the trained clinicians, the hospital, long term hospitalization."- Participant 6

4.1.5.3 **External influences**

Participants noted several challenges that stem from a variety of external sources such as patient and clinician pressure, US Food and Drug Administration (FDA), industry, media and political influences.

Participants noted uncertainty based on pressure from clinicians and patient groups. These groups have a higher tolerance for uncertainty since they tend to focus on the needs of individuals, rather than the population. Participants said that these groups do not always consider cost. There was a question whether clinicians ought to consider cost or whether that would be inappropriate given their objective to treat patients.

"I guess the challenge always is from a clinician perspective. They don't always consider the cost. In fact, they recognize that these drugs are costly, but it doesn't seem to slow down or reduce the pressure to fund them. […] In the face of a cancer diagnosis and the

treatment that potentially could help, cost is not something that they want to take into consideration."-Participant 1

One participant, a senior executive and clinician, noted a cultural trend for increasing access to medicines.

I guess it's a cultural thing - that people want drugs regardless of the price in a cancer situation. Uncertainty, you know, I worry about uncertainty and trying to make decisions based on evidence, the magnitude of benefit, cost effectiveness, all of those components, that doesn't seem to be what's driving the demand for cancer drugs. It's really based on, "could this drug potentially help this patient in front of me? And I will take whatever evidence there is, including a case study in order to try and get access to those drugs."- Participant 1

Further, a participant, a clinician, noted how the proximity of the United States to Canada creates pressure for payers and adds challenges to implement standards for value.

So, their [FDA] bar for approval is low. They don't have to think about the price, although people do have to think about the price. So, the bar is "it has some signal of activity and it doesn't immediately kill people". Then that drives the demand for drugs that potentially may help somebody in a situation when and maybe they don't have great choices or a cancer that would actually kill them. So that drives the clinical demand for us here in Canada. So, then that makes it very difficult for us to then impose an additional bar around what value is it providing and what prices or the cost effectiveness is in a culture that wants to use drugs whenever they want to use them.- Participant 6

Other sources of uncertainty included media and industry which can influence the public and political members to adopt certain therapeutics contrary to the evidence. Many drug benefits are overemphasized and described as "cures", but this is often not the case.

They [industry] thought it was going to be a cure, well I'm hearing them temper it down. Well, you might get a few years. That's not a cure!- Participant 2

Participants often expressed ambiguity about political agendas. Two outlined specific scenarios where they engaged in a reassessment that was overturned by the minister without any transparency.

"We spent a summer going through all the drugs with the tumour groups saying, OK, what could we do list if you want to free up money for these newer drugs. So, we went to our board with actually what I considered were underperforming drugs. And they said, no, no, no. We'll find the money. And I went, really??, you know, so I don't ever underestimate the politicalness of this stuff."- Participant 3 (Senior Executive)

4.1.6 **Managing uncertainty**

Participants suggested various approaches to managing uncertainty in provincial drug funding decisions. These strategies fell into four categories; financial risk management, real world evidence, reassessment of drugs with uncertain benefit and the opportunity to participate in pan-Canadian collaborations. A common challenge for each approach included the increasing pace of drug approvals at the federal level and the lack of required resources at a provincial level.

"But the challenge with drugs, particularly cancer drugs (or maybe any drugs), is that things move so fast. And our ability to tolerate the historical, "OK, it's going to take us four or five years to actually get an answer." Things will have moved on and there's new drugs and you've invested all of these resources to see whether something is behaving how you thought it would in the real world. And there's three new drugs in that cancer treatment space. And nobody cares."- Participant 1

4.1.6.1 **Financial management**

Participants also discussed risk-sharing agreements between public payers and industry to manage uncertainty and noted innovative strategies internationally. Payers seemed to favor sharing the

risks and cost burden with the pharmaceutical companies, especially in the initial stages of adoption where uncertainty is at its highest. One participant also noted the National Institute for Health and Care Excellence (NICE) Cancer Drugs Fund. This source of funding provides earlier patient access to novel treatments while further clinical evidence can be collected (National Health Service, 2020). These strategies can offset the burden to public health care systems while enabling earlier access to patients and ongoing data collection.

> *"They inserted the cancer drugs fund that used to be a rogue fund. And if it's iffy or is uncertain, they are throwing the drug into the cancer drug fund middle space where there is shared funding while they develop the real-world evidence to feed into NICE so that they can say yes or no. It's a two-year probation space. And then it's not de-listing or listing too early. It's a shared space where the funding isn't at the payer level or the industry - its shared."- Participant 2*

Other participants noted outcome-based reimbursement (OBR) between the province and pharmaceutical companies. Generally, OBR allows for staggered adoption of uncertain therapeutics into the health care system. There are multiple ways jurisdictions have approached these agreements; whether it be staged payments to manufacturers based on certain health outcomes or rebates for patients who die during a certain time period in treatment. OBR seems to be gaining traction with payers from countries with publicly funded health care systems to access the value of therapeutics with uncertain clinical evidence and high costs (Jørgensen, Hanna, & Kefalas, 2020).

> *"I just think I was the only thing that I noticed prior to negotiating nationally, we had done some pretty creative stuff I thought. We did pay for performance where the pivotal trial expected this survival. And it was like maybe fifteen patients a year. So, we actually entered into a contract with a manufacturer that it was we were going to pay for performance. So, we got different rebates depending on our patient's survival. And I could never do that on a big to a group like Breast. But it worked really well, and we tried it out."- Participant 4*

4.1.6.2 **Real world evidence**

All participants seemed to agree on the importance of collecting RWE and, at times, even negotiating these conditions into the initial contracts with pharmaceutical companies. Health Canada defines RWE as "evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of real-world data" (Health Canada, 2020a). This often means collecting data on health outcomes from a diversity of sources such as patient registries, electronic medical records, surveys, administration claims and even social media (Nabhan, Klink, & Prasad, 2019).

> *"If we were to collect data to find out their true experience from a payer's perspective, and not just clinical trial data that's based on a highly selected group that happens to be healthy enough to be in the trial."- Participant 5*

Challenges for collecting RWE stem from a historical reliance on clinical trials in oncology and subsequent reluctance to use other methods such as observational designs. There is a longstanding tradition in medicine to give preference to data generated from randomized clinical trials. Ideally, these trials create highly controlled settings where most confounding factors can be eliminated. However, trials have changed in recent years. The investigation of rare molecular alterations and personalized medicine in oncology means trials are smaller, more selective and not always randomized. However, despite these limitations in study design lending the aspects of the trial similar to an observational study, it seems some decision makers and clinicians still prefer the evidence generated from a "trial" based on its cultural significance in medical practice.

> *"Part of that, again, just stems from the fact that they know, and they trust something that's called a trial even if there is no actual randomization or even if there's no actual control arm - you know, it's a trial."-Participant 5*

4.1.6.3 **Reassessment for drugs with uncertain benefit**

All participants noted that reassessment of the treatment space generally does not occur and that this was a current gap. There were numerous reasons for this including the pace, limited human and financial resources to reassess drugs, political will and a lack of systematic ways for disinvestment. In response to a question about whether the province reassess therapeutics that have been approved, one decision maker responded with the comment below.

