HEALTH TECHNOLOGY REASSESSMENT FRAMEWORKS

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LAY ABSTRACT

This thesis focuses on overarching and decision-making assessment frameworks whose purpose is to aid policy-makers in recommending which prescription drugs should continue to be government-funded and/or if modifications to funding should occur. The goal of this work is to; 1) identify challenges and gaps in these frameworks and 2) develop or modify a framework to address findings. This thesis focuses on the Canadian public prescription drug reimbursement environment. Results identified Canadian reassessment framework enhancements which could address challenges to ultimately aid in maintaining financial and institutional stability of public health care systems.

ABSTRACT

BACKGROUND & OBJECTIVES

Overarching and decision-making frameworks may be used to facilitate the evaluation of prescription drug technologies to enable Health Technology Assessment (HTA) agency's reassessment recommendations. The objectives of this thesis were to; 1) identify overarching and qualitative decision-making reassessment framework challenges and methodological gaps and; 2) develop and/or modify a framework to address challenges/gaps. The focus was on Canadian public prescription drug reimbursement with the hope that the findings may inform other jurisdictions.

METHODS

The first paper systematically identified drug disinvestment frameworks to describe framework components, challenges and solutions. A qualitative descriptive study was conducted in the second paper to explore whether a qualitative benefit-risk framework (Universal Methodology for Benefit-Risk Assessment (UMBRA)) could be used or modified to further enable Health Technology Reassessment (HTR) recommendations. The last research paper assessed the Canadian Agency for Drugs and Technologies in Health's (CADTH's) Therapeutic Review Process. Enhancements to this process were developed based on previous research and published frameworks.

RESULTS

Qualitative framework components were identified, disinvestment terms captured and challenges and solutions to drug disinvestment were compiled in Chapter 2. The participants interviewed in chapter 3 recognized that the Therapeutic Review assessment process did not include a qualitative deliberative framework. However, participants did not consider that all steps of the UMBRA framework were transferable to the assessment phase of HTR. Assessment of CADTH's Therapeutic Review process, conducted in Chapter 4, found three areas for process enhancement: Therapeutic Review topic prioritization criteria; a qualitative assessment framework, and; publically accessible mechanisms for decision monitoring and performance measurement.

CONCLUSION

This thesis has identified reassessment framework enhancements that are hypothesized to address HTR challenges and specific solutions to enhance CADTH's Therapeutic Review Framework. Next steps include further evaluation and pilot testing of these proposed enhancements to enable additional Canadian stakeholder feedback.

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my children have learned how hard work pays off and how sacrifice for higher learning should be done in one’s twenties.

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CHAPTER 3

LIST OF ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CDEC	Canadian Drug Expert Committee
CIRS	Centre for Innovation in Regulatory Science
COBRA	Consortium on Benefit-Risk Assessment
EMA	European Medicines Agency
EtD	Evidence to Decision
FDA	Food and Drug Administration
FWG	Formulary Working Group
GRADE	Grading of Recommendations Assessment Development and Evaluation
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
HTIS	Health Technology Inquiry Services
HTR	Health Technology Reassessment
ICER	Incremental Cost Effectiveness Ratio
INAHTA	International Network of Agencies for Health Technology Assessment
MCDA	Multi Criteria Decision Analysis
NICE	National Institute for Health and Care Excellence

OECD	Organisation for Economic Co-operation and Development
OHTAC	Ontario Health Technology Advisory Committee
PBAC	Pharmaceutical Benefits Advisory Committee
pCODR	pan Canadian Oncology Drug Review
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UMBRA	Universal Methodology for Benefit-Risk Assessment
U.S.	United States

PREFACE

This thesis has been prepared in the form of a “sandwich thesis” that includes three scholarly works that either have been published or are under review in a respected journal. One of the papers has been published while two have been submitted for publication. Mary Alison Maloney’s contributions to the three papers within this thesis include developing the research ideas and research questions, performing the analyses, interpreting the results, writing the manuscripts, submitting the manuscripts for publication and responding to reviewer comments. The work in this thesis was conducted between January 2015 to October 2018.

CHAPTER 1: INTRODUCTION

1.1 TECHNOLOGY AND HEALTH CARE DECISIONS

Over the last hundred years, health technological progress has been a driving force in medicine, aimed at improving the lives of many. A health technology is defined as "an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation"[1]. Health technologies include vaccines, pharmaceutical medicines, devices, medical and surgical procedures and organizational systems used in health care[1]. Technologies such as antibiotics, vaccines and insulin have delivered remarkable gains in human health[2]. More recently, technology has helped to expand the number of treatable conditions, target a specific condition or patient type, and increase the options for treatment. The increasing pace of health care demand, innovative options and high-cost of new medicines (e.g. for cancer and rare diseases), in parallel with other factors (e.g. aging populations, rising prevalence of chronic diseases and lower economic growth), have been major drivers in health care expenditure growth in Organisation for Economic Co-operation and Development (OECD) countries and sustainability of health care services[2-4]. With a finite health care budget, policy makers must find a balance between spending on high quality, innovative technologies and on other health care services, ultimately safeguarding the principles of equity, access and choice[2-3].

Policy makers must ensure they pay for technologies that deliver value to patients, physicians and health care systems. However, the determination of value is

ambiguous as it depends on how benefits are defined and measured and the perspective adopted (health care system, patient or societal). The value of a health technology may be examined by three approaches. In an extra-welfarist approach, the benefit is health improvements where a health care system may limit value to health benefits related to incremental costs through a cost-effectiveness or –utility analysis. The welfarist approach focuses on a person's willingness to pay and whether this is higher than technology costs. Finally, an intermediary position adopts a societal perspective focusing not only on health systems and budgets but also on alternative public preferences surrounding costs and consequences[5-6].

In Canada, health care is considered a basic human right requiring the government to equitably fund, at least on a basic level, universal health care to all citizens[7]. However, Canadian universal health care does not cover all prescription drug costs. Instead, Canada has a mixed public-private payer system. Provinces and territories publicly fund prescription drug coverage for vulnerable populations, such as seniors or people on social assistance, and they pay for drugs administered in institutions like hospitals. In 2016, Canadian health care public drug program spending was approximately 9.2 billion dollars, a number that has increased steadily year over year[8]. This public program pays for about forty percent of prescription drug costs while the other sixty percent is paid either by private insurance companies (including employee drug plans) or by patients' themselves[8].

Canadian prescription drug costs are the second highest in the industrialised world, after Americans. These drug costs per person have now increased at a rate that has outpaced that for hospitals or physicians and are expected to continue to increase faster than any other category within the public health program[8].

Consequently, Canadian policy makers must make trade-off decisions between currently listed prescription medicines and new, potentially costly medicines. To successfully accomplish this, the right policy settings must be in place to maximize the value derived from listed medicines, to be attuned to fair and equitable distribution of medicines across disease types and to help to ensure the financial and institutional sustainability of the public health care system[2].

1.2 LIFECYCLE OF A PRESCRIPTION DRUG TECHNOLOGY

A prescription medicine progresses through a life cycle in stages. First, the development phase and registration. In the development phase, a drug is studied in animal and human models to demonstrate efficacy and safety for a particular use(s). These studies and additional data are then submitted to and reviewed by Regulatory agencies (e.g. Health Canada) who decide if a drug is allowed to be released to the market. Once a drug is registered for a particular disease indication(s), it enters the post registration and reimbursement phase. In Canada, to gain public reimbursement, a manufacturer must apply for a reimbursement recommendation through a Health Technology Agency, e.g., the Canadian Agency for Drugs and Technologies in Health (CADTH), who conducts an evaluation of a drug's clinical, economic, and patient

evidence. This evaluation provides reimbursement recommendations to Canada's federal, provincial, and territorial public drug plans, with the exception of Quebec. (see Section 1.3 below). Price negotiations between the manufacturer and provinces/territory drug plans follow to determine final reimbursement criteria and price. The introduction and growth phase follows, where a drug is distributed through reimbursement criteria (public or private) or out-of-pocket sales. In the mature phase, patents usually prevent generic manufacturers from replicating a brand name drug. Doctors and pharmacists help inform patients of their treatment choices, providing options and information on drug effectiveness, safety and costs[9]. During this phase, a drug's use may be further expanded by regulatory and reimbursement indication extension. To gain market access, new indications must follow the same process as outlined above of first gaining Health Authority approval and then going through a reimbursement/pricing process. As time passes, documentation collects of a drug's effectiveness and adverse event profile and the drug's benefit-risk assessment and the resulting safety profile continues to be revised through Health Authority updates to a products' labeling. Newer and potentially better treatment alternatives can enter the market creating an evolutionary process of selection and adaptation[10]. In addition, brand name drug patent expiry results in a loss of market exclusivity to generic competitors. The price for brand name drugs can fall by more than 70% with generic entries of the same active ingredient(s)[11-13]. This last drug lifecycle stage is called the declining phase due to competition between branded and generic drugs and therapeutic substitution[14]. Decommissioning and obsolescence is an end-point of all technology and can occur in the context of an indication, treatment, or clinical situation.

1.3 HEALTH TECHNOLOGY ASSESSMENT

A prescription medicine can improve the health, quality and length of life of a patient. Health care providers and patients value and expect access to new and improved medicines. However, suboptimal use of a medicine (e.g. misuse, underuse or overuse) can both affect the health of the patient and the efficiency of the health care system. The adoption of a medicine, while still ensuring value for money from a system perspective, can be challenging to health care system decision-makers (payers). Health Technology Assessment (HTA) is a comprehensive form of policy research used in Canada and around the world to inform decisions on whether, when and how a prescription medicine should be publicly reimbursed to efficiently and equitably address a population's health needs[15].

Although many definitions of HTA exist, for the purpose of this dissertation, HTA is defined as "a multi-disciplinary process of policy analysis that examines the medical, economic, social, and ethical implications of the incremental value, diffusion and use of a medical technology in health care"[16]. HTA seeks to determine a technology's optimal use, appropriate placement amongst care options and ultimately to target that patient population who will benefit from a treatment. In Canada, HTA focuses on clinical effectiveness, safety and cost effectiveness, as well as, other short- and long-term social (e.g. ethical, societal and legal) consequences of reimbursing a medicine within the health care system[17]. HTA for prescription medicines is built on a formal assessment of the available efficacy and safety data of a new technology compared to the available data of any relevant comparators (including comparators in the same

drug class, different drug classes used to treat the same disease and even alternative and nonpharmacologic comparators). This involves the collection and summary of data from available clinical trials (e.g. randomized clinical trials) as well as a systematic review of published literature. Data is commonly assembled into evidence tables, which describe the trial characteristics and results. Synthesis may also involve indirect comparison of clinical/safety outcomes across treatments. Decision-makers will assess the strength of the clinical evidence and consider how well these outcomes will translate into real-world effectiveness. To further inform understanding of a product's overall benefit-risk profile, an integration across benefit-risk outcomes must occur. This is frequently done quantitatively through cost-effectiveness analysis where the cost of a medicine is considered in the context of the benefits delivered[18]. Other HTA considerations include the disease burden (including the disease impact on patients and the extent of the disease within the population) and unmet need in the population of interest, as decision-makers need to understand how widely a new drug will be used within a given population[18].

HTA outcomes inform health care payers, providers and employers on whether a medicine could be included in health benefit plans or disease management programs. These outcomes help inform a health payer of comparative clinical and economic benefits and risks of reimbursing (how much and when to pay for a medicine under what conditions) a medicine. Actual approval of the technology for implementation usually resides at the local level within the specific health care provider infrastructure, hospital or health region (HTA user). For instance, Canadian provinces and territories

must contextualize the information provided in a CADTH recommendation report by considering local population needs, local effectiveness, local costs and local resources (sometimes through additional analysis, e.g. budget impact analysis).

1.4 CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH

Established in 1989, the Canadian Agency for Drugs and Technologies in Health (CADTH) is a federal, independent, not-for-profit agency funded by Canada's federal, provincial (excluding Quebec) and territorial governments. CADTH is the only national HTA organization in Canada. CADTH's activities are aligned with the Government of Canada's objective to increase access to, and use of, relevant evidence to inform the optimal and cost-effective use of health technologies[19]. CADTH has bucketed their services into 1) Drug Reimbursement Recommendations 2) Health Technology Management Program and 3) Scientific Advice[20]. Once Health Canada (Canada's Regulatory Authority) approves a new drug or existing drug for a new indication for use in Canada, public drug plans must determine if they will fund this new drug or new indication, and if so, determine a price and reimbursement conditions. To aid health care decision-makers, CADTH conducts evaluations of the clinical, economic, and patient data on drugs, and uses this evaluation to make reimbursement recommendations for a new drug or indication. The pan Canadian Oncology Drug Review (pCODR) provides recommendations for oncology drugs while the Common Drug Review (CDR) provides recommendations for all other prescription medicines. Canada's federal, provincial and territorial public drug plans, with the exception of Quebec, review these recommendations, to guide drug funding decisions[20].

The Health Technology Management Program includes five different CADTH services. Three of these services are focused on providing evidence to support Canadian decision-making about "health policy and purchasing, service management, and clinical practice"[20]. The amount of rigour applied to each service varies. For instance, the Rapid Response Service addresses questions related to prescription drugs, diagnostic tests, devices and medical procedures through six different report types ranging from producing a reference list to a rapid health technology assessment[21]. The HTA Service produces health technology assessments or reassessment reports of clinical effectiveness and/or cost-effectiveness evaluations, and "may include the ethical, legal, and social implications of health technologies on patient health and the health care system"[22]. These reports focus on topics of pan-Canadian interest. Finally, the Optimal Use Service produces the most rigorous reports. These reports are similar to HTA Reports but include a) ethical, legal and social implications b) recommendations from a CADTH expert committee and c) implementation tools and other decision aids to assist policy-makers and clinicians[23]. Optimal Use Reports are meant to not only inform policy and practice decisions, but to encourage the appropriate use of health technology at any point in the lifecycle. Therapeutic Reviews fall within this category. These reviews focus on a therapeutic category or a class of drugs[24]. The other two services within the Health Technology Management Program are scanning services. The Environmental Scanning Service utilizes literature searches and networks of health care stakeholders to produce reports which help to inform how new and existing technologies are being used and reimbursed[25]. The Horizon Scanning Service scans health information sources and works with health care

professionals, patients and industry to identify and publish information on new and emerging health care technologies[26].

1.5 HEALTH TECHNOLOGY DISINVESTMENT/REASSESSMENT

Rigorous processes (e.g. HTAs) have been established to ensure new technologies are clinically and cost-effective, safe and, if introduced, will result in better health outcomes[27-28]. As HTA developed, standard methods, process frameworks, and peer-reviewed publications were created[29]. HTA processes today incorporate "the contextual situation of a technology and increase the capacity to evaluate comparative effectiveness, cost-effectiveness, and overall value with a consideration of ethical, legal, and social issues" [29]. However, many drug technologies available today 1) were not subject to such processes as methodologies were not established or not applied[27, 30-32] 2) have unknown clinical and cost-effectiveness[33] 3) have studies which contradict the original benefits [33-35] 4) are used inappropriately or alternative technologies are available with greater benefits[36]. To reduce costs and maximize outcomes, focus has turned to identifying, prioritizing, reducing and/or withdrawing ineffective, wasteful, redundant or inappropriate drug technologies. The term disinvestment can be used to denote "the processes of (partially or completely) withdrawing health resources from existing health care practices, procedures, technologies, or pharmaceuticals that are deemed to deliver little or no health gain for their cost, and thus are not efficient health resource allocations"[37-39]. By disinvesting in inefficient technologies, an opportunity presents itself to reinvest in safer, more effective or more cost-effective substitutes[29].