> *"We don't - not in the formalized way that we list drugs. So that is currently a flaw. A part of it is there is so much pressure to list drugs that it's difficult to use the limited resources you have in order to make the listing of drugs work to apply to delisting. And as you know, it's difficult to delist once something is accepted and people are using it."- Participant 1*

4.1.6.4 **pan-Canadian collaborations**

Pan-Canadian collaborations such as pCODR, pCPA, CDIAC and others have increased opportunities for collaboration, partnership and transparency and had positive impacts on managing uncertainty in funding decisions. Positive aspects included streamlined processes based on one federal HTA process which generates comprehensive reports that identify areas of uncertainty. Further, another positive was "less neighbor checking" between provinces. One decision maker noted that prior to the formation of pCODR, some provincial payers would monitor what drugs other provinces were funding and make decisions based on this. However, with one recommendation from pCODR, provinces can rely on one source of reliable evidence to make their own decisions.

> *"So even though we talk about provincial, [there are] different processes and parallel patchwork processes, before was worse. It's actually better now in my opinion."- Participant 6*

> *"I think the pan-Canadian oncology review is getting, and has been really good, at calling out uncertainty." – Participant 2*

"Oh, they [pCODR] definitely help. The reviews that CADTH does are very helpful, it is very good, and thorough."- Participant 1

"There is a lot less neighbour checking now."- Participant 4

However, one participant noted that pCODR might also contribute to uncertainty in formulary decisions as there is no obvious bar for what constitutes as "good evidence." This can incentivize manufacturers to submit earlier and earlier evidence as there seems to be little consistency for what receives a positive or negative recommendation in terms of immature evidence. However, other decision makers noted that it was not clear who ought to be setting a bar for the standard of evidence – whether that be Health Canada or CADTH. Payers are struggling to understand what is acceptable.

"And do they [pCODR] contribute to uncertainty? Absolutely. Because they keep moving the bar. So, you know a company can't predict what's coming out of pCODR. They should be able to predict and therefore not put stuff in when it's too early in evidence. But they are throwing it at it [pCODR] because sometimes they let it through and sometimes, they don't."- Participant 2

4.1.7 **Summary of key informant interviews**

The key informant interviews identified numerous sources of uncertainty in funding decisions for cancer therapeutics. These included the lack of a solid evidence base due to methodological limitations from clinical trials, increasing costs and external influences such as pressure from the FDA, patients and clinicians and political will. Strategies to manage uncertainty included financial risk management, mechanisms for reassessment and collection of RWE.

There were several challenges noted. These included the increasing pace from regulatory approval to payers. The speed of which drugs are currently approved, often through accelerated pathways, means payers have limited time to make funding decisions before the next drug arrives which introduces additional pressure for decision makers. Further, there is a lack of formal

mechanisms and resources (human and financial) to reassess drugs once they have been on the market, otherwise known as "health technology management" (Bryan, Mitton, & Donaldson, 2014). Finally, the deterioration of the quality of evidence from the trials, combined with a historical reluctance to use alternative study designs outside of clinical trials creates challenges for the use of additional methods, such as observational studies used often in the collection of RWE.

4.2 Phase II: Summary of uncertainties in pCODR submissions

4.2.1 Sample characteristics

Overall, there were a total of 73 distinct submissions to pCODR between 2015-2019. One report per tumor type was included in this analysis, for a total of 47 distinct submissions. This choice in the inclusion and exclusion criteria is discussed within the Methods and Limitations sections. A list of drugs that met the study inclusion criteria were compiled into one dataset. An overview of the drugs included in this study, along with the indication and year of approval is available in Appendix B. Any inconsistencies in the pERC documents were resolved with further analysis of the Final Clinical Guidance Report.

4.2.2 Sources of uncertainty in pCODR submissions

The pCODR documents specified a number of uncertainties related to methodological limitations of the clinical trials. Overall, sources of uncertainty were associated with five broad categories; trial validity, population, comparators, outcomes and intervention. The quotes provided in this section were sourced from the pCODR submission documents, more specifically the Clinical Report or the pERC recommendation.

4.2.2.1 Trial validity

In approximately 50% of the submissions, reviewers noted uncertainties related to methodological limitations in the study design which raised questions about meaningful long-term benefit. The most common were selection bias, reporting bias, performance bias and attrition bias. Selection bias can occur when patients are selectively recruited into trials based on characteristics that differ from the wider population. For example, some participants were chosen on performance status which might ensure resilience to withstand treatment which can lead to better outcomes.

"Uncertainties about the heavily pre-treated patient population"

Further, reporting and performance bias can be introduced when patients and clinicians are aware of the treatment assignments.

> *"The open label nature of the trials might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the treatment assignments."*

Uncertainty related to attrition bias is introduced when participants exit studies for unknown reasons. One common example was data related to health-related quality of life. Often, some studies report favorable outcomes. However, upon closer inspection, it is common that a number of patients left the study. Therefore, the reported outcomes only pertain to a select number of patients who were retained in the study and is likely not a reflection of the original sample.

4.2.2.2 **Population**

In 47% of the submissions, there was uncertainty about whether the sample of participants in clinical trials is generalizable to clinical practice. Due to the investigation of often rare molecular alterations, it can be difficult for clinical trials to recruit enough participants to adequately power a trial. To remedy this, trials can have an international scope where patients are enrolled from centers around the world. The varying demographics from those enrolled can create uncertainty about its effectiveness in a specific population, such as Canada. Indeed, assessing the generalizability of the trial results can be a challenge for all countries in all international trials. An example of the challenge would be a molecular alteration found more often in one part of the world and therefore leads to a large proportion of the study population from that geographic area. It would be difficult for decision makers to generalize these study results to a diverse multi-cultural population in Canada.

> *"From a methodological perspective the low number of Canadian patients in the study make it uncertain how generalizable results are to the broader Canadian population."*

4.2.2.3 **Comparators**

In 40% of the submissions, reviewers noted how the lack of inappropriate use of a comparator added uncertainty. It is common that trials do not compare to clinically relevant standards of care. At times, trials will only have an experiment arm or compare against placebo. This can make a drug benefit appear substantial. However, this might not be the case. It can be hard to make a reimbursement recommendation when there is uncertainty to its performance compared to the drug used in current clinical practice.

> *"Substantial uncertainty due to non-comparative data"*

> *"Uncertainty in results of indirect comparisons"*

4.2.2.4 **Outcomes**

Uncertainties related to outcomes were indicated in 72% of the submissions and fell into two categories; the use of unvalidated endpoints and missing data related to important patient-centered outcomes such as overall survival and health-related quality of life. There were numerous issues with the use of unvalidated endpoints for certain tumor types which raised questions about whether the efficacy translated into effectiveness in real world conditions. Many drug approvals are made on the basis of a surrogate endpoints, such as progression free survival. This causes challenges for decision makers as it is an approximate measure of overall survival (a more meaningful patient-centered outcome), and its use is only validated with certain tumor types. Surrogate-survival validation studies are important to confirm the correlation between overall survival and surrogate endpoints since their predictive value is justifiable only in specific circumstances. For example, a meta-analysis of surrogate-survival trial validation studies found low correlation between progression free survival and overall survival in metastatic breast cancer, but high correlation in metastatic colorectal cancer (Prasad et al., 2015). Therefore, even a favorable measure of progression free survival without data on overall survival increases uncertainty in funding decisions as payers will have to estimate long term benefits.

"Progression free survival may be a surrogate outcome for overall survival, but it has not been determined if benefits of PFS translates into overall survival benefits in patients with pancreatic neuroendocrine tumors."

"Modest improvement in progression free survival"

"There were uncertainties with regard to the magnitude of the progression free survival benefit"

Further, there were additional uncertainties when trials did not collect important patient centered information such as health related quality of life.

"Neither study reported quality of life data."

4.2.2.5 **Intervention**

Although this analysis mainly focused on clinical uncertainties, there were substantial references to the resources required for implementation of a therapeutic. These uncertainties were indicated in almost all of the submissions (83%) and were related to the duration of treatment, adoption feasibilities and administration of the drug.

The duration of a treatment has important effects of the quality of life of a patient. If a drug seems beneficial yet has a long duration of treatment, it might not be the best option.

"pERC acknowledged a substantial uncertainty regarding duration of treatment."

There were additional uncertainties related to the administration of certain therapeutics. Some therapeutics require additional resources such as staff with special training or new facilities for administration.

"pERC noted that the administration of intravenous daratumumab is resource-intensive due to the duration, frequency, and changing pattern of dosing."

The uncertainties generated from the duration of treatment and resource-intensive administration flow into considerations for their adoption in a health care system. It is often the case that the therapeutic itself is also costly. Therefore, high costs and additional resources creates uncertainty for the feasibility of its adoption.

> *"[There is a] concern that implementation could lead to significantly increased resource utilization (e.g., nursing, pharmacy, clinic, and chemotherapy chair time."*

4.2.3 **Summary of pCODR document review**

The pCODR document review identified five sources of uncertainty in the clinical evidence. These included issues with trial validity, non-generalizable population, lack of or unreliable comparators, unvalidated or missing outcome measurements and resource intensive implementation. This analysis demonstrates specific areas of uncertainty that plague decision makers during the reimbursement process.

Chapter 5: Discussion

The key informant interviews confirm that there are many areas of uncertainty that challenge decision makers in oncology, most of which are related to the evidence generated from clinical trials. The results from the document review add to this finding by systematically categorizing these uncertainties into five main themes. Both these findings demonstrate how uncertainty is prevalent in oncology. Overall, pCODR and payers raised similar concerns, especially about the generalizability of the trial results into a broader patient population. However, payers were more focused on how well a therapeutic will translate into existing lines of treatment, whereas pCODR focused on recommendations for one submission at a time.

There is no doubt that many sources of uncertainty stem from clinical trials. Historically, there has been a reliance on randomized clinical trials in medicine. These trials are mainly used to compare an experimental treatment with either a placebo or the current standard of care to determine its efficacy. In ideal studies the clinical trial is tightly controlled so that the result can be confidently extrapolated to similar patient populations. The controlled settings are what makes clinical trials the "gold [evidential] standard" in treatment evaluation (Nardini, 2014). However, there are many confounding factors in practice that can affect the final results. These include the lack of randomization or blinding, smaller and more selective study population, and even the absence of significance testing. These deviations from traditional study designs raise important ethical questions about whether the risks and benefits are balanced for participants.

Although the most common purpose of clinical trials is to establish efficacy, trials are also used to determine the value of a given therapeutic for resource allocation purposes. Payers need to decide if there is a good reason for their expenditure compared to other drugs and health services across the health system. However, different stakeholders throughout the approval and reimbursement process have different objectives and therefore different tolerances for uncertainty. One example of this would be between payers and clinicians. The participants in the key informant interviews raised concerns about pressure from clinicians and patients who often push for treatments despite low quality evidence. Here, clinicians have a duty to treat their patient and alleviate suffering. For this reason, they might have a higher tolerance for uncertainty. Whereas payers often have less tolerance for uncertainty due to the task of equitably allocating resources across the entire health care system. Further, the results from the document review and key

informants highlight how payers are concerned about managing a portfolio of approved drugs with multiple different lines of treatment. When one drug is approved in one line of therapy, it can disrupt existing treatment regimes. This is in contrast with the pCODR document review where the focus was on one drug at a time. Many drugs had uncertainties about their adoption into the health care system, therefore it will be important to focus on implementation and not on one-off assessments. It is encouraging that there has been recent movement towards a focus on implementation at the pan-Canadian level. As of July 2019, pCODR has included federal collaboratives such as CDIAC into the assessment process to focus on mechanisms for implementation. This shift might have a positive future effect but will require future research as to its effect in reducing uncertainty at provincial levels.

The movement towards precision medicine in oncology raises important issues for how evidence is conceptualized in medicine and how analytic methods in HTAs adapt to evaluate the value of these new therapeutics (Love-Koh, Peel, Rejon-Parrilla, et al., 2018; Raymakers, Regier, & Peacock, 2019). Oncology has been on the forefront of precision medicine due to the identification of specific molecular alterations and tumor biomarkers that new biologics can target (Hunter, 2016). These targeted therapies have shifted traditional designs of clinical trials. One example of this shift is "basket trials" where a trial population is recruited based on a molecular alteration and not on tumor types. Generally, this occurs in very rare cancers where it is not feasible to recruit large samples. Since precision medicine targets specific (and often rare) molecular alterations, it might not be feasible to recruit hundreds of patients to participate. However, the small and selective sample population make it increasingly difficult to predict its effectiveness in the real world. This situation leads to uncertainty for both clinicians and funders as the group can be highly selective and unique in the way that they respond. Further, small sample sizes often rely on surrogate endpoints to enable statistical power. This is because surrogate endpoints facilitate measurement from the start of the trial in lieu of patient-centered such as overall survival that reflect long-term benefit but take longer to collect (Kimmelman & Tannock, 2018).

Provinces generally rely on the reimbursement recommendations from pCODR. However, the document review revealed many sources of uncertainty that are embedded within these evaluations. Although these uncertainties often translate into conditional recommendations, it has been shown that provinces often interpret conditional drugs as a positive recommendations

(Srikanthan et al., 2018). Further, preliminary data that receive conditional recommendations are rarely revisited. For example, olaratumab remains conditionally listed on the pCODR website despite updated evidence that demonstrates no survival benefit. Provincial negotiations ended in November 2019, presumably for these reasons, however, it reveals a weakness for revisiting the initial recommendation should mature data present a different picture. As such, decisions based on uncertain data, without a plan for post market studies might have negative effects for population health outcomes. If these trials continue to be used for reimbursement decisions, analytical methods need to properly appreciate the uncertainty associated with the evidence. Recommendations based on uncertain evidence require a strengthening of mechanisms for temporary approvals and reassessment which seems challenging given the current institutional context in Canada.