The concept of Health Technology Reassessment (HTR), incorporates a broader perspective of both disinvestment and reinvestment through an evidence-based process preceding an informed decision. HTR "involves a structured, evidence-based assessment of the clinical, social, ethical and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives[29]. HTR is more complex than HTA given the inherent lack of comparison data between alternatives, the number of alternatives that are included and the need to demonstrate the lack of benefit or harm should a recommendation further restrict technology use. Reassessment requires an even greater systematic assessment of social values, patient preferences, ethics, and stakeholder requirements[40]. An HTR outcome could be a change in scope-of-use (increased or decreased investment), removal of funding, or no change in use[41].

A lifecycle approach of screening new drug technologies or indications to the reassessment of drug technologies at points during their marketed lifecycle (e.g. mature phase and declining phase) may improve funding equilibrium[29]. Methodologically, overarching frameworks are being developed and/or used, to conduct HTR[42].

1.6 HEALTH TECHNOLOGY REASSESSMENT FRAMEWORKS

Frameworks, which use a set of underlying principles, are commonly adopted to provide an overarching, stepwise structured approach, within which reside processes to be carried out to achieve the framework's objectives[43, 44]. Overarching,

disinvestment (or reassessment) frameworks are available and involve a series of process steps. First, low-value or sub-optimal technologies are identified within the health care system. Prioritization is required if a number of technologies are identified. Assessment follows and can include data collection, interpretation, organization and summary to determine the clinical, economic, social and ethical effects of a technology's use. The assessment stage frequently adopts HTA methodology to develop a recommendation for a technology and its comparators. Finally, to ensure HTR recommendation outcomes are realized a recommendation/decision dissemination stage is required, ideally using knowledge translation, to shift recommendations into practice[40, 45-46]. However, decision-making frameworks used to consider benefits and risks in the HTR assessment phase to enable recommendations are less evident.

Decisions surrounding benefit-risk balance are subjective in nature, as this requires judgement about the relevance of the available (and unavailable) information to the decision or recommendation to be made. Thus, the answer to a benefit-risk decision is dependent on the perspective that is adopted for the decision and the processes and criteria used to assess the trade-off between the benefits and risks to reach that decision[44]. Frameworks can be classified into quantitative and descriptive (qualitative and semi-quantitative) approaches. Each type of approach is used in the assessment phase to enable benefit-risk decisions. Quantitative frameworks, such as cost effectiveness modeling using quality-adjusted life years, can assess and integrate multiple benefits and risks criteria simultaneously, and compare different options[44].

Qualitative frameworks do not necessarily perform an integrated benefit-risk assessment (as quantitative frameworks do) but they do accommodate the inclusion of various benefit-risk quantitative assessment tools and outcomes and provide structured support to frame decision problems to ensure a better definition and transparency of that decision context[44]. These frameworks and underlying processes have been found to enhance the clarity of the decision-making process by helping to set internal standards and consistency. They encourage assessment and discussion around evidence and the articulation of benefit-risk decisions through consistency of communication and visualization of benefits and risks to stakeholders[43,47]. HTA agencies must deliberate, during the assessment phase, on the trade-offs between the benefits and risks of a specific HTR recommendation. With increasing health care costs and patient exposure to drug technologies, effective overarching HTR frameworks and embedded qualitative assessment decision-making frameworks, which enhance priority setting and decision-making are becoming critical to allocate limited resources.

1.7 OUTLINE OF THE THESIS

This sandwich thesis includes three papers focused on overarching and qualitative decision-making frameworks whose purpose is to facilitate the evaluation of drug technologies to enable HTA agency's disinvestment/reassessment recommendations. The objectives of this work are to: 1) identify overarching and qualitative decision-making reassessment framework challenges and methodological gaps; and, 2) develop and/or modify a framework to address challenges/gaps. This thesis focuses

on the Canadian public prescription drug reimbursement environment. This is an important endeavour for two reasons. First, the concept of HTR is not widely practiced and as such, further research is needed to develop consistent and substantiated HTR frameworks and processes. Second, identification of HTR challenges may help generate solutions for qualitative framework improvements, ultimately aiding in the maintenance of financial and institutional stability of the public health care system. The first paper encompasses a systematic literature search to review drug technology frameworks (including types and disinvestment terms and definitions), framework components as well as challenges and solutions (Chapter 2). The next paper is a descriptive study to determine if a qualitative benefit risk framework could be used or modified to further enable HTR assessment for prescription medicines. The Universal Methodology for Benefit-Risk Assessment (UMBRA) framework was chosen. Health Technology Agency assessors' experiences and insights were gathered and study participants were asked to compare the UMBRA framework to an existing Canadian process for HTR (CADTH's Therapeutic Review process) (Chapter 3). The last paper (Chapter 4) assesses a current HTR framework (CADTH Therapeutic Review process) to determine if it 1) includes HTR framework process components detailed in Chapter 2, and 2) embodies the ethical concepts of CADTH's Guiding Principles and the Accountability for Reasonableness Framework. HTR framework enhancements, based on this assessment and previous research, are provided. The final chapter (Chapter 5) summarizes this research, provides major contributions and future areas of study.

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CHAPTER 2: DRUG DISINVESTMENT FRAMEWORKS: COMPONENTS, CHALLENGES, AND SOLUTIONS

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INTRODUCTION

This chapter was designed to systematically identify, retrieve and review available literature pertaining to health technology disinvestment for drug technologies and containing information relevant to the practice or theory of disinvestment of drug technologies. The search included available literature from January 1, 2000 until November 14, 2015. Data was extracted and synthesized to capture disinvestment terms and definitions, disinvestment framework components as well as disinvestment challenges and solutions. Disinvestment framework components included a review of drug identification and prioritization criteria, disinvestment methodologies and stakeholder information dissemination strategies. It was hoped that this research would identify framework challenges and methodological gaps, that if filled through future framework development, could address disinvestment challenges and help allocate limited resources.

ABSTRACT

Objectives: Value assessments of marketed drug technologies have been developed through disinvestment frameworks. Components of these frameworks are varied and implementation challenges are prevalent. The objective of this systematic literature review was to describe disinvestment framework process components for drugs and to report on framework components, challenges and solutions.

Methods: A systematic literature search was conducted using the terms: reassessment, reallocation, reinvestment, disinvestment, delist, decommission or obsolescence in MEDLINE, EMBASE, NLM PubMed, the Cochrane Library, and CINAHL from January 1, 2000, until November 14, 2015. Additional citations were identified through a gray literature search of Health Technology Assessment international (HTAi) and the International Network of Agencies for Health Technology Assessment (INAHTA) member Web sites and from bibliographies of full-text reviewed manuscripts.

Results: Sixty-three articles underwent full text review and forty were included in the qualitative analysis. Framework components including disinvestment terms and definitions, identification and prioritization criteria and methods, assessment processes, stakeholders and dissemination strategies, challenges, and solutions were compiled. This review finds that stakeholders lack the political, administrative and clinical will to support disinvestment and that there is not one disinvestment framework that is considered best practice.

Conclusions: Drug technology disinvestment components and processes vary and challenges are numerous. Future research should focus on lessening value assessment challenges. This could include adopting more neutral framework terminology, setting fixed reassessment timelines, conducting therapeutic reviews, and modifying current qualitative decision-making assessment frameworks.

Keywords: Technology assessment, Disinvestment, Budgets, Reassessment

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Manuscript: Drug Disinvestment Frameworks: Components, Challenges, and Solutions

Internationally, strained economies have resulted in limited health care system resources. To maximize investment, health technology assessment (HTA) agencies, governments, policy makers, and academics are exploring the development of decision-making frameworks to value marketed drug technologies. The premise of these frameworks is to proactively conduct an evidence-based HTA of a drug technology to inform use by identifying "low-value" technologies to allow for reallocation of resources to technologies considered "high-value". The term "disinvestment" is commonly used within the literature to describe decision-making frameworks that value marketed technologies. Although, the concept of disinvestment also includes reallocation of funding to value-added technologies, the literature rarely reviews the process and outcome of reallocation following a disinvestment decision.

For ease of review, this study will adopt the term disinvestment to reflect HTA frameworks that value marketed technologies. It is important to consider the context of these frameworks, as the emphasis should not be placed on cost-savings but instead on optimizing the use of a drug technology, thereby improving the efficiency and quality of care within a public health care system (1;2). Disinvestment frameworks value marketed drug technologies that were not initially subject to rigorous HTA or after initial prescription medication coverage approval as a matter of course, due to new clinical/safety/cost data or comparator changes.

Disinvestment frameworks include some or all of the following process steps: identification and prioritization, assessment (including interpretation, organization and summarization of data and decisions), and decision dissemination strategies. However, the components within these steps and methodology associated with each step differs within the literature.

The objective of this study is to systematically review disinvestment framework process components for drugs and to report on framework components and disinvestment challenges and solutions. In doing so, it is hoped that this information can highlight methodological gaps and better inform the development of applicable frameworks to value marketed drugs.

METHODS

Literature Search Strategy

A literature search strategy was developed and the following bibliographic databases searched: MEDLINE, EMBASE, NLM PubMed, the Cochrane Library, and CINAHL. The search strategy was comprised of both controlled vocabulary and keywords as follows: reassessment, reallocation, reinvestment, disinvestment, delist, decommission, or obsolescence. The search was limited to English language documents only available from January 1, 2000, onward, and was completed on November 14, 2015. In addition, a gray literature search was completed. Web sites of organizations listed as members of the International Network of Agencies for Health Technology Assessment (INAHTA) and Health Technology Assessment international (HTAi) were searched. References

from the included papers and gray literature were searched to identify further items for consideration. Details of the literature search strategy may be found in Supplementary Table 1.

Selection Criteria

Titles and abstracts retrieved from the literature search were screened for relevance using a screening form. Literature was included if it pertained to health technology disinvestment for drug technologies and contained information relevant to practices or theory of disinvestment of drug technologies. Literature was excluded if it was focused on budgeting or economic analysis without context to disinvestment or reported on case studies without context to a model and/or framework or program for disinvestment. The full text of any relevant items passing title/abstract screening (Level 1) was retrieved. Full-text review was conducted in duplicate with a second reviewer who had no direct involvement in this research. Discrepancies were discussed, consensus was achieved, and a Cohen's kappa statistic was calculated.

Data Extraction

The author extracted relevant data from the selected literature using a standard extraction form (Supplementary Table 2) which was designed *a priori*. Data extracted included: focus and summary of the key messages; methods; country of focus; disinvestment terms and definitions; identification and prioritization criteria and methods; assessment process; stakeholder engagement and delivery arrangements; and

disinvestment challenges and solutions. A second reviewer verified the data on 20 percent of the extraction forms.

Quality Assessment

A modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach was used as the literature selected is descriptive, fact based and/or theoretical in nature.

Data Synthesis

The characteristics of included articles were summarized using a narrative synthesis. Each of the selected articles was reviewed for terms describing an evidence-based assessment of a drug technology. These terms, their definition and the number of articles referring to a specific term were recorded. Common identification and prioritization criteria or methods were grouped with reference to their use and the number of articles referencing each term were noted. Disinvestment assessment methods and stakeholder information dissemination strategies were grouped and references captured. Finally, disinvestment challenges and solutions were organized by key theme and specific components captured.

RESULTS

The systematic literature search identified 4,774 articles after duplicates were removed. Of these, 4,711 were excluded after initial screening and 63 progressed to full-text article review. The full-text review excluded twenty-three articles. Nine articles were

excluded as they did not refer to disinvestment for drug technologies; twelve were excluded as they contained no information relevant to practices or theory of disinvestment of drug technologies; and two were excluded as they reported on case studies without context to a model and/or framework or program for disinvestment.

Forty articles met the selection criteria and were included in this systematic review. A Cohen's kappa statistic of 0.83 was found for interrater reliability of the inclusion of articles for data extraction. No discrepancies in data extraction were found. A PRISMA flowchart (3) (Figure 1) details the number of publications selected through each stage of the systematic review.

Study Characteristics

Supplementary Table 3 provides a summary of the study characteristics. Methods used in the selected literature varied. Four articles contained systematic reviews; three articles were mixed methods, two articles were qualitative studies; a survey was conducted in one article; three articles focused on guideline development; four articles were reviews (but not systematic reviews); fifteen papers were discussion/commentary or position papers, two were PowerPoint presentations; and six were content from Web sites. Supplementary Table 3 contains additional study information including the focus of the citation, a description of the paper, and the country(ies) referenced within the literature.

Disinvestment Terms and Definitions

Disinvestment terms, their definition and the number of articles referring to a specific term may be found in Table 1. The most commonly used term, referenced twenty times, was “disinvestment”. Consensus seems to have settled around the definition of disinvestment originally proposed by Elshaug et al. (4) with eleven other references also defining disinvestment as “the processes of (partially or completely) withdrawing health resources from existing health care practices, procedures, technologies or pharmaceuticals that are deemed to deliver little or no health gain for their cost, and thus are not efficient health resource allocations” (1;5-14). The other term used, also specific to a disinvestment outcome, was “obsolete/obsolescence” (referenced 5 times) (6;10;15-17). *Obsolescence* was generally defined as the end of the lifecycle of a technology when it has been superseded by another alternative. There was one reference to “appropriateness”. *Appropriateness* is “the proper or correct use of health services, products and resources” (27), which is juxtaposed to terms such as disinvestment and obsolescence. Finally, *reassessment* (referenced three times) is defined as “a structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives” (2;17;18).

Frameworks for HTA Disinvestment

Various framework components for the identification, prioritization, assessment, and decision dissemination strategies have been proposed or are in use. Publically available, passive disinvestment lists are meant to spark discussion and action through

a reduction in the use of identified low-value tests and treatments. Passive disinvestment lists are generated through national speciality societies experience (e.g. “Choosing Wisely US or “Choosing Wisely Canada”) (8;13), during clinical guidance development (e.g., the National Institute for Health and Care Excellence [NICE] searchable database of “do not do” recommendations) (2), and through scanning Cochrane reviews (e.g., Cochrane Quality and Productivity Topics available publically through the NHS Evidence Web site) (2;19;20).

Conventional health technology assessment frameworks for evaluation are being used infrequently for disinvestment decisions. Examples include NICE’s health technology appraisal system (20) and the Pharmaceutical Benefits Advisory Committee’s (PBAC) explicit criteria for removing drugs from the Pharmaceutical Benefits Scheme (21). Finally, frameworks such as the Ontario Reassessment Framework (22) and two Spanish frameworks: “Guidelines on the Identification, Prioritising, and Evaluation of Obsolete Technologies” and “Guideline for Not Funding Health Technologies” (GuNFT tool) (23) have been developed. Little information is available regarding the use and utility of these frameworks.