Participants offered suggestions for ways uncertainty can be managed in oncology. These strategies included the collection of RWE, outcome-based agreements and mechanisms for reassessment. Many participants discussed risk-sharing agreements between public payers and industry to manage uncertainty. There are some innovative strategies internationally. For example, one participant cited a Cancer Drugs Fund from NICE (in the UK) that is utilized for uncertain therapeutics while RWE is collected. This strategy provides a holding space for drugs with high degree of uncertainty prior to funding at a national level. Other participants were in favor of outcome-based agreements. These agreements are made where provincial funders only pay manufacturers based on positive patient outcomes from the therapeutic. This way, the uncertainty is shared. All participants seemed to agree on the importance of collecting RWE and even negotiating conditions into contracts with manufacturer. Further, the key informants noted the absence of mechanisms to revisit drugs with uncertain benefit despite their interest in the ways this might occur, otherwise known as “health technology management” (Bryan et al., 2014). However, challenges for these strategies included limited resources and pace. Participants stated that reassessment was a resource-intensive process, especially in provinces with segregated health care systems. Further, the pace from approval to payer is increasing and participants often noted how by the time they collected evidence for the most recent drug, the next one would arrive. It might also be true that external factors outside of evidence can override decision making processes such

as shown in the example where one decision maker noted their efforts to reevaluate and delist underperforming drugs but was turned down at the executive level without reasons.

Given the uncertainty of benefit with new therapeutics and potential for external factors to affect the decision making process, there is a need for more transparent frameworks at all levels of the regulatory and reimbursement process. The key informants all noted that they could name the pieces of the evidence in the provincial decision making process but did not know exactly how each one was weighed in the final decision. Similarly, pCODR publishes a deliberative framework of four criteria; clinical, economic, patient values and adoption feasibility. However, the weighting scheme of each of these components is unknown. It might be assumed that each review team apply their own implicit weights to these criteria which might create questions about the consistency of the process (Skedgel & Younis, 2016). A recent empirical analysis of pCODR recommendations demonstrated that clinical aspects, such as efficacy, appear to carry the greatest weight whereas cost-effectiveness did not seem to have any effect at all (Skedgel, Wranik, & Hu, 2018). Similarly, all key-informants noted how costs did not play any role in the funding decisions and two specifically described how they would fund a drug based on small incremental benefit even if it were double the price. Their justification for this was to provide transparency to the funding process with an intentional weight placed on efficacy as a primary criterion for adoption. They noted how other HTA bodies have multiple criterion, for example "cost-effectiveness" and "patient values" but it is unknown how much weight each criterion was given in the final decision. A larger weight on efficacy was meant to add transparency and consistency to the formulary decisions. However, these findings are surprising given the objective to evaluate the *value* of a new therapeutic. The cost-effectiveness of a given therapeutic (including the incremental benefits and costs) are integral to any adoption decision given the constrained budgets in publicly funded systems. Further, economic analyses (such as cost-effectiveness) provide important information for how we can maximize patient outcomes with given resources while comparing the new therapeutic with the current standard of care. This is especially important given the trend of approving drugs from early phase non-comparative designs where this information might be lacking.

Priority setting processes can be outweighed by external processes such as media or political priorities. However, these external factors are almost never recognized as formal criteria

in a reimbursement decision. These decisions, especially at the provincial level, tend to occur behind closed doors. This notion of non-transparency reduces the principle of a "legitimate and fair process" (Daniels, 2000). Without recognition of external factors beyond quantifiable considerations, funding decisions might lead to inequitable resource allocation. This leads to opportunity costs in a publicly funded system, such as not funding other more effective treatments.

5.1 **Study limitations**

The current study provides a qualitative analysis of the uncertainties for oncology drugs at the time of the provincial reimbursement decision in Canada. However, the results should be interpreted in light of several methodologic limitations. First, the key informant interviews were from a small group of participants therefore it might be hard to generalize the findings to other provinces (external validity). However, concerns related to a small sample size are not as limiting in qualitative analyses. In qualitative designs, a small number of interviews can be analysed with more depth, increasing the internal validity of the study (Sandelowski, 2000). Additionally, interviews with senior decision makers who are accountable to their organizations and the public can stimulate political responses. This means that some questions were answered in ways that might not be representative of what actually happens in practice. To offset this concern, recruitment ensured a diversity of participants involved in various aspects of the decision making process. For example, where a senior executive or CEO might give a relatively political answer, a methodologist might provide more insight into current practice. Further, interview questions were compared between participants to ensure findings were representative of the diversity of backgrounds within the study.

The pCODR document review also should be interpreted in light of other limitations. First, the study relied on publicly available documents. Since pCODR considers all available evidence in its evaluation process, some of which may not be clear in public documents, it might be difficult to draw conclusions solely examining one portion of the process. Further, the document review was limited to comments of the pCODR reviewer in lieu of an independent critical appraisal. This is important to consider as a critical appraisal would likely generate a more realistic, and perhaps more substantial list of uncertainties. This is especially relevant in the quantitative content analysis to indicate the frequency at which these uncertainties occurred. Although, it is important to note

that despite this limitation other studies have found similar results to the ones presented here. For example, Naci et al. (2019) used the Cochrane risk of bias tool to critically appraise the trials of the drugs approved by the European Medicines Agency. The study found nearly half if the clinical trials were assessed to be high risk of bias due to limitations to study design and analysis. Similarly, this study found that approximately 50% had issues related to trial validity. Another limitation is the choice in the exclusion and inclusion criteria to include one submission per drug rather. This resulted in a total of 47 out of 74 submissions that was included in the qualitative analysis. It is recognized that this type of criteria can introduce selection bias to the study. However, after the criteria was applied, the characteristics of the drugs included in this analysis were compared to characteristics of those found in a database of all submissions to pCODR since inception (n=104). Table 3, in Appendix B.2, demonstrates that the characteristics were similar and therefore might mitigate significant additional bias.

5.2 **New Knowledge and Future Research**

The lack of formal priority setting processes for implementing or reassessing therapeutics has created a challenging environment for Canadian decision makers in cancer control. This challenge, combined with the high levels of uncertainty from pivotal clinical trials identified during the document review, means that making decisions with limited evidence or data is a reality for those involved in provincial cancer drug funding. However, it is also evident from this study that there is an appetite for mechanisms to manage uncertainty, namely ways to reassess uncertain therapeutics. Future research might consider revisiting this concept of uncertainty with a larger sample of stakeholders across Canada (e.g. patients, front line clinicians, ethicists, health economists, pharmaceutical industry representatives), in addition to senior decision makers. One strength of this study was the inclusion of a variety of participant roles within the decision making process which served to triangulate the responses from senior executives. It can be difficult for the leadership team to speak openly about uncertainty, therefore including participants who are involved in various facets of the decision (e.g. methodological assessments) allowed for more transparency during the interview process.

Future studies might also consider applying a critical appraisal to the clinical trials submitted to pCODR instead of relying on review comments. This has been done previously with

standardized tools such as the Cochrane Risk of Bias tool with submissions to the European Medicines Agency (Naci et al., 2019). Since pCODR review teams change from one submission to the next, approaching the trials in a standardized way would likely generate a more holistic picture of the uncertainties these trials introduce.

Chapter 6: Conclusion

The key informant interviews identified numerous sources of uncertainty, many of which were associated with a lack of solid clinical evidence which stemmed from methodological limitations in clinical trials. These results were similar to other studies that have reported several inconsistencies in trials with new therapeutics in oncology. For example, Driedger et al., (2018) surveyed decision makers across Canada about areas of uncertainty when funding drugs between 2016-2017. They also found that a lack of solid clinical evidence from limitations in clinical trials was the primary source of uncertainty. Further, the interviews confirmed that priority setting processes occur as a patchwork of processes that can be subjected to a variety of external influences such as politics, media or patient advocacy groups. The notion of a lack of transparency raises important concerns for how decision making occurs in Canada.

The pCODR document review adds to these findings by systematically categorizing uncertainties into five main categories. These categories highlight the substantial challenges decision makers face when funding therapeutics at a provincial level. Many of the uncertainties in the document review were raised by provincial decision makers. However, one major difference was the focus on the management of a therapeutic space in contrast to pCODR who generally focuses on individual drug submissions. Although there has been federal movement to focus on implementation with the incorporation of agencies such as CDIAC into the pCODR process, the impact has yet to be evaluated. This study raises important questions about the evidential standard in oncology and how might this adapt in the era of precision medicine.

Bibliography

Abola, M. V., & Prasad, V. (2016). Characteristics and conflicts of public speakers at meetings of the oncologic drugs advisory committee to the US food and drug administration. *JAMA Internal Medicine*, *176*(3), 389–391. https://doi.org/10.1001/jamainternmed.2015.7805

Ahn, R., Herrera-Perez, D., & Prasad, V. (2019). Characteristics of Public Comments Submitted to State Health Technology Assessment Programs in Oregon and Washington. *JAMA Internal Medicine*, 1–2. https://doi.org/10.1001/jamainternmed.2019.5145

Andersen, S. K., Penner, N., Chambers, A., Trudeau, M. E., Chan, K. K. W., & Cheung, M. C. (2019). Conditional approval of cancer drugs in Canada: accountability and impact on public funding. *Current Oncology (Toronto, Ont.)*, *26*(1), e100–e105. https://doi.org/10.3747/co.26.4397

Bach, P. B. (2009). Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs. *The New England Journal of Medicine*, *260*(6).

Booth, C. M., Dranitsaris, G., Gainford, M. C., Berry, S., Fralick, M., Fralick, J., … Clemons, M. (2007). External influences and priority-setting for anti-cancer agents: a case study of media coverage in adjuvant trastuzumab for breast cancer. *BMC Cancer*, *7*(1), 110. https://doi.org/10.1186/1471-2407-7-110

Booth, C. M., & Tannock, I. (2008). Reflections on Medical Oncology: 25 Years of Clinical Trials—Where Have We Come and Where Are We Going? *Journal of Clinical Oncology*, *26*(1), 6–8. https://doi.org/10.1200/JCO.2007.13.8156

Bryan, S., Mitton, C., & Donaldson, C. (2014). BREAKING THE ADDICTION TO TECHNOLOGY ADOPTION. https://doi.org/10.1002/hec.3034

Canadian Association for Provincial Cancer Agencies. (2020). About us. Retrieved September 18, 2020, from http://www.capca.ca/about-us

Chafe, R., Culyer, A., Dobrow, M., Coyte, P. C., Swaka, C., & O'Reilly, S. (2011). Access to Cancer Drugs in Canada : Looking Beyond Coverage Decisions Accès aux médicaments pour traiter le cancer au Canada : voir au-delà des décisions concernant la couverture. *Healthcare Policy*, *6*(3), 27–36. Retrieved from https://www.researchgate.net/profile/Jeffrey_Hoch2/publication/259714199_Access_to_Cancer_Drugs_in_Canada_Looking_Beyond_Coverage_Decisions/links/53d794710cf2926532

3cd0e8.pdf

Costa, S., Bentley, C., Regier, D. A., Mctaggart-Cowan, H., Mitton, C., Burgess, M. M., & Peacock, S. J. (2019). Public perspectives on disinvestments in drug funding: results from a Canadian deliberative public engagement event on cancer drugs. *BMC Public Health*, *19*(977), 1–10. https://doi.org/10.1186/s12889-019-7303-2

Cressman, S., Browman, G. P., Hoch, J. S., Kovacic, L., Peacock, S. J., Li, E., & Shing, K. (2015). Economics of Oncology Practice A Time-Trend Economic Analysis of Cancer Drug Trials. *The Oncologist*, *20*, 729–736. https://doi.org/10.1634/theoncologist.2014-0437

Daniels, N. (2000). Accountability for reasonableness. *British Medical Journal*, *321*, 1300–1301. Retrieved from www.doh.gov.uk/pdfs/

de Oliveira, C., Weir, S., Rangrej, J., Krahn, M. D., Mittmann, N., Hoch, J. S., … Peacock, S. (2018). The economic burden of cancer care in Canada: a population-based cost study. *CMAJ Open*, *6*(1), E1–E10. https://doi.org/10.9778/cmajo.20170144

Driedger, S. M., Cooper, E., Annable, G., & Brouwers, M. (2018). "There is always a better way": Managing uncertainty in decision making about new cancer drugs in Canada. *International Journal of Health Planning and Management*, *33*(2), e485–e499. https://doi.org/10.1002/hpm.2492

Health Canada. (2020a). Elements of real world data/evidence quality throughout the prescription drug product life cycle - Canada.ca. Retrieved October 20, 2020, from https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html

Health Canada. (2020b). How Drugs are Reviewed in Canada - Canada.ca. Retrieved October 26, 2019, from https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html

Hunter, D. (2016). Uncertainty in the Era of Precision Medicine. *The New England Journal of Medicine*, *375*(8), 711. https://doi.org/10.1056/NEJMp1606458

Jørgensen, J., Hanna, E., & Kefalas, P. (2020). Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *Journal of Market Access & Health Policy*, *8*(1), 1715536. https://doi.org/10.1080/20016689.2020.1715536

Kantarjian, H. (2014). The unsustainable prices of cancer drugs : from the perspective of a large group of CML experts Blood Forum The price of drugs for chronic myeloid leukemia (CML) is a re fl ection of the unsustainable prices of cancer drugs : from the perspective of a l. *Blood*, *121*(Cml), 4439–4442. https://doi.org/10.1182/blood-2013-03-490003

Kemp, R., & Prasad, V. (2017). Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? *BMC Health Services Research*, *15*(134), 1–7. https://doi.org/10.1186/s12916-017-0902-9