Identification and Prioritization Criteria and Methods

Drug technology disinvestment criteria for identification and prioritization were numerous and varied by author and framework. However, almost all criteria were developed based on the concept of disinvestment or obsolescence and, therefore, focused on risk to the patient (safety concerns) or lack of improvement to health

coupled with a high budget impact or failure to show cost-effectiveness. The most prevalent criteria for drug identification were unacceptable potential risk for patient (6;7;9;10) and evidence that the technology causes overall worsening of health (6;7;9).

There lacked a clear differentiation between the actions of identifying or prioritizing a drug for disinvestment as often the same criteria could be found as an indicator for identification, prioritization or both within the literature. Most frequently cited criteria for identification or prioritization or both included: no scientific clinical evidence proving a technology improves health (6;7;9;10;24), lack of disease burden (7;9;10;16;24;25), high budget technologies (9;10;16;24-26), and lack of cost-effectiveness (7;9;10;13;16). Most prevalent prioritization criteria were safety concerns (7;10;16;27) and impact to public health (7;10;18). Supplementary Table 4 outlines identification and prioritization criteria found through the systematic review.

Methods found for identification of drugs for disinvestment almost always involved a search or monitoring and review of publically available literature and databases (10;16; 19;21;23;25;26;28). Consultation with clinical speciality groups, clinicians, health care administrators, and funders (6;9;10;16;25;26), and assessment of variation in technology use (e.g., geographic, provider variation in care) (9;10;23;25;26;27) were suggested methods for identification or prioritization or both by many authors. Identification and prioritization methods may be found in Supplemental Table 5.

Disinvestment Assessment Methods

Little information on specific disinvestment assessment methods used to finalize a drug technology disinvestment decision could be found in the selected articles. Authors have provided high-level direction on methods to measure costs, benefit, and value and reference standard HTA evaluation methods. These include evaluating the: disease burden, safety, clinical effectiveness, health gains, cost-effectiveness, opportunity costs (29) and overall value (including ethical, legal and social issues) (30). Noseworthy and Clement (31) indicated that a review must contain an assessment of feasibility and an analysis of consequences, intended and unintended.

Stakeholders and Decision Dissemination Strategies

Politicians, clinicians, speciality societies, health system leaders, industry and patients are critical components of any disinvestment process. The literature identified that a transparent engagement and consultation process is needed (1). Decision makers and experts should be actively involved in each step of the disinvestment process to identify candidate technology for disinvestment, to continually improve the methods and infrastructure for disinvestment, and to ensure the feasibility and barriers to disinvestment decisions have been carefully considered (26).

Both passive and active methods for information dissemination were discussed by Garner and Littlejohns (1). Passive dissemination strategies included publication of recommendations on searchable databases or Web sites to encourage stakeholder change (1). Slightly more active dissemination strategies included incorporating a

decision in clinical guidelines or utilizing decision support tools (26). Finally, active disinvestment methods, suggested in the literature, included changes to formulary and/or coverage reimbursement listings (26).

Disinvestment Challenges and Solutions

Disinvestment challenges were prevalent and detailed within the literature while solutions were broad and hypothetical (Table 2). Stakeholders lack the political, clinical and administrative will to support disinvestment (4;6;9;13;17;21). Without perceived value or benefit, stakeholders are resistant to losing access to a drug therapy that may still provide some benefit (4;6;9;13;17;21). As an outcome, stakeholders are hesitant to allocate resources to disinvestment. Without resources, solutions such as methodology and framework development, training of health technology assessors, incentives to clinicians and patients, research to fill data gaps and pilot programs are not possible and a disinvestment strategy will not progress.

Confounding concept uptake even further are the country/region specific complexities of decentralized health care structures, variability in insurance services, purchasing processes for drugs and lack of agreed international disinvestment methodology (4;6;9; 13;29). Solutions such as multi-stakeholder agreements on health technology processes, international collaboration, and transparent, adaptable disinvestment models require political and administrative will fueled by a perception of value (2;9;10;15).

DISCUSSION

Practical solutions are needed to optimize the use of marketed drug technologies due to shrinking or slow-growing budgets. With greater emphasis on the value for money, there has been an increased interest and study of frameworks which can facilitate disinvestment. This systematic literature search aimed to review drug technology frameworks and to report on the framework components, challenges and solutions as found within the literature. In doing so and reporting on the result findings, three broad areas for further study are described below.

Disinvestment and Cost Containment

Country initiatives have focused on “disinvestment” of drug technologies, where costs are reduced by partially or completely withdrawing a drug technology from a health system. The terminology chosen (such as disinvestment) to describe the assessment of a marketed drug can influence stakeholder engagement in the process by inferring a foregone process conclusion (2). The use of more decision neutral terms, such as “reassessment,” could improve stakeholder (clinicians, patients, industry) engagement. Reassessment, as defined by MacKean et al., focuses on optimal use and achieving value for money (2). Health Technology Reassessment (HTR) may result in numerous economic re- or dis- investment outcomes, which include stopping funding (disinvestment), partial disinvestment (narrowing what is paid for), reinvestment (broadening what is paid for), or no change in use (2). By using terms that suggest the possibility of broader outcomes, collaboration and partnerships between stakeholder (clinicians, patients, industry) and governments (policy makers and HTA agencies)

could improve. This in turn could lead to multi-stakeholder data generation (e.g., registries, clinical trials) and further political and administrative will.

Identification and Prioritization: Timing and Engagement

The reviewed literature included a variety of identification and prioritization criteria focused mainly on patient risk, high budget impact, and/or lack of cost-effectiveness. Criteria are aligned with the purpose of disinvestment initiatives, that is, one of rationalism where costs of inefficient drug technologies are removed from a finite health system budget to allow for investment in technologies with greater clinical or cost-effective outcomes (23). Even though disinvestment identification and prioritization criteria are increasingly being adopted internationally, there still exists a question on timing, when and how often technologies are reviewed for disinvestment. In addition, there is a lack of researcher, clinician, consumer and policy-maker engagement in working together to realize rationalism (6;9;13;15;26).

Two actions might be considered by HTA agencies to meet these challenges. First, HTA agencies could adopt fixed time periods for HTR (for instance, 5 years after a product is launched on a market, or when new comparators are being assessed) (32). This would eliminate the need for drug technology identification and prioritization reassessment criteria. A standardized process could also incentivize invested stakeholders, such as industry, to generate additional research to fill data gaps or to collect and contextualize data (1;13;21;24). Alternatively, if this is seen as too resource intensive for government funded budgets (an additional challenge to the concept of

disinvestment), an efficient and transparent identification and prioritization process needs to be validated through transparent and collaborative methods by country. After prioritizing a drug for disinvestment, stakeholder engagement could be increased by conducting a therapeutic review reassessment of all drugs within that of the prioritized drugs therapeutic category. In doing so, disinvestment recommendations may result, but at the same time, reinvestment in other drug technologies is also a possibility.

Lack of Tailored Evaluation Frameworks

The valuation of marketed drugs requires a process that is tailored to the assessment, adaptable, transparent, and makes reasoning explicit but also identifies limitations and uncertainty of the evidence and has a structured approach to decision dissemination and implementation (9;10;14;15;26;29). Qualitative assessment frameworks have been developed which frame decision problems through a structured, consistent approach to decision making by "facilitating the selection, organization, summarization, and interpretation of data and preferences relevant to the decision" and aid decision documentation and communication (2). This systematic literature review confirms that, to date, there is not one universally accepted qualitative assessment framework that meets the desired criteria mentioned above or that has been widely adopted for the purpose of drug technology disinvestment.

However, regulatory agencies, such as the European Medicines Agency (EMA) (33) and U.S. Food and Drug Administration (FDA) (34) have now developed and are using qualitative assessment frameworks to aid in benefit-risk decision making and decision

dissemination. One area of future research is to consider adapting a qualitative assessment framework used by Regulatory Authorities for marketed drug health technology reassessment to aid in decision-making transparency and information dissemination.

LIMITATIONS

Traditional systematic literature searches for terms related to disinvestment have been documented to have high sensitivity and poor specificity (7;21-24). This research encountered the same limitation, where the magnitude of search results was high and required extensive review to target relevant articles. In addition, there is a documented publication bias as government and payer disinvestment initiatives are generally absent from publication (7). This bias made it difficult to ensure all current frameworks, their components, challenges and solutions were documented within this review. Only disinvestment frameworks for drug technologies were targeted for review. At times, the literature was not explicit as to whether a framework was meant to review drug technologies, therefore, some frameworks included in this review may not be proposed or in use with drug technologies.

CONCLUSIONS

Disinvestment components and methods for identifying and prioritizing technologies, undertaking assessments and disseminating review outcomes vary within the literature and challenges are prevalent. This paper suggests that stakeholder engagement could be increased through refocusing the terminology from disinvestment to reassessment or

another neutral term. Increased engagement may also be realized through the adoption of fixed time HTRs or therapeutic reviews. Decision-making frameworks developed to assess the benefit-risk of drug technologies within the regulatory context may be appropriate, if modified, for use in the health technology assessment phase of marketed drugs. These frameworks, address some of the challenges cited in the literature. For instance, they allow for stakeholder involvement, encourage transparent processes, allow for flexibility and uncertainty and can be used to define and communicate the context and drivers of a decision. The ultimate goal of a reassessment framework should be to inform the optimal use of drug technologies to improve the efficiency and quality of care within a public health system.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: https://doi.org/10.1017/S0266462317000277

Supplementary Table 2: https://doi.org/10.1017/S0266462317000277

Supplementary Table 3: https://doi.org/10.1017/S0266462317000277

Supplementary Table 4: https://doi.org/10.1017/S0266462317000277

Supplementary Table 5: https://doi.org/10.1017/S0266462317000277

CONFLICT OF INTEREST

This work has been completed in partial fulfillment of the requirements for Mary Alison Maloney's PhD degree in Health Research Methodology at McMaster University. In addition, Mary Alison Maloney works full-time as the Vice-President of North America Consumer Health Regulatory Affairs for Bayer HealthCare LLC. Dr. Lisa Schwartz's

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[1] Please note that References 35-45 are cited on Supplementary Table 3.

Table 1: Definitions of Disinvestment Terms

Term	Definition	Number of references
Appropriateness (27)	Appropriateness: In the context of health care appropriateness is the proper or correct use of health services, products, and resources. Inappropriate care, in contrast can involve overuse, underuse, and/or misuse of health services, products and resources. Appropriateness is primarily determined by analyses of the evidence of clinical effectiveness, safety, economic implications, and other health system impacts. The practical application of appropriateness is made when these analyses are qualified by a) clinician judgement, particularly in atypical circumstances, and b) societal and ethical principles and values, including patient preferences.	1
Disinvestment (35)	A common element of all definitions of disinvestment is that the subject of disinvestment is considered to be not cost-effective. Cost-effectiveness is a relative description that is made compared with a specific alternative. Thus, disinvestment can apply equally to interventions that are clearly ineffective or harmful, as it does to interventions that are beneficial, and once shown to be cost-effective but are no longer compared with new competing approaches (obsolescence) (3). Similarly, it can apply when an intervention is used more often than is indicated (overuse) (1) or for purposes other than those for which it was originally intended in the absence of evidence	1

Term	Definition	Number of references
	that doing so is clinically effective and cost-effective (misuse) (1).	
Disinvestment (1; 4-14)	The processes of (partially or completely) withdrawing health resources from existing health care practices, procedures, technologies, or pharmaceuticals that are deemed to deliver little or no health gain for their cost and, thus, are not efficient health resource allocations.	12
Disinvestment (29)	The complete or partial withdrawal of resources from health care services and technologies that are regarded as unsafe, ineffective or inefficient, with those resources shifted to health services and technologies with greater clinical or cost-effectiveness.	1
Disinvestment (21)	Processes by which a health system or service removes technologies, without necessarily replacing them.	1
Disinvestment (24)	An explicit process of taking resources from one service to use them for other purposes that are believed to be of better value.	1
Disinvestment (36)	Withdrawal of funding from existing treatments.	1
Disinvestment (23)	Resource allocation decisions based on withdrawing funding from no or low added-value health interventions, freeing up these resources for reinvestment in other health technologies that meet the criteria of safe and cost-effective care. It is therefore, a supply-centered strategy or rationalism.	1
Disinvestment (37)	Disinvestment seeks to improve health outcomes by evaluating existing health services, identifying those that do not provide safe, effective or cost-effective care and redirecting funding away from these services	1

Term	Definition	Number of references
	and towards those with superior safety, effectiveness, and cost-effectiveness profiles through a variety of policy approaches. It does not need to be a dichotomous choice to fund or not to fund; disinvestment can occur by degrees, whereby subsidies may be restricted to subgroups of patients for whom there is evidence of potential of benefit based on specific clinical characteristics.	
Reassessment (17)	A systematic review of a health technology, occurring after an initial assessment, to determine whether it is safe, clinically effective, and cost effective.	1
Reassessment (18)	Purpose of reassessment program is to examine technologies towards the end of their life-cycle and technologies scheduled for routine assessment at a pre-determined time after their acquisition.	1
Reassessment (2)	A structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives.	1
Obsolete (15)	Those technologies whose clinical benefit, safety or cost-effectiveness has been superseded by other available alternatives, or demonstrated to be ineffective or harmful.	1
Obsolete/Outdated/ Abandoned (6;10)	Superseded by other technologies or demonstrated to be ineffective or harmful.	2
Obsolete (16)	Any health technology in use for one or more indications, whose clinical benefits, safety, or cost-effectiveness has been significantly	1

Term	Definition	Number of references
	superseded by other available alternatives that improve its overall outcome.	
Obsolescence (17)	The endpoint in the lifecycle of a health technology (occurs when a new technology supersedes the old).	1