Kimmelman, J., & Tannock, I. (2018). The paradox of precision medicine. *Nature Reviews. Clinical Oncology*, *15*(6), 341–342. https://doi.org/https://dx.doi.org/10.1038/s41571-018-0016-0

Lexchin, J. (2018). Quality of evidence considered by Health Canada in granting full market authorisation to new drugs with a conditional approval: A retrospective cohort study. *BMJ Open*, *8*(4). https://doi.org/10.1136/bmjopen-2017-020377

Lexchin, J. (2019). Financial conflicts of interest of clinicians making submissions to the pan-Canadian Oncology Drug Review: a descriptive study. *BMJ Open*, *9*, 30750. https://doi.org/10.1136/bmjopen-2019-030750

Love-Koh, J., Peel, A., Juan, ·, Rejon-Parrilla, C., Ennis, · Kate, Lovett, R., … Taylor, M. (2018). The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. *PharmacoEconomics*, *36*, 1439–1451. https://doi.org/10.1007/s40273-018-0686-6

Love-Koh, J., Peel, A., Rejon-Parrilla, J. C., Ennis, K., Lovett, R., Manca, A., … Taylor, M. (2018). The Future of Precision Medicine: Potential Impacts for Health Technology Assessment. *PharmacoEconomics*, *36*(12), 1439–1451. https://doi.org/https://dx.doi.org/10.1007/s40273-018-0686-6

Nabhan, C., Klink, A., & Prasad, V. (2019). Real-world Evidence - What Does It Really Mean? *JAMA Oncology*, *5*(6), 781–783. https://doi.org/10.1001/jamaoncol.2019.0450

Naci, H., Davis, C., Savović, J., Higgins, J. P. T., Sterne, J. A. C., Gyawali, B., … Booth, C. M. (2019). Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014-16: cross sectional analysis. *British Medical Journal*, *366*(5221), 1–17.

https://doi.org/10.1136/bmj.l5221

Nardini, C. (2014). The ethics of clinical trials. *Ecancermedicalscience*, *8*(1), 1–9. https://doi.org/10.3332/ecancer.2014.387

National Health Service. (2020). Cancer Drugs Fund. Retrieved October 20, 2020, from https://www.england.nhs.uk/cancer/cdf/

Peacock, S. J., Regier, D. A., Raymakers, A. J. N., & Chan, K. K. W. (2019). Evidence, values, and funding decisions in Canadian cancer systems. *Healthcare Management Forum*, *32*(6), 293–298. https://doi.org/10.1177/0840470419870831

Pinto, A., Naci, H., Neez, E., & Mossialos, E. (2020). Association Between the Use of Surrogate Measures in Pivotal Trials and Health Technology Assessment Decisions: A Retrospective Analysis of NICE and CADTH Reviews of Cancer Drugs. *Value in Health*, *23*(3), 319–327. https://doi.org/10.1016/j.jval.2019.10.010

Prasad, V., Kim, C., Burotto, M., & Vandross, A. (2015). The strength of association between surrogate end points and survival in oncology: A systematic review of trial-level meta-analyses. *JAMA Internal Medicine*, *175*(8), 1389–1398. https://doi.org/10.1001/jamainternmed.2015.2829

Raymakers, A. J. N., Regier, D. A., & Peacock, S. J. (2019). Health-Related Quality of Life in Oncology Drug Reimbursement Submissions in Canada: A Review of Submissions to the pan-Canadian Oncology Drug Review. *Cancer Month*, *0*. https://doi.org/10.1002/cncr.32455

Raymakers, A. J., Regier, D. A., & Peacock, S. J. (2019). Modelling uncertainty in survival and cost-effectiveness is vital in the era of gene therapies: the case of axicabtagene ciloleucel. *Health Policy and Technology*. https://doi.org/10.1016/j.hlpt.2019.05.009

Sandelowski, M. (2000). Whatever Happened to Qualitative Description? *Research in Nursing & Health*, *23*(8), 334–340. https://doi.org/10.1016/S0009-9260(05)82940-X

Skedgel, C., Wranik, D., & Hu, M. (2018). The Relative Importance of Clinical, Economic, Patient Values and Feasibility Criteria in Cancer Drug Reimbursement in Canada: A Revealed Preferences Analysis of Recommendations of the Pan-Canadian Oncology Drug Review 2011–2017. *PharmacoEconomics*, *36*(4), 467–475. https://doi.org/10.1007/s40273-018-0610-0

Skedgel, C., & Younis, T. (2016). The politicization of oncology drug funding reviews in Canada. *Current Oncology*, *23*(3), 139–141. https://doi.org/10.3747/co.23.3126

Smith, N., Mitton, C., Hall, W., Bryan, S., Donaldson, C., Peacock, S., … Urquhart, B. (2016). High performance in healthcare priority setting and resource allocation: A literature- and case study-based framework in the Canadian context. *Social Science and Medicine*, *162*, 185–192. https://doi.org/10.1016/j.socscimed.2016.06.027

Srikanthan, A., Penner, N., Chan, K. K. W., Sabharwal, M., & Grill, A. (2018). Understanding the reasons for provincial discordance in cancer drug funding— A survey of policymakers. *Current Oncology*, *25*(4), 257–261. https://doi.org/10.3747/co.25.3993

Stone, D. (1997). Policy Paradox. In *Classics of public administration*. https://doi.org/10.1007/s13398-014-0173-7.2

Vokinger, K. N., & Kesselheim, A. S. (2019). Application of orphan drug designation to cancer treatments (2008-2017): A comprehensive and comparative analysis of the USA and EU. *BMJ Open*, *9*(10). https://doi.org/10.1136/bmjopen-2018-028634

Vreman, R. A., Naci, H., Goettsch, W. G., Mantel-Teeuwisse, A. K., Schneeweiss, S. G., Leufkens, H. G. M., & Kesselheim, A. S. (2020). Decision Making Under Uncertainty: Comparing Regulatory and Health Technology Assessment Reviews of Medicines in the United States and Europe. *Clinical Pharmacology and Therapeutics*, *0*(0). https://doi.org/10.1002/cpt.1835

Appendices

Appendix A Key informant interviews

A.1 Sample Interview Guide

Introduction: The purpose of this study is to understand uncertainty in funding cancer drugs from the perspective of the provincial decision-maker. The cancer space has been rapidly changing and we are interested in how provincial stakeholders are managing the uncertainty that might come with these shifts

The first few questions will ask you about your experience with priority setting processes in your organization. In the middle, I will ask you a few questions related to a specific scenario where you endured a high level of uncertainty in a funding decision for a cancer drug. And finally, the interview will conclude with broad reflections on your experience with uncertainty for funding cancer drugs and any suggestions or recommendations you might have for managing this uncertainty going forward.

Questions:

1. Can you briefly describe your role and responsibilities within your organization?
   Prompts:
   - How long have you been [position] here?

2. Could you describe your role in decision making for funding cancer drugs [in your province]?
3. Could you briefly describe the process for making funding decisions related to new cancer drugs in your organization?
   Prompts:
   - Any formal processes or ethical framework?
   - Is this process the same for all cancer drugs? Including highly expensive drugs?

4. What do you see as the strengths in this process? What do you see as the challenges?

5. The next few questions are going to ask you specifically about uncertainty in decision making for cancer drugs. Can you describe a current or recent decision where you experienced high levels of uncertainty?

   Prompts:

   - What was the drug?
   - Can you describe what happened?

6. What would you characterize as the main sources of uncertainty in this scenario?

   Prompts:

   - If needed probes for other uncertainties: clinical evidence (study design, randomization, surrogate outcomes, lack of long-term efficacy), economic uncertainty (cost-effectiveness, model assumptions), ethical uncertainty (external influences-patient group + clinician advocacy, political influence, pharmaceutical industry pressure), safety and access issues and feasibility concerns (budget impact)

7. Where there any strategies you or your organization used to manage this uncertainty?

   Prompts:

   - What worked well?
   - What did not work well?
   - Statistical techniques?
   - Non-statistical techniques?

8. In hindsight, is there anything you would have done differently?

The next few concluding questions will ask you more broadly about your experience with uncertainty in funding decisions.

9. In your opinion (and as someone involved in the priority setting process), what would you say are the greatest sources of uncertainties when funding new cancer drugs?

   Prompts:

   - If needed probes for other uncertainties: clinical evidence (study design, randomization, surrogate outcomes, lack of long-term efficacy), economic uncertainty (cost-effectiveness, model assumptions), ethical uncertainty (external influences-patient group + clinician advocacy, political influence, pharmaceutical industry pressure), safety and access issues and feasibility concerns (budget impact)

10. What effect do expensive drugs (e.g. new costly immunotherapies, CAR-T) have on uncertainty in funding decisions, if any?

    Prompts:

    - Are the strategies for managing these uncertainties the same? If not, what are they?

11. What effect have national bodies, such as the pan-Canadian Oncology Drug Review (pCODR), pan-Canadian Pharmaceutical Alliance, or Canadian Partnership Against Cancer had on managing this uncertainty?
    - Do they help manage uncertainty? If so, how?
    - Do they contribute to uncertainty? If so, how?
12. In your opinion, what decision making *strategies* would help decrease or manage these uncertainties when funding new drugs?
    - What *components* of decision making help decrease uncertainty?
13. Is there anything else you would like to share on the topic of uncertainty and funding new cancer drugs?
14. Is there anyone else that you might recommend that we can talk to about uncertainty and funding cancer drugs?

A.2 Standard Invitation Message

Monday, January 24, 2020

Dear [participant name]

On behalf of Drs Stuart Peacock and Craig Mitton, along with Dr. Michael Burgess, I am writing to invite you to participate in a pan-Canadian research project that aims to understand the process of policy development and decision making for cancer drugs when there is uncertainty, ambiguity, or controversy related to factors for making informed decisions.

As the pace of regulatory approvals and innovation increases, cancer drugs are being approved off of limited evidence and provincial decision makers face more uncertainty than ever before (for e.g. tradeoffs between high drug prices and benefit). In this rapidly changing regulatory landscape, we feel it is important to understand the sources of this uncertainty and the strategies used to manage these situations in different jurisdictions. A summary of the project findings will be shared with interviewees.

We are conducting interviews with key decision makers across different provinces in Canada (BC, Manitoba, Quebec, Ontario, and Nova Scotia). The reason why you are being invited is that we have identified you as an important stakeholder in priority setting practices within your province.

The interview is expected to take 30-60 minutes of your time and can occur in-person, over the phone, or on Skype. Please 'reply all' to this email to arrange a time to connect. We appreciate your willingness to participant in this study. Your responses will not be attributable to you individually. All findings will be reported in a way that does not identify specific individuals or organizations.

Participation in this study is voluntary. If you choose not to participate, please disregard this message. If you know anyone else in your province that might be able to contribute to this project, please forward this message and ask them to reach out to the project coordinator (Kristina Jenei, contact details below).

Sincerely,

Kristina Jenei
Study Coordinator
School of Population and Public Health
University of British Columbia

A.3 Consent form

Principal Investigators: Dr. Craig Mitton, Centre for Clinical Epidemiology and Evaluation, School of Population and Public Health, University of British Columbia
Dr. Michael Burgess, School of Population and Public Health, University of British Columbia

Co-Investigators: Kristina Jenei, MSc graduate student, School of Population and Public Health, University of British Columbia
Dr. Stuart Peacock, Canadian Centre for Applied Research in Cancer Control, Simon Fraser University

Purpose:
You are being invited to take part in this research study because you have been identified as a 'decision maker' or 'involved in decisions' for funding cancer drugs at a provincial level. We want to learn more about what uncertainties provincial bodies currently face when making decisions about which cancer drugs to fund for reimbursement. We are also interested in priority setting strategies used to manage these uncertainties. We are inviting people like you who have experience in this area to help us learn about these challenges.

Eligible Participants
To be eligible, you must identify as a 'decision-maker' or someone who is 'involved in decisions' in funding cancer drugs at a provincial level.

Voluntary participation
This study is voluntary, and participation is optional. You may choose to stop the interview at any time and skip any question that you do not want to answer.

Procedures
The interview consists of 14 questions (open-ended) and will take a maximum of 60 minutes to complete. The interview will either take place in-person, over the phone, or on Skype – dependant on your location. This study seeks to understand uncertainty in funding cancer drugs from the perspective of the provincial decision-maker. The first few questions will ask you about your experience with priority setting processes in your organization. In the middle, we will ask you a few questions related to a specific scenario where you endured a high level of uncertainty in a funding decision for a cancer drug. And finally, the interview will conclude with broad reflections on your experience with uncertainty for funding cancer drugs and any suggestions or recommendations you might have for managing this uncertainty going forward. Each interview will be audio-recorded with permission. This study will be used for a graduate degree and form part of a thesis (public document).

Study Results
The results of this study will be reported in a graduate thesis and may also be published in journal articles. We will also provide all participants with a brief report of the main study findings.

Potential Risks of the Study

No personal identifiable characteristics will be shared in any project outputs (manuscript, presentation, or report). However, based on the information you provide; your organizational role might be identifiable. You do not have to answer any question you do not want to.

Potential Benefits of the Study
Knowledge regarding how other provinces manage uncertainty with new cancer drugs might help your own provincial strategies.

Payment
We will not pay you for the time you take to be in this study. However, we can reimburse you for any incurred expenses due to this study, if applicable (i.e., transport, parking, etc..).

Confidentiality:
Your confidentiality will be respected. Participants will not be identified by name in any reports or publications of the completed study. Information that discloses your identity or organization will not be released without your consent. All interview recordings will be deidentified and transcribed verbatim. All study files (audio-recorded files, transcripts, field notes, consent forms) will be kept for a period of five years on a secure password-protected folder located on a UBC network at the Centre for Clinical Epidemiology and Evaluation. Only the principal investigator (Dr. Craig Mitton) will have access to them during this time. After five years, the recordings will be destroyed. There are no plans for secondary use of these data. Any paper documents will be identified only by code number and kept in a locked filing cabinet.