Table 2: Key Challenges and Solutions for Drug Disinvestment

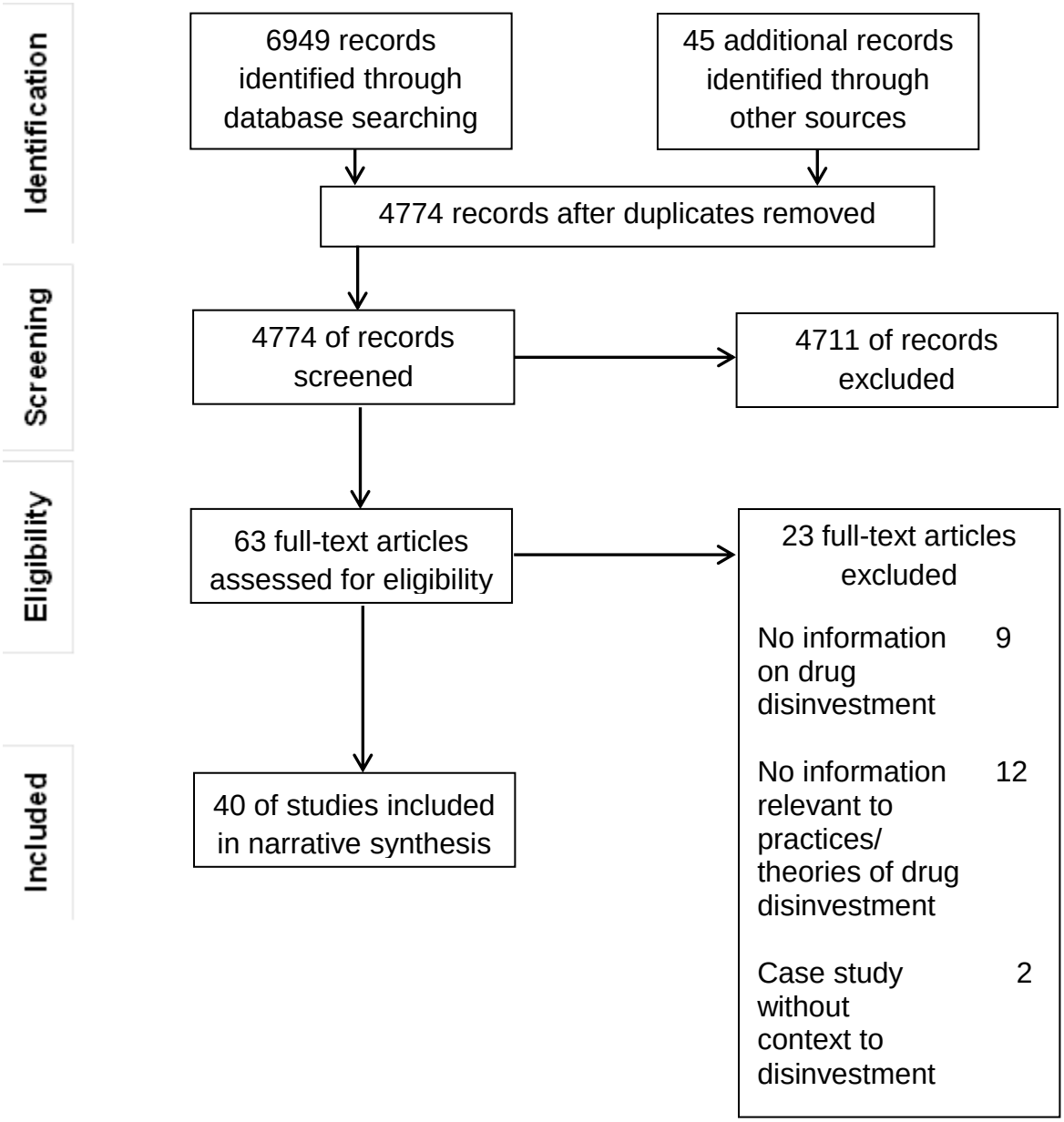
Key Challenges	Challenge Components	Key Solutions	Solution Components
Lack of evidence/data	No data showing lack of benefit (4, 6, 9, 14, 27)	Evidence/data generation	Research to fill data gaps (14)
	No effectiveness/safety data (13, 14, 29)		Routine data collection and accurate coding (19)
	No data in subgroups (1, 26)		Improved, transparent evidence (e.g. registries, linked datasets) (9, 13)
	No usage data (1, 26)		
	No cost data (29)		
Resistance to removing an established technology	Lack of political, clinical and administrative will (4, 6, 9, 13, 17, 21)	Stakeholder collaboration/ involvement	Partnerships with stakeholders to prioritize disinvestment (4, 9)
	Clinical training, practice paradigms or thought that a technology is still useful (13, 14, 23)		Researcher, clinician, consumer and policy-maker engagement and involvement (6, 9, 13, 15, 26)
	Competing clinical, consumer, and political interests (13, 14)		State/province collaboration with central HTA institution (9)
	Value of options for patients (21)		International disinvestment collaboration (9, 10)

Key Challenges	Challenge Components	Key Solutions	Solution Components
	Loss aversion and entitlement (7, 23, 26)	Knowledge transfer	Stakeholder communication to explain decision rationale and benefits (2, 6, 13, 26)
		Incentives	Financial or non-financial incentives to clinicians (6, 16, 26)
			Reinvestment of resources to benefit patients with same/similar conditions (26)
			Ongoing access to patients who benefit (26)
Lack of resources or resource reallocation	Additional research to fill data gaps or to contextualize data (1, 13, 21, 26)	Increased resources	Increase health technology committees capacity to conduct disinvestment (9, 10)
	Advance disinvestment methods needed (4, 13, 38)		Disinvestment process jointly funded by all stakeholders (10)
	Disinvestment policy mechanisms lacking (2, 4, 6, 9)		Continued research to advance disinvestment methods (14)

Key Challenges	Challenge Components	Key Solutions	Solution Components
	Need to formulate incentive and disinvestment mechanisms (13, 14, 21)		
	Sunk costs are required to build a disinvestment model (7, 14, 26)		
	Decision-makers require training and development time (2, 17, 29)		
Lack of frameworks and administrative mechanisms	Technology identification and prioritization lacking (4, 6, 9, 13, 29)	Administrative mechanisms	Embedding disinvestment into existing HTA structures (2)
	No agreed international disinvestment methodology (13)		Multi-stakeholder agreements on disinvestment processes (9)
	Decentralized health care structure (9)		Develop adaptable disinvestment models (2)
			A structured implementation and follow-up approach to enact recommendations (14, 26, 29)
			Overall program budget considered while prioritizing funding decisions (29)
			Consider cost-saving disinvestment options (e.g. narrowing of patient population, conditional treatment

Key Challenges	Challenge Components	Key Solutions	Solution Components
			rules, copayment, capping, encourage generic prescribing etc.) (7, 23)
			Preparation and dissemination of technology guidance/protocols (23)
			Pilot test disinvestment framework before roll-out (10)
Patient outcomes	Heterogeneity in patients outcomes (26, 35)		
	Ethical outcomes of at risk populations (e.g. elderly, children) (13)		
Disinvestment success not evident	Few candidates have been referred to or disinvested (5, 15)		

Figure 1: PRISMA Flow Diagram (3)



Supplementary Table 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) and Daily and Ovid MEDLIN(R) 1946 to present and MEDINE (R) 1996 to Present with Daily Update
Date of Search:	Nov. 14, 2015
Study Types:	No methodologic filters for study types were included
Limits:	English language and yr=”2000-Current”

SYNTAX GUIDE	
adj2	Adjacent too
exp	Explode a subject heading
mp	Search all fields
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Wildcard representing variations in exactly one character

Database Strategy

Search	Add to builder	Query	Items found
1	Add	exp Technology Assessment, Biomedical /	9604
2	Add	(technology assessment* or technology overview* or HTA*).mp	12977
3	Add	exp Budgets/	12637
4	Add	(cost-ineffective* or costineffective* or (cost adj2 ineffective) or obsolete* or obsolescen* or ineffective* or in-effective* or (little adj2 value) or “low-value” or abandon* or decommission* or de-commission* or delist* or de-list* or disinvest* or dis-invest* or (reduc* adj2 (coverage* or use*)) or suboptimal* or sub-optimal*).mp	142364

Database Strategy			
Search	Add to builder	Query	Items found
5	Add	(cost-effective* or costeffective* or (cost adj2 effective) or reassess* or re-assess* or reallocat* or re-allocat* or reinvest* or re-invest*).mp	110786
6	Add	1 or 2	14082
7	Add	3 or 4 or 5	263142
8	Add	6 and 7	1767
9	Add	Limit 8 to (english language and yr="2000-Current")	1336
10	Add	Remove duplicates from 9	1261

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE 1974 to 2015
Date of Search:	Nov 14, 2015
Study Types:	No methodologic filters for study types were included
Limits:	English language and yr=”2000-Current”

SYNTAX GUIDE	
adj2	Adjacent too
exp	Explode a subject heading
mp	Search all fields
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Wildcard representing variations in exactly one character

Database Strategy

Search	Add to builder	Query	Items found	
1	Add	exp biomedical technology assessment/	11765	
2	Add	(technology assessment* or technology overview* or HTA*).mp.	19368	
3	Add	exp budget/	21615	
4	Add	(cost-ineffective* or costineffective* or (cost adj2 ineffective) or obsolete* or obsolescen* or ineffective* or in-effective* or (little adj2 value) or “low-value” or abandon* or decommission* or de-commission* or delist* or de-list* or disinvest* or dis-invest* or (reduc* adj2 (coverage* or use*)) or suboptimal* or sub-optimal*).mp	184566	
5	Add	(cost-effective* or costeffective* or (cost adj2 effective) or reassess* or re-assess* or reallocat* or re-allocat* or reinvest* or re-invest*).mp	205001	
6	Add	1 or 2	19368	

Database Strategy

Search	Add to builder	Query	Items found	
7	Add	3 or 4 or 5	404986	
8	Add	6 and 7	2857	
9	Add	Limit 8 to (English language and yr =”2000-Current”	2384	
10	Add	Remove duplicates from 9	2343	

OVERVIEW	
Interface:	NLM PubMed
Databases:	PubMed
Date of Search:	Nov 14, 2015
Study Types:	No methodologic filters for study types were included
Limits:	Publication date from 2000/01/01; English

SYNTAX GUIDE	
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings

Database Strategy

Search	Add to builder	Query	Items found
#1	Add	Search biomedical technology assessment[MeSH Terms]	9463
#2	Add	Search ((technology assessment* [Title/Abstract]) OR technology overview* [Title/Abstract]) OR HTA* [Title/Abstract]	6243
#3	Add	Search budgets [MeSH Terms]	12449
#4	Add	Search ((((((((((((((((((cost-ineffective*) OR costineffective*) OR “cost ineffective”) OR obsolete*) OR obsolescen*) OR ineffective*) OR in-effective*) OR “little value”) OR “low-value”) OR abandon*) OR decommission*) OR de-commission*) OR delist*) OR de-list*) OR disinvest*) OR dis-invest*) OR “reduc*) coverage*”) OR “reduc* use*”) OR suboptimal*) OR sub-optimal*	2676069
#5	Add	Search ((((((((((cost-effective*) OR costeffective*) OR “cost effective”) OR reassess*) OR re-assess*) OR reallocate*) OR re-allocate*) OR reallocation*) OR re-allocation*) OR reinvest*) OR re-invest*	116019
#6	Add	Search (#1) OR #2	13759

Database Strategy			
#7	Add	Search ((#3) OR #4) OR #5	2776104
#8	Add	Search (#6) AND #7	2885
#9	Add	Search (#6) AND #7) Filters: Publication date from 2000/01/01	2278
#10	Add	Search (6 AND 7) Filters: Publication date from 2000/01/01; English	2148
		Duplicates removed	2145

OVERVIEW	
Databases:	Cochrane Library
Date of Search:	Nov 6, 2015
Study Types:	No methodologic filters for study types were included
Limits:	Publication year from 2000, in Cochrane Reviews (Reviews and Protocols)

SYNTAX GUIDE	
MeSH	Medical Subject Heading

Database Strategy

Search	Add to builder	Query	Items found	
#1	Add	MeSH descriptor: [Technology Assessment, Biomedical] explode all trees	599	
#2	Add	technology assessment or technology overview or HTA	29453	
#3	Add	MeSH descriptor: [Budgets] explode all trees	65	
#4	Add	cost-ineffective or costineffective or cost next ineffective or obsolete or obsolescen or ineffective or in-effective or little next value or low-value or abandon or decommission or de-commission or delist or de-list or disinvest or dis-invest or reduc next coverage or reduc next use or suboptimal or sub-optimal	7268	
#5	Add	cost-effective or costeffective or cost next effective or reassess or re-assess or reallocat or re-allocat or reinvest or re-invest	12465	
#6	Add	#1 or #2	29456	
#7	Add	#3 or #4 or #5	19426	
#8	Add	#6 and #7 Publication Year from 2000	571	

OVERVIEW	
Interface:	EBSCOhost
Databases:	CINAHL
Date of Search:	Nov 14, 2015
Study Types:	No methodologic filters for study types were included
Limits:	Published Date: 20000101-20151231; English Language Search modes: Boolean/phrase

SYNTAX GUIDE	
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
AB	Abstract
MM	Exact major subject heading
N1	Near operator within 1 word of one another regardless of order
TI	Title
TX	All Text

Database Strategy

Search	Add to builder	Query	Items found	
S1	Add	TI technology assessment* OR TI technology overview* OR TI HTA*	497	
S2	Add	AB technology assessment* OR AB technology overview* OR AB HTA*	912	
S3	Add	(MM “Budgets”)	2694	
S4	Add	TX cost-ineffective* OR TX costineffective* OR TX cost N1 ineffective OR TX obsolete* OR TX obsolescen* OR TX ineffective* OR TX in-effective* OR TX little N1 value OR TX “low-value” OR TX abandon* OR TX decommission* OR TX de-commission*	201440	
S5	Add	TX delist* OR TX de-list* OR TX disinvest* OR TX dis-invest* OR TX (reduc* N1 coverage* OR use*) OR TX suboptimal* OR TX sub-optimal*	8735	

Database Strategy				
Search	Add to builder	Query	Items found	
S6	Add	TX cost-effective* OR TX costeffective* OR TX cost N1 effective OR TX reassess* OR TX re-assess* OR TX reallocate* OR TX re-allocate* OR TX reallocation* OR TX re-allocation* OR TX reinvest* OR TX re-invest*	23410	
S7	Add	S1 OR S2	1286	
S8	Add	S3 OR S4 OR S5 OR S6	213843	
S9	Add	S7 AND S8	558	
S10	Add	S7 AND S8 Limiters – English Language	553	
S11	Add	S7 AND S8 Limiters – Published Date: 20000101-20151231; English Language	510	
		Duplicates removed	459	

GREY LITERATURE	
Dates for Search:	Jan 2, 2016 until Feb 4, 2016
Keywords:	Reassessment, reallocation, reinvestment, disinvestment, delist, decommission or obsolescence
Limits:	English language

Websites of organizations listed as members of International Network or Agencies for HTA (INAHTA) and HTAi
INHATA: http://www.inahta.org/our-members/members/
HTAi: http://www.htai.org/membership/organisational-members.html

Databases Searched	Outcome of Search
AETS –Agencia de Evaluación de Tecnologias Sanitarias, SPAIN http://www.isciii.es/ISCIII/es/general/index.shtml	Searched; nothing found in English
AETSA – Andalusian Agency for Health Technology Assessment SPAIN http://www.juntadeandalucia.es/salud/servicios/aetsa/	Searched; nothing found in English
AGENAS – The National Agency for Regional Health Services ITALY http://www.agenas.it	Searched; nothing found in English
Agency for Quality & Accreditation in Health CROTIA http://www.aaz.hr/	Searched; nothing found in English
AHRQ – Agency for Healthcare Research and Quality USA http://www.ahrq.gov	Searched; nothing found
AHTA – Adelaide Health Technology Assessment AUSTRALIA http://www.adelaide.edu.au/ahta/	Searched; found additional publications (handpicked)
AHTAPol – Agency for Health Technology Assessment in Poland POLAND http://www.aotm.gov.pl	Searched; nothing found in English
AHS – Alberta Health Services CANADA http://www.albertahealthservices.ca/default.aspx	Searched; 4 results found
AIFA – Italian Medicines Agency ITALY http://www.agenziafarmaco.gov.it/en	Searched; nothing found in English
ANHATA – Ankara Numune Training & Research http://www.anhhta.org/index.php/hakkimizda	Searched; nothing found in English
AQuAS – Agència de Qualitat i Avaluació Sanitàries de Catalunya SPAIN http://aquas.gencat.cat	Searched; nothing found in English

Databases Searched	Outcome of Search
ASERNIP-S – Australian Safety and Efficacy Register of New Interventional Procedures-Surgical AUSTRALIA http://http//www.surgeons.org/racs/research-and-audit/asernip-s	Searched; nothing found
ASSR – Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care) ITALY http://asr.regione.emilia-romagna.it/asr/index.htm	Searched; nothing found in English
Australian Government, Department of Health & Ageing: MSAC AUSTRALIA http://www.msac.gov.au/	Searched; nothing found
Australian Government, Department of Health & Ageing: PBAC AUSTRALIA http://www.pbs.gov.au/info/industry/listing/participants/pbac	Searched; nothing found
AVALIA-T – Galician Agency for Health Technology Assessment SPAIN http://avalia-t.sergas.es	Searched; nothing found in English
Blue Cross Blue Shield Association USA http://www.bcbs.com/	Searched; nothing found
CADTH Canadian Agency for Drugs and Technologies in Health CANADA https://www.cadth.ca/	Searched; 2 results found
CDE – Center for Drug Evaluation TAIWAN http://www.cde.org.tw	Searched; nothing found in English
CEDIT – Comité d´Evaluation et de Diffusion des Innovations Technologiques FRANCE http://cedit.aphp.fr	Searched; nothing found in English
CEM – Inspection générale de la sécurité sociale (IGSS), Cellule d'expertise médicale LUXEMBURG http://www.mss.public.lu/acteurs/igss/index.html	Searched; nothing found in English
CENETEC – Centro Nacional de Excelencia Tecnológica en Salud MEXICO http://www.cenetec.salud.gob.mx	Searched; 1 result found
CONITEC – National Committee for Technology Incorporation BRAZIL http://www.conitec.gov.br/	Searched; nothing found in English
CMeRC – Charlotte Maxeke Research Consortium SOUTH AFRICA http://cmerc.org.za/health-technology/	No access, website expired
CMTP - Center for Medical Technology Policy USA http://www.cmtpnet.org/	Searched; nothing found in English
CNHDRC – China National Health Development Research Center CHINA	Searched; nothing found in English

Databases Searched	Outcome of Search
http://www.nhei.cn/nhei_en/center_en/web/index.jsp	
CRD – Centre for Reviews and Dissemination UNITED KINGDOM http://www.york.ac.uk/inst/crd/	Searched; nothing found
DACEHTA http://sundhedsstyrelsen.dk/English/DACEHTA.aspx	Searched; nothing found in English
DAHTA @DIMDI – German Agency for HTA at the German Institute for Medical Documentation and Information GERMANY http://www.dimdi.de	Searched; nothing found in English
DECIT-CGATS – Coordenação Geral de Avaliação de Tecnologias em Saúde; Departamento de Ciência e Tecnologia BRAZIL http://portal.saude.gov.br/portal/saude/area.cfm?id_area=1026	Searched; nothing found in English
Department of Health, Basque Government, SPAIN http://www.euskadi.eus/gobierno-vasco/departamento-salud/inicio/	Searched; 1 result found
FinOHTA – Finnish Office for Health Technology Assessment FINLAND http://www.thl.fi/finohta	Searched; nothing found in English
G-BA – The Federal Joint Committee (Gemeinsamer Bundesausschuss) GERMANY http://www.g-ba.de	Searched; nothing found in English
GÖG – Gesunheit Österreich GmbH AUSTRIA http://www.goeg.at	Searched; nothing found in English
HAD-MSP Uruguay: Health Assessment Division of the Ministry of Public Health URUGUAY http://www.msp.gub.uy	Searched; nothing found in English
HAS – Haute Autorité de Santé FRANCE http://www.has-sante.fr	Searched; nothing found in English
HCT-NHSRC – Division of Healthcare Technology, National Health Systems Resource Center INDIA http://nhsrcindia.org/index.php?option=com_content&view=article&id=173&Itemid=642	Searched; nothing found in English
HealthPACT – Health Policy Advisory Committee on Technology AUSTRALIA http://www.health.qld.gov.au/healthpact/	Searched; nothing found
HIQA – Health Information and Quality Authority IRELAND http://www.hiqa.ie	Searched; nothing found in English

Databases Searched	Outcome of Search
HIRA – Health Insurance Review and Assessment KOREA http://www.hira.or.kr/eng/#&panel1-2	Searched; nothing found in English
HIS – Healthcare Improvement Scotland UNITED KINGDOM http://www.healthcareimprovementscotland.org	Searched; 3 results found
Hospital Clinic Porto Alegre BRAZIL http://www.hcpa.edu.br/content/blogsection/5/927/	Searched; nothing found in English
HQO – Evidence Development and Standards Branch CANADA http://www.hqontario.ca/	Searched; nothing found
HTA-HSR/DHTA – HTA & Health Services Research DENMARK http://www.mtv.rm.dk	Searched; nothing found in English
ICER – Institute for Clinical & Economic Review USA http://www.icer-review.org/	Searched; nothing found in English
IECS – Institute for Clinical Effectiveness and Health Policy ARGENTINA http://www.inahta.org/our-members/members/iecs/	Searched; nothing found in English
IETS – Instituto de Evaluación Tecnológica en Salud COLOMBIA http://www.iets.org.co	Searched; nothing found in English
IHE – Institute of Health Economics CANADA http://www.ihe.ca	Searched; nothing found
INASanté – National Instance for Accreditation in Health Care TUNISIA http://www.inasante.tn	Searched; nothing found in English
INESSS – Institut national d'excellence en santé et en services sociaux CANADA http://www.inesss.qc.ca	Searched; nothing found in English
IQWiG – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen GERMANY http://www.iqwig.de	Searched; nothing found in English
Kaiser Permanente USA https://healthy.kaiserpermanente.org/html/kaiser/index.shtml	Searched; nothing found in English
KCE – Belgian Health Care Knowledge Centre BELGIUM http://kce.fgov.be	Searched; nothing found in English
LBI-HTA – Ludwig Boltzmann Institute for Health Technology Assessment AUSTRIA http://hta.lbg.ac.at	Searched; 2 results found
MaHTAS – Health Technology Assessment Section, Ministry of Health Malaysia MALAYSIA	Searched; nothing found in English

Databases Searched	Outcome of Search
http://medicaldev.moh.gov.my	
Ministry of Health, Malaysia MALAYSIA http://www.moh.gov.my/	Searched; nothing found in English
MTAA – Medical Technology Association of Australia AUSTRALIA http://mtaa.org.au/	Searched; nothing found
MTU-SFOPH – Medical Technology Unit – Swiss Federal Office of Public Health SWITZERLAND http://www.bag.admin.ch	Searched; nothing found in English
National Institute for Health & Welfare FINLAND https://www.thl.fi/fi/web/thlfi-en	Searched; nothing found in English
National University of Colombia COLOMBIA https://www.thl.fi/fi/web/thlfi-en	Searched; nothing found in English
NECA – National Evidence-based healthcare Collaborating Agency KOREA http://www.neca.re.kr	Searched; nothing found in English
NHC – New Zealand National Health Committee NEW ZEALAND http://nhc.health.govt.nz/home	Searched; 3 results found
NHMRC CTC – NHMRC Clinical Trials Centre AUSTRALIA http://ctc.usyd.edu.au/	Searched; nothing found
NHS Lothian SCOTLAND https://nhslothian.scot.nhs.uk/Pages/default.aspx	Searched; nothing found
NICE – National Institute for Health and Clinical Excellence UNITED KINGDOM https://www.nice.org.uk/	Searched; nothing found
NIHR – National Institute for Health Research UNITED KINGDOM http://www.nihr.ac.uk/	Searched; nothing found
NOKC – Norwegian Knowledge Centre for the Health Services NORWAY http://www.nokc.no	Searched; nothing found in English
OSTEBA – Basque Office for Health Technology Assessment SPAIN http://www.osakidetza.euskadi.eus/r85-pkoste01/en/	Searched; nothing found in English
PHARMAC – Pharmaceutical Management Agency of NEW ZEALAND http://www.pharmac.health.nz/	Searched; nothing found
Queensland Health – AUSTRALIA https://www.health.qld.gov.au/	Searched; 1 result found
RCHD-CS – Centre of Standardization of the Republican Centre for Health Development KASAKHSTAN	Searched; nothing found in English

Databases Searched	Outcome of Search
http://www.rcrz.kz	
RedArets – Public HTA network of Argentina ARGENTINA http://www.saludneuquen.gob.ar/index.php?option=com_content&view=article&id=1467:neuquen-miembro-fundador-de-la-red-argentina-publica-de-evaluacion-de-tecnologias-sanitarias-redarets&catid=89:noticias-breves&Itemid=268	Searched; nothing found in English
SBU – Swedish Council on Technology Assessment in Health Care SWEDEN http://www.sbu.se	Searched; nothing found in English
Swiss Sickness Funds Insurance Body SLOVAK REPUBLIC http://www.sukl.sk/en?page_id=256	Searched; nothing found in English
UCEETS – The National Coordination Unit of Health Technology Assessment and Implementation ARGENTINA http://www.msal.gov.ar/pngcam/tecnologias2.htm	Searched; nothing found in English
University of Sheffield UNITED KINGDOM http://www.sheffield.ac.uk/	Searched; nothing found in English
UVT – HTA Unit in A. Gemelli Teaching Hospital ITALY http://www.policlinicogemelli.it/area/?s=206	Searched; nothing found in English
VASPVT – State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania LITHUANIA	Searched; nothing found in English
ZIN – Zorginstituut Nederland NETHERLANDS http://www.zorginstituutnederland.nl/	Searched; nothing found in English
ZonMw – The Netherlands Organisation for Health Research and Development NETHERLANDS http://www.zonmw.nl	Searched; nothing found in English
For Profit Organizations	
Abbott Vascular International BVBA http://www.abbottvascular.com/int/index.html?fbefk7i	Searched; nothing found
ADVI http://www.advi.com/#reimbursement-story	Searched; nothing found
AMGEN http://www.amgen.com/	Searched; nothing found
AstraZeneca PLC https://www.astrazeneca.com/	Searched; nothing found
Bayer Healthcare/Bayer Pharma Schering www.bayer.com	Searched; nothing found
Bristol Myers Squibb	Searched; nothing found

Databases Searched	Outcome of Search
http://www.bms.com/pages/default.aspx	
Eli Lilly and Company https://www.lilly.com/home.aspx	Searched; nothing found
F. Hoffmann-La Roche AG http://www.roche.com/index.htm	Searched; nothing found
GlaxoSmithKline, Belgium &USA http://www.gsk.com/	Searched; nothing found
IMS Health http://www.imshealth.com/en/solution-areas/services/services-our-work/strategy-management-consulting	Searched; nothing found
Johnson & Johnson Medical Products http://www.jnj.com/	Searched; nothing found
Medtronic http://www.medtronic.com/us-en/index.html?cmpid=mdt_com_orcl_us_home_f52_plc_home&utm_source=mdt_com_orcl_us_home&utm_medium=f5_redirect&utm_campaign=PLC_Launch_2015	Searched; nothing found
Merck & Co http://www.merck.com/index.html	Searched; nothing found
Merck Serono International SA http://www.emdserono.com/en/index.html	Searched; nothing found
Novartis https://www.novartis.com/	Searched; nothing found
Pfizer Limited http://www.pfizer.com/	Searched; nothing found
Sanofi-Aventis http://en.sanofi.com/rd/rd.aspx	Searched; nothing found
St. Jude Medical, Inc. http://sjm.com/corporate.aspx	Searched; nothing found
UCB Pharma Ltd. http://www.ucb.com/patients/Conditions/neurology/epilepsy	Searched; nothing found

Supplementary Table 2: Data Extraction Form

Reference:

Focus of the document:

Summary of key findings from the document:

Document characteristics (check all the apply)

Methods used/type of paper

Primary research

☐ Systematic review (needs to have explicit search and selection criteria)
☐ Randomized Control Trial
☐ Qualitative study
☐ Case study
☐ Mixed methods (select other methods as applicable)
☐ Other (specify)

Non-research

☐ Review (not systematic)
☐ Theory/discussion/policy or position paper
☐ Commentary/editorial
☐ Website content

Publication status

☐ Peer-reviewed journal
☐ Grey literature

Country or region focus

☐ General/global focus
☐ Specific
- Number of countries:
- List specific countries:

Data extraction of key findings

Brief summary of the text in the paper as it relates to each data extraction criteria

Category	Subcategories	Data extraction	Brief summary of information related to the data extraction questions
☐ Disinvestment/ reassessment approach	☐ Definitions	List definitions of terms referring to disinvestment or reassessment	
	☐ Purpose and benefits	Provide purpose of disinvestment/ reassessment (e.g. efficacy/safety or financial) and benefits	
	☐ Process	Provide detail on: • Type of process (e.g. HTA based) • Top-down and/or bottom-up approach • Passive or active approach • General process	
☐ Identification	☐ Methods	How is information obtained to identify technology for disinvestment/reassessment	
	☐ Criteria	List criteria used/proposed to identify technology for disinvestment/reassessment	
☐ Prioritization	☐ Methods	Detail on process related to prioritization	
	☐ Criteria	List criteria used/proposed to identify technology for disinvestment/reassessment	

Category	Subcategories	Data extraction	Brief summary of information related to the data extraction questions
☐ Evaluation	☐ Process	Include description of assessment bodies, stakeholders providing input, details of process	
	☐ Methods	Describe methodological components for disinvestment/reassessment	
☐ Implementation	☐ Challenges	Describe challenges encountered to disinvest/reassess	
	☐ Financial arrangements	Explain any financial arrangements to implement disinvestment/reassessment • financing systems • funding organizations • renumerating providers • purchasing products and services • incentivizing stakeholders	
	☐ Delivery arrangements	Explain delivery arrangements (i.e. what medium is used to communicate results)	
	☐ Implementation process	How decision is implemented (e.g. reinvestment in health care system)	
☐ Other	☐ Stakeholder engagement	List stakeholders involved in each step of disinvestment/	

Category	Subcategories	Data extraction	Brief summary of information related to the data extraction questions
		reassessment process	
	☐ Lessons Learned/ Solutions to overcome barriers	Describe any lessons learned or solutions to overcome barriers	
	☐ Other	Any other information not captured above	

Supplementary Table 3: Characteristics of Included Articles

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Fenwick et al., 2000 (39)	Discussion	Proposal of a probabilistic model	Proposed probabilistic model employed in a case study whose analysis can be used to identify research protocols and to concentrate research upon particular parameters requiring precise estimates	General
Elshaug et al., 2007 (4)	Discussion	Examination of key challenges for disinvestment	Five challenges were identified and examined and potential policy-related solutions discussed to advance disinvestment	Australia
Ibargoyen-Roteta et al., 2007 (37)	Guideline development	Report on the development of a guideline for health technology disinvestment	Guideline meant to establish a transparent, systematic and explicit process for disinvestment assessment	Spain