Contact:
If you have any questions or concerns about what we are asking of you, please contact the study leader or one of the study staff. The names and telephone numbers are listed at the top of the first page of this form.

Concerns
If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the UBC Office of Research Ethics at 604-822-8598 or if long distance e-mail RSIL@ors.ubc.ca or call toll free 1-877-822-8598.Taking part in this study is entirely up to you. You have the right to refuse to participate in this study. If you decide to take part, you may choose to pull out of the study at any time without giving a reason.

Your signature indicates that you consent to participate in this study.

_____

Participant Signature Date

Printed Name of the Participant signing above

Appendix B pCODR Document Review

B.1 Overview of the drugs included in the document review

Table 2 Overview of the drugs included in the document review

Label	Brand Name	Generic Name	Notification to Implement	Tumour Type	Decision	Trial #
1	Afinitor	Everolimus	16-Dec-16	Endocrine	Conditional	NCT01524783
2	Alecensaro	Alectinib	19-May-17	Lung	No	NCT01871805
3	Avastin	Bevacizumab	08-Apr-15	Gynecology	Conditional	NCT00803062
4	Alecensaro	Alectinib	10-Aug-18	Lung	Conditional	NCT02075840
5	Alunbrig	Brigatinib	19-Aug-19	Lung	No	NCT02094573
6	Avastin	Bevacizumab	20-May-16	Gynecology	Conditional	NCT00976911
7	Avastin (with capecitabine)	Bevacizumab	06-Aug-15	Colorectal	Conditional	NCT00484939
8	Bavencio	Avelumab	06-Apr-18	Skin	Conditional	NCT02155647
9	Cabometyx	Cabozantinib	07-Mar-19	Genitourinary	Conditional	NCT01865747
10	Caprelsa	Vandetanib	17-Apr-17	Endocrine	Conditional	NCT00410761
11	Cotellic	Cobimetinib	18-Jul-16	Skin	Conditional	NCT01689519
12	Cyramza	Ramucirumab	13-Nov-15	Gastrointestinal	Conditional	NCT01170663
13	Erleada	Apalutamide	16-Nov-18	Genitourinary	Conditional	NCT01946204
14	Faslodex	Fulvestrant	16-Feb-18	Breast	Conditional	NCT01602380
15	Ibrance (with Faslodex)	Palbociclib (with Fulvestrant)	21-May-19	Breast	Conditional	NCT01942135

16	Imfinzi	Durvalumab	21-May-19	Lung	Conditional	NCT02125461
17	Keytruda	Pembrolizumab	21-Oct-19	Genitourinary	No	NCT02335424
18	Kisqali	Ribociclib	03-May-18	Breast	Conditional	NCT01958021
19	Lartruvo	Olaratumab	03-May-18	Sarcoma	Conditional	NCT01185964
20	Lenvima	Lenvatinib	09-Aug-19	Gastrointestinal	Conditional	NCT01761266
21	Lonsurf	Trifluridine and Tipiracil	16-Sep-19	Gastrointestinal	No	NCT03306394
22	Lutathera	Lutetium Lu 177 dotatate	19-Aug-19	Gastrointestinal	Conditional	NCT01578239
23	Lynparza	Olaparib	20-Dec-19	Gynecology	Conditional	NCT01844986
24	Lynparza (Resubmission)	Olaparib	05-Oct-17	Gynecology	Conditional	NCT01874353
25	Nerlynx	Neratinib	20-Dec-19	Breast	No	NCT00878709
26	Nexavar	Sorafenib	31-Jul-15	Endocrine	No	NCT00984282
27	Onivyde	Irinotecan Liposome	22-Jan-18	Gastrointestinal	Conditional	NCT01494506
28	Opdivo	Nivolumab	22-Mar-19	Skin	Conditional	NCT02388906
29	Opdivo & Yervoy in combo	Nivolumab & Ipilimumab in combo	15-Dec-17	Skin	Yes	NCT01844505
30	Opdivo in combination with Yervoy	Nivolumab in combination with Ipilimumab	16-Nov-18	Genitourinary	Conditional	NCT02231749
31	Perjeta or Perjeta-Herceptin Combo Pack	Pertuzumab	31-Jul-15	Breast	No	NCT00545688

32	Perjeta-Herceptin Combo Pack	Pertuzumab-Trastuzumab Combo Pack	14-Dec-18	Breast	No	NCT01358877
33	Proleukin	Aldesleukin (IL-2)	08-Jul-15	Skin	Yes	NCT00204581
34	Stivarga	Regorafenib	03-May-18	Gastrointestinal	Conditional	NCT01774344
35	Tafinlar & Mekinist in combo	Dabrafenib & Trametinib in combo	21-May-19	Skin	Conditional	NCT01682083
36	Tagrisso	Osimertinib	21-Jan-19	Lung	Conditional	NCT02296125
37	Tecentriq	Atezolizumab	06-Jul-18	Lung	Conditional	NCT02008227
38	Unituxin	Dinutuximab	10-Apr-19	Neurological	Conditional	NCT00026312
39	Vectibix	Panitumumab	16-Apr-18	Gastrointestinal	No	NCT00364013
40	Verzenio	Abemaciclib	22-Jul-19	Breast	Conditional	NCT02246621
41	Vitrakvi	Larotrectinib	15-Nov-19	Other	No	NCT02122913, NCT02637687NCT02576431
42	Vizimpro	Dacomitinib	17-Jun-19	Lung	Conditional	NCT01774721
43	Xalkori	Crizotinib	07-Jun-19	Lung	Conditional	NCT00585195
44	Xtandi	Enzalutamide	10-Apr-19	Genitourinary	Conditional	NCT02003924
45	Yervoy	Ipilimumab	14-Jan-15	Skin	Conditional	NCT00324155
46	Yondelis	Trabectedin	22-Aug-16	Sarcoma	No	NCT01343277
47	Zykadia	Ceritinib	18-Dec-15	Lung	No	NCT01283516

B.2 Characteristics of the 47 submissions included in the qualitative review

Table 3 Comparison of submissions included in the qualitative review to full dataset

Submission Characteristic	**N (%)**	**N (%)**
Total number	104 (100)	47 (100)
Submission Type		
New Indication	54 (51.9)	25 (52.1)
New Drug	41 (39.4)	19 (41.6)
Resubmission	9 (8.7)	3 (6.2)
Tumour Site		
Lung	25 (24.0)	9 (18.7)
Gastrointestinal	18 (17.3)	7 (15)
Breast	14 (13.5)	7 (15)
Genitourinary	14 (13.5)	5 (10.4)
Melanoma	14 (13.5)	7 (14.5)
Gynecological	6 (5.8)	4 (8.3)
Other	13 (12.5)	8 (16.6)
Final Decision		
Conditionally Recommend	72 (69.2)	33 (70.2)
Do Not Recommend	26 (25.0)	12 (25.5)
Recommend	6 (5.8)	2 (4.2)