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Pearson and Littlejohns, 2007 (24)	Position	NICE's current and future support of the English National Health Service (NHS) and technology value	Exploration of NICE policy options to provide NHS guidance on disinvestment	United Kingdom
Ruano-Ravina et al., 2007 (16)	Guideline development	Guideline for assessment of obsolete health technologies	Methodological guideline developed which proposes how to identify, prioritize and assess a technology	Spain
Elshaug et al., 2008 (14)	Qualitative	Challenges of disinvestment and potential solutions	Exploratory study to determine policy stakeholder perspectives on the challenges and nature of disinvestment	Australia
Elshaug et al., 2009 (9)	Discussion	Challenges related to decommissioning and obsolescence of health technologies	Assessment of barriers and challenges to decommissioning technology and potential strategies to address technology obsolescence	Canada

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
			and a plan to carry out disinvestment in Canada	
Elshaug et al., 2009 (32)	Discussion	Health technology disinvestment program proposal	Criteria discussed to identify existing, ineffective practices and to prioritize candidates for assessment	Australia
Ibargoyen-Roteta et al., 2009 (28)	Survey	Identification and ranking of sources for the identification of potentially obsolete technologies	Questionnaire to identify the most relevant sources sent to HTA speciality group members and results ranked	General
Joshi et al., 2009 (17)	Discussion	Health technology obsolescence and potential framework	Discusses practices and policies surrounding obsolescence and proposes a framework for reassessment and decommissioning of health technologies	Canada

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Hughes and Ferner, 2010 (30)	Discussion	NICE's disinvestment initiatives	Summary of NICE's disinvestment activities and suggestion of a framework for identification and appraisal of medicines	United Kingdom
Ibargoyen-Roteta et al., 2010 (6)	Guideline development	Development of a guideline for health technology disinvestment	GuNFT hospital and patient level guideline for not funding technologies includes six domains as well as a software component	Spain
Morland, 2010 (15)	PowerPoint presentation	National quality and priority setting decisions and clinical practice outcomes	Case study used to examine how national quality and priority setting decisions (including disinvestment) altered clinical practice	Norway
Alberta Health Services, 2011 (18)	Website content	Annual report for the Health Technology Assessment & Innovation Department	Mentions development of a reassessment program for end of life-cycle	Canada

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
			technologies and routine reassessment	
Garner and Littlejohns, 2011 (1)	Review	NICE's disinvestment initiatives	Summary and suggested outcomes of NICE's disinvestment initiatives	United Kingdom
Gerdvilaite and Nachtnebel, 2011 (10)	Systematic review	International frameworks and guidelines for disinvestment	Investigates identification, assessment and dissemination of disinvestment recommendations	Australia, Canada, Spain, UK
Hollingworth and Chamberlain, 2011 (40)	Commentary	NICE and disinvestment processes	Recommends NICE reconsider a shift away from HTA of existing technologies for disinvestment decisions	United Kingdom
Haas et al., 2012 (21)	Review	Exploration of issues related to disinvestment	Description of HTA disinvestment processes, discussion of candidate identification, implementation of activities and lack of	Australia, UK, Germany, Denmark

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
			progress/challenges in designing a disinvestment framework	
Henshall et al., 2012 (26)	Discussion	Summary of main points from HTAi Policy Forum meeting held January 2012	Review of candidate disinvestment identification, prioritization, and implementation of decisions	General
Jaurlaritza, 2012 (41)	Website content	Describes annual meeting of Health Technology Assessment International which occurred in Balboa	Purpose of summit to examine disinvestment and most cost-effective ways to manage current health technology	General
Moynihan, 2012 (36)	Commentary	Summary of disinvestment activities and support of process	Support of disinvestment for treatments where costs and harm outweighs benefits	Australia
Scottish Health Technologies Group, 2012 (42)	Website content	Audit method of NICE disinvestment mechanisms in Scotland	Pilot of MaCSWise group's method of auditing whether or not NICE cost-saving and	Scotland

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
			"do not do" guidance are current practice in NHSScotland	
Watt et al., 2012 (37)	Systematic review and qualitative research (mixed methods)	Stakeholder engagement in disinvestment initiatives	Wide stakeholder engagement; if and how this can improve decision-making processes for disinvestment	Australia
Watt et al., 2012 (43)	Review, case study and qualitative research (mixed methods)	Use of evidence from systematic review in disinvestment decisions	Assessment of the value of evidence from systematic reviews to inform expert stakeholder disinvestment deliberations	General
Garcia-Armesto et al., 2013 (23)	Discussion	Development of a Spanish disinvestment framework	Review of global disinvestment strategies and proposal of a Spanish disinvestment strategy	Spain

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Garner et al., 2013 (19)	Review	To determine if Cochrane reviews can be used to identify low value practices to support disinvestment decisions	Reviewed results from the first 6 months of the Cochrane Quality and Productivity project	United Kingdom
Health Policy Advisory Committee on Technology, 2013 (13)	Discussion	Disinvestment in Australia and New Zealand	Part One: Disinvestment Fundamentals and Part Two: Summary of workshop presentations focused on disinvestment strategies in the Australian and New Zealand Healthcare Systems	Australia and New Zealand
Healthcare Improvement Scotland 2013 (11)	Website content	Scoping report	Ascertain the quality and quantity of published strategies used to identify, consider and potentially include public perspectives in disinvestment decisions	Scotland

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
MacKean et al., 2013 (2)	Qualitative	Environment assessment and next steps in technology reassessment	Discovery and description of key themes in Health Technology Reassessment and proposed way forward	General
Mayer and Nachtnebel, 2013 (44)	Systematic review (only abstract available in English)	International models and strategies for identification of ineffective technologies	Investigates identification, prioritization and assessment of ineffective technologies	General with focus on Austria
Polisena et al., 2013 (29)	Systematic review	Review the application of frameworks and tools for disinvestment and resource allocation	Description of the multiple criteria considered for decision making and the strengths and limitations of frameworks in fourteen cases	General
Scotland Health Technologies Group, 2013 (25)	PowerPoint presentation	Scottish Health Technologies Group development day presentations	Challenges to disinvestment; identification and prioritization of technologies for	General with focus on Scotland

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
			disinvestment and applicability to the Scottish Health Technologies Group	
Haines et al., 2014 (35)	Position	Description of a clinical research design for use in disinvestment decisions	Development of a research design which can be used to evaluate a technology for disinvestment where uncertain effectiveness or cost-effectiveness exists	General
Health Quality Ontario, 2014 (22)	Website content	Description of the Appropriateness Initiative	Appropriateness Working Group and Health Quality Ontario developed a framework for identifying, prioritizing and assessing interventions that may be being used inappropriately	Canada/Ontario

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Wilson et al., 2014 (8)	Systematic review and qualitative research (mixed methods)	Development of an explanatory framework for disinvestment	Describes research outline including conduct of a systematic literature search and the use of qualitative research methods to develop a framework for disinvestment	General
Gnjidic and Elshaug, 2015 (5)	Commentary	Review of a scoping review	Highlights a scoping review which summarized the current literature on low-value clinical practices	General
O'Callaghan et al., 2015 (45)	Discussion	Relevance of US Choosing Wisely campaign for Australia and recommendations for modification	Reviewed, based on a South Clinical Senate exercise, how the US Choosing Wisely campaign list validity could be maximized while minimizing the US list limitations	Australia

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Paprica et al., 2015 (27)	Review	Development of tools and processes for use in disinvestment decisions	Literature review and colloquial evidence (policy stakeholders) combined to develop a definition of appropriateness and a disinvestment framework for selective disinvestment	Canada/Ontario
Parkinson et al., 2015 (7)	Systematic review	Review of disinvestment strategies in OECD countries	Systematic review to outline key approaches to identification, assessment and methods of disinvestment. Value-based purchasing, lessons learned, potential role of coverage with evidence and stakeholder management were also determined	UK, France, Canada, Australia, New Zealand

Citation (Author and Publication/Access Year)	Methods Used/ Type of Paper	Focus of Citation	Description	Countries Described in Article
Alberta Health Services, 2016 (12)	Website content	Alberta Health Reassessment Program	Schematic of Alberta Health Reassessment Program process	Canada/Alberta

Supplementary Table 4: Identification and Prioritization Criteria

Criteria	Identification and/or prioritization	Number of references
Unacceptable potential risk for patient (6-10)	Identification	4
Evidence technology causes overall worsening of health (6-9)	Identification	3
Conflict with clinical practice guidelines, clinical college position statements, Cochrane Review recommendations (9)	Identification	1
Quality of life poor for patient (6)	Identification	1
Public interest or controversy (9)	Identification	1
Off-label reimbursed indications (9)	Identification	1
Legacy items: Long-established technologies that have never had cost-effectiveness established (9)	Identification	1
Sufficient evidence available. Evidence should be available and adequate to offer decision-making utility (9)	Identification	1
Scope of time limited funding with pay for evidence or only in research provisions (9)	Identification	1
No scientific evidence proving technology improves health (6;7;9;10;24)	Identification or Prioritization	5
Temporal variations in volume between time points (9;10;27)	Identification or prioritization	3
High budget technologies (9;10;16;24;25;26)	Identification or prioritization	6
Cost effectiveness (7;9;10;13;16)	Identification and/or prioritization	5

Criteria	**Identification and/or prioritization**	**Number of references**
Nomination of a technology by individuals, associations or groups (9;10;27)	Identification or prioritization	3
Availability of alternative technologies (6;7;24;26)	Identification or prioritization	4
Lack of disease burden (Technology not used to treat very severe or life-threatening conditions or vulnerable populations) (7;9;10;16;24;25)	Identification or prioritization	6
Infrastructure (26)	Prioritization	1
Level of consensus among stakeholders (including clinicians and consumers) (13; 26)	Prioritization	2
Ability to overcome stakeholder perceptions (26)	Prioritization	1
Policy environment and political readiness (26)	Prioritization	1
Funding to reinvest (26)	Prioritization	1
Resources for KT implementation (26)	Prioritization	1
Resources for monitoring impact (26)	Prioritization	1
Measurable outcomes (13)	Prioritization	1
An evidence-based recommendation against use by an external body (10;27)	Prioritization	2
Safety concerns (7;10;16;27)	Prioritization	4
Change likely to provide benefit to a significant number of people (17)	Prioritization	1
Change would be cost saving (10;27)	Prioritization	2

Criteria	**Identification and/or prioritization**	**Number of references**
Impact to public health (e.g. significant percentage of patients received inappropriate technologies) (7;10;27)	Prioritization	3
Disease frequency (16)	Prioritization	1
Frequency of use of technology (10;16)	Prioritization	2
Patient preference (10;16)	Prioritization	2
Efficacy/effectiveness/ Validity (10;16)	Prioritization	2
Reasonably prevalent to warrant disinvestment (13)	Prioritization	1
Ability to use financial incentives with changes to: coverage/reimbursement; vendor contracts; formularies/inventories; alignment with existing work program (13)	Prioritization	1

Supplementary Table 5: Identification and Prioritization Methods

Method	Identification and/or prioritization	Number of references
Clinical effectiveness research (19;21)	Identification	2
Monitoring published studies, guidelines and systematic reviews (e.g. CADTH, Cochrane Collaboration, BMJ, JAMA, FDA and ECRI Institute) (6;10;16;23;25;26)	Identification	6
Review of health technology reports and/or new or emerging health technology databases (16)	Identification	1
New intervention undergone regulatory assessment and considered as a replacement for old technology (9)	Identification	1
Consultation with clinical speciality groups, clinicians, health care administrators and funders (6;9;10;16;25;26)	Identification and/or prioritization	6
Assessment of variation in technology use (e.g. geographic, provider variation in care) (9;10;23;25-27)	Identification or prioritization	6
Feasibility assessment (25)	Prioritization	1

CHAPTER 3: HEALTH TECHNOLOGY AGENCY INSIGHTS: INFORMING MODIFICATION OF A QUALITATIVE BENEFIT RISK FRAMEWORK FOR HEALTH TECHNOOGY REASSESSMENT OF PRESCRIPTION MEDICATIONS

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INTRODUCTION

Pursuant to the systematic literature review reported in Chapter 2, the authors recommended that a more decision neutral term other than “disinvestment” should be used to describe the process of conducting a review of the clinical, economic, and ethical data of a marketed drug technology compared to its alternatives. A term such as “reassessment” suggests a review could have both re- and dis-investment outcomes potentially improving stakeholder engagement in this process and its outcomes. As such, the term Health Technology Reassessment (HTR), instead of disinvestment, has been adopted for research detailed in Chapters 3 and 4. Chapter 2 research also confirmed that there is not one universally accepted qualitative framework used during the assessment phase of HTR to frame decision making and to aid in decision communication. However, such decision frameworks are used by regulatory authorities to enable benefit-risk decisions. Given the common foundational need to assess benefit-risk by regulators and HTA agencies and the differences in regulatory and HTR assessments, this chapter attempts to answer the question: Can a qualitative benefit-risk framework be used or modified to further enable prescription medicine health technology reassessment? To answer this question, a qualitative descriptive study was conducted. This research methodology was chosen to gain the opinions, insights and experiences of the participants and to generate themes that would guide future research. The Universal Methodology for Benefit-Risk Assessment (UMBRA) Framework, a general principled qualitative framework for benefit-risk assessment, was selected given its universal construction and acceptance by Health Canada. This framework prioritizes benefits and risks by using value trees derived from decision analysis. It allows for customization and incorporates the quality and limitations of the available data along with stakeholder

preferences. The purpose of this research was to understand Canadian HTA agency assessors' prior experience with the UMBRA framework and to collect their insights on the use of or the modification to such a framework for HTR. For the purpose of relevance, assessors were asked to compare the UMBRA framework to an existing Canadian HTR process (CADTH's Therapeutic Review process).

A fixed exploratory sequential research design was planned for this study and the Hamilton Integrated Research Ethics Board approved two stages of research. The first-phase was the above described qualitative descriptive study, which was completed. A second-phase quantitative study was meant to entail a modified electronic Delphi (e-Delphi) technique to correlate informed judgements of expert panellists to gain consensus on the included items in a modified qualitative benefit-risk framework (UMBRA framework) for use in HTR. It was planned that in Phase 1 of this research, HTA agency assessors would identify themes of high pertinence. These pre-selected themes would then define the hypothesis and item pool of a questionnaire provided to expert panellists upon which to judge the appropriate content of a modified qualitative benefit-risk framework for use in HTR. However, upon completion of Phase 1, it was determined that HTA agency assessors did not consider that all steps of the UMBRA framework were transferable to the assessment phase of HTR and, therefore, Phase 2 of this research was canceled.

Appendix 1 in Chapter 3 provides additional study materials, not included in the manuscript for publication. Please note that this study material refers, in places, to both original stages (Phase 1 and 2) as this was the original material approved by the Hamilton Integrated

Research Ethics Board prior to cancellation of Phase 2 research. In addition, following Phase 1 study completion, HTA agency assessor management asked that further study anonymity be implemented, which has resulted in hiding text to protect anonymity.

ABSTRACT

Objectives: This study's intent was to determine if a qualitative benefit risk framework could be used or modified to further enable Health Technology Reassessment (HTR) of prescription medicine recommendations. The purpose of this research was to understand Canadian Health Technology Agency assessors past experiences and insights to inform any modifications to the Universal Methodology for Benefit-Risk Assessment (UMBRA) qualitative framework. The UMBRA framework consists of an 8- step process, used during the assessment phase, to aid in decision-making and dissemination.

Methods: A qualitative descriptive study was conducted and included a purposeful, criterion-based sample of eight assessors who had participated in Health Technology Assessment (HTA) or HTR for prescription medicines or in qualitative decision-making frameworks.

Results: Participant interviews lead to four common themes: "adoption of a qualitative benefit risk framework", "data (either too much or not enough)", "importance of incorporating stakeholder values" and "feasibility of the UMBRA framework". Methodological challenges with HTR were highlighted including the lack of clinical outcome data and the ability to compare clinically relevant meaningful differences. The implementation of a ranking or weighing process found within the UMBRA framework was not favoured by half of the participants.

Conclusions: Research participants did not consider all steps of the UMBRA framework to be transferable to the assessment phase of HTR given the need for simplicity, resource efficiency and stakeholder input throughout the process. Assessor experiences and insights and

resultant key themes can be used in future research to aid in the development of a qualitative recommendation framework for HTR.

Keywords: Technology assessment, disinvestment, qualitative benefit risk framework, reassessment

Manuscript: Health Technology Agency insights: Informing modification of a qualitative benefit-risk framework for Health Technology Reassessment of prescription medications

Qualitative frameworks frame decision problems through “a structured, consistent approach to decision making by facilitating the selection, organization, summarization, and interpretation of data and preferences relevant to the decision” and aid decision documentation and communication (1). The use of qualitative frameworks has been well documented in the context of Regulatory decision-making through numerous systematic literature reviews (2-7).

Regulatory agencies or health authorities, such as the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), as well as academics (e.g. Centre for Innovation in Regulatory Science (CIRS)), are using qualitative benefit-risk frameworks (EMA PrOACT-URL, US FDA Benefit-Risk Framework and The Universal Methodology for Benefit-Risk Assessment (UMBRA) Framework) to aid benefit-risk decision-making and information dissemination (8-10).

Health Canada (Health Products and Food Branch), is the Canadian Health Authority responsible for national public health. Before new prescription drug products (or major variations to a product) are authorized for sale in Canada, a manufacturer must present significant scientific evidence of the product's efficacy, safety and quality to Health Canada. Health Canada assesses this information and makes a benefit-risk decision as to whether the product should be granted market authorization. Health Canada has worked closely with other regulatory agencies (The Consortium on Benefit-Risk Assessment (COBRA)) and with CIRS to

evaluate UMBRA (10). The UMBRA framework (Figure 1) is comprised of an eight-step decision making process. It was developed by conducting a comparative review of key qualitative benefit-risk frameworks with the goal of harmonizing the common process elements into a universal, overarching qualitative decision-making framework (10). The UMBRA framework was meant to be a single internationally acceptable platform for the benefit-risk assessment of medicines. Health Canada has evaluated UMBRA for use in benefit-risk decision-making and has found it to be fit for purpose (11).

Similar to Regulatory agencies, Health Technology Assessment (HTA) agencies use judgement to assess the relevance of the data to make a decision or recommendation. A recommendation depends on the "perspective that is adopted for the decision and the processes used to reach that decision" (1). HTA agencies are beginning to make recommendations which relate to Health Technology Reassessment (HTR). HTR is a "structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives" (12). HTR may be used with prescription medicines that were not initially subjected to rigorous HTA or after initial prescription medication coverage approval as a matter of course, due to new clinical/safety/cost data or comparator changes. Overarching HTR frameworks involve a series of process steps. First, low-value or sub-optimal technologies are identified within the health care system. Prioritization is also required if a number of technologies are identified. Assessment follows and can include data collection, interpretation, organization and summary to determine the clinical, economic, social and ethical effects of a technology's use. The assessment stage frequently adopts HTA methodology to

develop a recommendation for a technology and its comparators. However HTR is more complex given the inherent lack of comparison data between alternatives, the number of alternatives that are included and the need to demonstrate the lack of benefit or harm should a recommendation further restrict technology use. Reassessment requires an even greater systematic assessment of social value, patient preferences, ethics, and stakeholder requirements. Finally, to ensure HTR recommendation outcomes are realized, a recommendation/decision dissemination phase is required, ideally using knowledge translation, to shift recommendations into practice (13-15).

One HTA agency, the Canadian Agency for Drugs and Technologies in Health (CADTH), is conducting HTR, including the above outlined process steps, through the Therapeutic Review framework for non-oncology prescription medicines to further enable provincial/territorial reallocation of investment to maximize the value for money. Further information on CADTH and the Therapeutic Review Process may be found in Table 1 (16).

Regulatory agencies and HTA agencies interested in decision-making assessment can have both commonalities and differences in review elements. The health problem, current use of a technology, technical characteristics, safety and clinical effectiveness elements may be common. However, differing perspectives, values and priorities can exist (5). For instance, Regulators are concerned with safety and efficacy in a general population while HTA agencies are focused on safety and efficacy in a specific population versus comparators with the added criteria of cost effectiveness (17). The common foundational need of Regulatory and HTA agencies, that is to assess a wide variety of evidence and make subjective decisions pertinent

to many stakeholders, suggests an opportunity to assess and modify, as required, a qualitative benefit-risk framework for the use by HTA agencies and their expert committees in the HTR assessment phase. Qualitative benefit-risk frameworks can: enhance the clarity of the decision-making process by helping to set internal standards and consistency for decision-making; encourage appropriate documentation; ensure each benefit and risk is articulated including their relative importance; and provide a standardized way to communicate benefits and risks to various stakeholders (7). Qualitative frameworks accommodate the inclusion of benefit-risk quantitative assessment tools and outcomes and provide structured support through a process to frame decision problems to ensure a better definition and transparency of that decision context (1). These frameworks include steps to ensure identified benefits and risks, applicable data, and other decision considerations are well documented in tabular or graphical displays and presented transparently.

Common foundational needs between Regulators and HTA agencies coupled with the differences in regulatory and HTR assessment raises a question of interest, that is, can a qualitative benefit-risk framework be used or modified to further enable prescription medicine health technology reassessment? As such, the purpose of this study was to understand Canadian HTA agency assessors' past experience with a qualitative decision framework (UMBRA) and to collect their insights on the use and or modification to such a framework for HTR. The UMBRA framework was chosen given its overarching and universal construction and Health Canada's acceptance. For the purposes of relevance, assessors were asked to compare the UMBRA framework to an existing Canadian framework for HTR (CADTH's Therapeutic Review).

METHODS

Qualitative description was chosen as the research method for this study for two reasons. First, this research method facilitates the translation of results directly to pressing health care situations and provides clear information about ways for improvement (18) and second, the purpose of this study is directly aligned with the aim of qualitative description which is rich, straight description of an experience or an event from the participant's point of view (19).

Setting, Participants, Sampling

Fundamental qualitative description principles guided all sampling, data collection and analysis decisions (20-22). A purposeful sample of HTA agency assessors were asked to participate in one telephone interview between 30 and 60 minutes in length as well as to respond to a member checking email. Criterion based sampling was used to ensure participants could provide data which was information-rich and highlighted their experience (20). Study inclusion criteria were: 1) Ability to speak English 2) Current HTA agency employment or participation on an HTA agency expert committee 3) Experience in the use of decision processes for HTA and/or HTR for prescription medicines or participation in any research regarding qualitative decision-making frameworks.

Eight participants were interviewed. This sample size was considered to be operational as we identified relatively few participants who could meet the inclusion criteria. Maximum variation sampling included searching for variation in participants experience with a qualitative decision framework and insights into the use or modification of the UMBRA framework. Participants

continued to be added to the study until theoretical saturation was achieved. Theoretical saturation was achieved as themes were consistent between participants, the relationship in the data between existing themes was clear and no new potential participant names were suggested by interviewees (21).

Snowball strategies were used to identify the purposeful sample. First, key informants identified some potential participants who could provide rich, straight description of their experience with HTA/HTR qualitative decision frameworks. Second, participants were asked to identify other assessors/expert committee members who met the inclusion criteria. In either case, potential participants were contacted by a person in authority at the agency who agreed to assessors being approached. Research sampling was fairly homogeneous given the similarity of participant member's socio-economic group status and professional and educational background. In addition, participants all experienced the phenomenon under study. Hamilton Integrated Research Ethics Board approval was received prior to the commencement of any study activities.

Data collection and analysis

An individual, semi-structured telephone interview with open-ended questions was conducted with each participant. Semi-structured interviews allowed the researcher and participant to engage in a dialogue where initial questions could be modified in light of the participant's response and the researcher could probe for further understanding (23). The qualitative study was described to each participant via a telephone call and inclusion criteria confirmed. If participants agree to proceed with the study an introductory email was sent which included the

Qualitative Participant Information Sheet and Consent Form. Each participant's consent was obtained (via email) prior to conducting the participant interviews. All identifying information was removed from the data by use of an ID code to ensure participant and organizational anonymity and confidentiality. An initial interview guide was developed. This interview guide and pursuing methods were verified by a colleague with expert knowledge in this area and pilot tested with different colleagues with expertise in framework development to ensure questions were refined and research procedures operational (21).

Data analysis used the framework of content analysis as proposed by Miles and Huberman (1994) (22). Interviews, with the permission of participants, were captured verbatim through tape recording, transcribed, reread and any field notes reviewed after each transcription while listening to the tapes to ensure reflection of the rich description, accuracy of the data and a flavour of the responses.

One primary analyst coded all transcripts while a secondary analyst ensured peer review through coding a random sample (25%) of all transcripts. This process served as quality control analysis to ensure codes reflected what was in the data and not the primary investigators biases. Transcripts were coded and codes grouped into themes using NVivo (version 11) qualitative data analysis software. The review of coding and themes was an iterative process using constant comparison analysis (24-25), given that each participant's experience might result in a modification to previous codes or themes. Themes were discussed with the secondary reviewer to ensure they flowed from the findings and alternative interpretations were not the most plausible. The primary investigators own biases were

assessed and how these were influencing the interviews and data analysis process through ongoing reflection.

Each participant received an email for validation or member checking. Member checking involved asking each participant to confirm the coding developed from their interview and to review themes. Participants were asked for permission to use any direct quotations in this publication. Further details on the data strategy may be found in Supplementary Table 1.

Data representation is a straight descriptive summary of the themes found through analysis of the interview data. Themes are presented in a language similar to the participant's own language (20).

TRUSTWORTHINESS

Trustworthiness is explained by the term rigour, which is defined as the "goodness" of qualitative research (26). To assess and establish rigour within this qualitative descriptive study, the framework of Whittemore *et al* (2001) (27) was used in combination with enhancement techniques proposed by Milne & Oberle (2005) (28). This framework identifies credibility, authenticity, criticality, and integrity as primary validity criteria and enhancement techniques, related to these criteria, describe study methodology to ensure validity criteria are met. Please see Supplementary Table 2 for the expressions of rigour and enhancement techniques used in this research.

RESULTS

Participants

Qualitative interviews were conducted with eight participants meeting the inclusion criteria. One additional interview was scheduled but this participant was excluded as they did not have experience with HTA and/or HTR for prescription medicines and had not participated in qualitative decision-making framework research. Participants ranged from individual contributors to director level positions and held clinical, economic, stakeholder outreach and policy positions. Amongst participants there was a varying degree of knowledge of qualitative benefit-risk frameworks and this research was not top-of-mind. Two participants of the eight indicated that they had participated directly in research regarding qualitative benefit-risk frameworks (one within an agency and another in a previous role) while a third indicated some involvement in such research. None of the participants were currently involved in research in qualitative benefit-risk frameworks. Participant interviews resulted in four common themes emerging (Table 2).

Adoption of a Qualitative Benefit Risk Framework

All participants agreed that their organization does not currently employ “a defined qualitative decision-making framework” (Interviewee 4). Participants were familiar with a few general Canadian frameworks and a process for HTR. These included, the Common Recommendation Framework which supports the Canadian Agency for Drugs and Technologies (CADTH) drug expert committees in making recommendations to the participating jurisdictions to guide reimbursement decisions (29). This framework includes CADTH’s recommendation categories (reimburse, reimburse with clinical criteria and/or

conditions and do not reimburse) and highlights some of the factors that CADTH's drug expert committees, in formulating a reimbursement recommendation, will consider to provide guidance to the participating jurisdictions (29). CADTH's Therapeutic Review Framework and Process was discussed. This framework is used for non-oncology prescription medicines by CADTH's and their expert committee to make HTR recommendations (16) (Table 1). Finally, the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee Deliberative Framework was described as outlining considerations for the oncology expert review committee to formulate a funding recommendation (30).

In general, participants felt that CADTH's Therapeutic Review Process was considered to embody the steps found in the UMBRA framework.

One participant re-emphasized this point by stating:

"You know each of these eight elements, I would say, are already part of the [CADTH Therapeutic Review] process they are just not laid out in this sort of discrete parcel of steps." (Interviewee 2).

Participants were divided as to whether UMBRA's structured set of decision steps would provide additional value in light of current agency processes. About half of the participants felt that the UMBRA framework could provide a more structured approach to HTR assessment. One participant felt, it would be:

"Nice to have this kind of framework in place, from a conceptual perspective, to say that this is the approach we take and we consistently apply, so that it is clearer." (Interviewee 2). He continued:

"It's actually a long standing question for us…we have a more defined

> recommendation framework but the deliberative sort of framework and other pieces of the framework that we use for coming up with our reviews have always been a bit more nebulous and not well defined. There's been many people... that said well we already do it, so what is the point of actually documenting it… others have said it needs to be clear to our stakeholders,… that we take a consistent approach to every review. I see the benefit of having something laid out because I like the idea … that we apply consistency across each of the reviews. I think the one caveat to that would be that sometimes…, especially from the expert committee, … they feel handcuffed by a framework." (Interviewee 2).

Another participant reiterated the need for HTR reviewers and experts to have a more systematic approach to evaluating drug therapies and provided additional comment on the steps in the UMBRA framework where it was felt more clarity would be welcomed.

> "I think we need a more systematic approach in our process for evaluating therapies and part of that is being explicit on the guiding principles that we have… I think really being clear on Steps 1 through 4 can help us." (Interviewee 3).

Data (Either Too Much or Not Enough)

Data requirements were a consideration when it came to an HTA agency adopting a qualitative benefit-risk framework. Participants highlighted the number of treatments and associated studies with potentially relevant HTR outcomes but which may not be comparable given different clinical study designs. Specifically the additional resource requirements to enact a structured benefit-risk framework for HTR assessment versus a Regulatory review were a

concern for two participants. The lack of data, as it relates to comparable evidence, was also highlighted. One participant states:

> "There are a lot of outcomes that you would love to have but you know based on experience, based on inputs from clinical experts, they are simply not studied in clinical trials." (Interviewee 4).

In these cases, if feasible and justified methodologically, assessors may generate their own comparative evidence of a technology undergoing HTR and its alternatives through indirect comparison. Even so, data gaps can exist and some participants felt this concern was alleviated, through transparent disclosure, when called out in a HTR recommendation.

Importance of Incorporating Stakeholder Feedback

Stakeholder feedback (in addition to the contribution from agency and expert committee members) was considered crucial to the HTR process. Participants defined stakeholders broadly, but mainly identifying clinicians, patients/patient groups and drug plan personnel as stakeholders and less frequently mentioning industry and the public at large as stakeholders. One participant particularly emphasized the need for additional stakeholder input from the patient.

> "I think you would need more stakeholders to really work in the values, within our process you have the evidence from clinical trials but the values come from the lived experience from the patients." (Interviewee 6).

For the most part, it was felt that stakeholder input should be sought and/or considered in Steps 1-4 (Table 3). One participant provided a different perspective indicating that additional stakeholder feedback could refine the list of benefits and risks in Step 3. This participant felt

that stakeholder feedback may not be required in Step 2 – Building the Value Tree where reviewers/assessors select relevant risks and benefits for consideration but instead stakeholder feedback should be integrated into Step 3 – Refining the Value Tree.

Feasibility of the UMBRA Framework

Participants reviewed each step of the UMBRA framework providing their insights on if and how these steps could be modified for applicability to HTR. Table 3 describes participant's feedback, specifically, UMBRA framework additions, deletions and general comments.

The main criticism of the UMBRA framework by some participants related to Steps 2-6 and their applicability to HTR. First, the approach to defining/prioritizing risks and benefits was considered to be different for HTR. One participant stated:

> "the process makes a lot of sense… but, I really feel it is important to talk about the change in benefit that is important and not just the outcome. It's talking about identifying the relevant outcomes and what would be a meaningful impact to people." (Interviewee 3).

This participant went on to say:

> "You have to think about how these outcomes are able to be measured and collected and whether you are able to actually capture a meaningful difference. You kind of need to know which ones matter but also, what is a meaningful difference in each of these outcomes?" (Interviewee 3).

The ability to consider comparative effectiveness, clinical relevance and meaningful differences in multiple treatment outcomes was seen as a challenge for HTR. Given this complexity, some

participants felt it would be challenging to methodically complete some steps in the UMBRA framework.

Step 4 of the UMBRA framework involves (as applicable) the reviewer applying "expert judgment to rank or weigh the relative importance of the benefits and risks/harms, according to the perspective of the decision makers or other stakeholders." (10). However, half of the participants felt that the number of different outcomes (e.g. efficacy, safety, societal, economic) considered in a HTR and differing stakeholder values could pose a challenge in gaining consensus. One participant stated:

> "You are going to have to reconcile differences of opinion on how the clinical expert feels about a particular endpoint versus how a patient group feels versus a manufacturer, there's always going to be some differences there so I think it can be really challenging to put a discreet weight on something." (Interviewee 4).

Two participants believed this step to sound like Multi Criteria Decision Analysis (MCDA) which one believed had not "caught on the way people thought it would" (Interviewee 8) or didn't "think there is clear consensus in the HTA world on this idea of ranking or weighing endpoints" (Interviewee 4).

Instead a few participants mentioned the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework as a way to rank or weigh endpoints (31).

> "I think it is done, in an informal manner, but more so in that GRADE style of individual values and preferences as to how particular experts feel about

particular outcomes." (Interviewee 4).

This participant also believed that these types of statements were important to ensure transparency around a committee's thinking and how they interpreted all the different endpoints. A few participants believed existing frameworks, such as pCODR's deliberative framework (30), could be an alternative to ranking and weighing and one felt the incremental cost-effectiveness ratio (ICER) already accomplished this goal. Another reference was made to the potential value of using GRADE tables (31) for presentation of summary data to ensure consistency and user comprehension.

DISCUSSION

In today's environment, policy-makers face considerable challenges. They are asked to meet a population's demands and expectations however, they must do so with limited health care budgets. Scarce resources, must be allocated strategically to maximize population health outcomes. Reassessing the value of potentially wasteful health technologies would allow the partial or full cessation of funding allocation to these technologies with the possibility to reallocate funds to technologies with greater benefits (e.g. clinical effectiveness, quality of care, and cost effectiveness) (15).

HTR is one tool to realize this goal as the assessment phase allows traditional health technology assessment methods (usually reserved for managing the adoption of new technologies into a health care system) to be applied to a therapeutic category or class of drugs to actively manage economic re- or dis- investment opportunities. This allows a greater economic equilibrium as funds can be reallocated throughout a health system budget,

optimizing value for money. Overarching challenges do exist in conducting and implementing HTR for medicinal products. These include; lack of relevant evidence and comparative data; lack of transparent HTR mechanisms, heterogeneity in patient outcomes; lack of collaboration; political and social barriers; and stakeholder loss aversion, entitlement, inertia and entrenchment (13, 32-34).

The UMBRA framework, a qualitative benefit-risk framework, was developed to improve the transparency, consistency and rigour of health authority's decision-making processes and to facilitate the presentation and dissemination of relevant decisions/recommendations and accompanying rationale in a systematic and standardized way (10). This framework includes steps to: gather relevant data, determine and refine the benefit and risk outcomes of interest, rank these benefits and risks, compare to comparators/alternatives, evaluate the uncertainty regarding the type and magnitude of the benefits and risks, provide a conclusion and recommendation (including expert judgement) and present results/conclusions (10). Given the purpose of qualitative benefit-risk frameworks and the structure of the UMBRA framework, it was postulated that the implementation of this framework within the HTR assessment process could alleviate some of the above described challenges.

Canadian HTA agency assessors provided their insights as to whether the UMBRA framework could be used or modified for HTR to meet decision-making and communication needs. Four common themes were identified. In general, participants felt that CADTH's Therapeutic Review Process embodied the steps of the UMBRA framework. However, the Therapeutic Review Process was preferred for both the variety and timing of stakeholder feedback, and for

the absence of ranking or weighing. Participants recognized that the Therapeutic Review Process does not currently include a transparent, deliberative qualitative framework (e.g. the UMBRA framework) to aid CADTH and CADTH's expert committee in decision-making and recommendation dissemination. The authors and several participants believe that integrating a qualitative framework into the Therapeutic Review Process could aid deliberations to produce a recommendation, ensure specific criteria are considered, provide consistency in considerations and frame recommendations through a concise summary of the evidence considered and judgements made. This could further progress the implementation of a recommendation at the jurisdictional level and provide additional context for stakeholders affected by a decision. To develop a deliberative qualitative framework, both a process and a set of guiding recommendation criteria are required.

LIMITATIONS

The aim of qualitative description is a rich, straight description of an experience or an event (19). However, "descriptions depend on the perceptions, inclinations, sensitivities and sensibilities of the describer" (35). This introduces the possibility that researcher bias could be present in reporting the results of the study. To minimize such limitations this qualitative descriptive study design included various expressions of rigour and enhancement techniques (Supplemental Table 2).

This research focused on Canadian HTA agency assessors past experiences and insights to inform any modifications to the Universal Methodology for Benefit-Risk Assessment (UMBRA) qualitative framework. Experiences and insights from other key stakeholders such as other

drug formulary managers (budget holders), patients (users), and prescribers (health care providers) were not sought in this research and therefore did not inform the study results. Future research, should a proposed qualitative benefit-risk framework be drafted or modified, ought to include stakeholder framework feedback to ensure useability and functionality.

It is unknown whether the experiences and themes revealed by this study, conducted with eight participants, can be extrapolated to other Health Technology Agencies across geographical areas and social contexts. This is a methodological and qualitative question that needs to be addressed through further research, potentially by developing a qualitative recommendation framework for one HTA agency and assessing the need for modification with other agencies.

CONCLUSIONS

This research highlighted that a deliberative qualitative recommendation framework for use by both HTA agency assessors and expert committees could be a beneficial addition to an HTR process. Such a framework could enhance the consistency (through development of a standard set of criteria for consideration) and transparency (with the use of a publicly available dashboard) of the decision-making process. Research participants did not consider all steps of the UMBRA framework to be transferable to the assessment phase of HTR though they did acknowledge some strengths. Participants emphasized the complexity of HTR, given the lack of comparative data yet need to consider comparative effectiveness, clinical relevance and meaningful differences. They also emphasized the importance of stakeholder input throughout the HTR process (particularly that of the patient, their caregivers and the clinician). Simplicity,

resource efficiency and stakeholder input are points for consideration in the development of a qualitative recommendation framework for HTR. HTA agency assessor experiences and insights and resultant key themes can be used in future research to aid in the development of a qualitative recommendation framework for HTR.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Data Analysis www.journals.cambridge.org/

Supplementary Table 2: Expressions of rigour and enhancement techniques for a qualitative description design www.journals.cambridge.org/

CONTACT INFORMATION

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CONFLICT OF INTEREST

This work has been completed in partial fulfillment of the requirements for Mary Alison Maloney's PhD degree in Health Research Methodology at McMaster University. In addition, Mary Alison Maloney works full-time as the Vice-President of North America Consumer Health Regulatory Affairs for Bayer US LLC. This work was done independently of any affiliation or information exchange with Bayer. Dr. Lisa Schwartz's Arnold L. Johnson Chair in Health Care Ethics is funded through a private endowment; Dr. Schwartz was a member of an Expert Review Panel for CADTH until April 2017. Dr. Mitchel Levine and Dr. Daria O'Reilly have no potential conflicts of interest. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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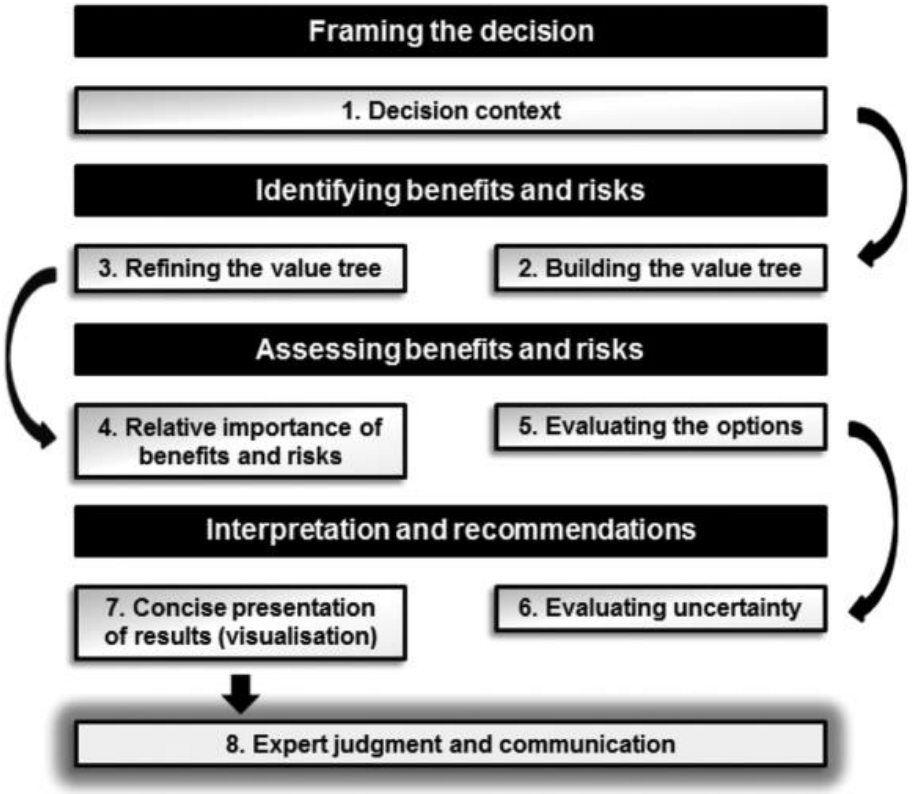
FIGURE 1: Components of an Eight-Stage Decision Framework (UMBRA) (10)



Step 1: Decision Context	Drug names, active ingredients, strength, dose forms, formulation, proposed indication, approved indication, Regulatory history (including previous reviews), treatment options evaluated in submission, whether it meets an unmet medical need, local clinical guidelines or other issues to contextualize decision context, summaries of submission components (including patient population, comparator(s), time horizon for outcomes and any significant findings)
Step 2: Building the Value Tree	Identify and select all relevant outcomes (both as inferred in the submission or found by reviewers) and create an initial value tree (alternatively, list all benefits and risks/harms)
Step 3: Refining the Value Tree	Indicate which benefits/risks are justified to be included in the assessment and document the rationale for including in or excluded from the initial value tree. Modify the value tree based on further review of the data and clinical expertise.
Step 4: Relative Importance of Benefits and Risks	If applicable, reviewer applies expert judgment to rank or weigh (relative importance) of the benefits and risks/harms, according to the perspective of the decision makers or other stakeholders.
Step 5: Evaluating/scoring the Options	Score/assess the performance/outcome of the benefits and risks/harms against options, placebo drug under investigation and/or comparator. Provide either qualitative (high/med/low/absent) or quantitative values (from study outcomes) for each benefit and risk/harms.
Step 6: Evaluating Uncertainty	Conduct sensitivity analyses to assess the impact of uncertainty in data sources/evidence package. While uncertainties cannot be ruled out, the objective of this step is to make the analysis more transparent and increase confidence in the benefit-risk assessment process and the results. Describe the variability both within and between studies: uncertainty regarding whether or not the available information predicts the true relationship between the study drug and the range of benefit-risk outcomes. Consider how the balance between benefits and harms is affected by uncertainty.
Step 7: Concise Presentation of Results (Visualization)	Summarize the data in tabular (i.e. key benefit-risk summary tables) and, if possible, by graphical displays (e.g. forest plot, waterfall diagram) to aid review and interpretation. Where possible, the quantitative measures of the criteria should be explicitly provided.
Step 8: Expert Judgment and Communication	Expert judgement provides the overall outcome/conclusion and whether the benefit-risk balance is positive or negative. Describe any outstanding issues and other significant information and how they will be addressed and need, if any, for further studies. Finally, a clear conclusion and recommendation should be provided. This judgement can be combined with the objective outcome measures to communicate the benefit-risk of the decision maker in a transparent way.

Table 1: CADTH Therapeutic Review Process (16)

	Definition
The Canadian Agency for Drugs and Technologies in Health (CADTH)	• A Canadian not-for-profit organization which provides health-care decision-makers (e.g. provincial and territorial government drug plan administrators, outside of Quebec) with evidence/recommendations to help make informed decisions on the optimal use of health technologies, including prescription medicines.
Health Technology Assessment (HTA)	• CADTH conducts HTAs with prescription drugs to evaluate the clinical and cost effectiveness, as well as, the ethical, legal, and social implications of these drugs on patient health and the health care system. This process manages the adoption of new technologies into the Canadian health care system.
Therapeutic Review Process	• CADTH conducts Therapeutic Reviews (which are Health Technology Reassessments) in regards to a therapeutic category of drugs or a class of drugs. This process includes the steps of identification/prioritization, assessment and dissemination and allows traditional health technology assessment methods to be applied to a therapeutic category or class of drugs to actively manage economic re- or dis-investment opportunities. • The Therapeutic Review Process does not specify specific differences from HTA (e.g., prioritization criteria; levels or types of evidence).

	Definition
	• Therapeutic Reviews result in CADTH issuing reimbursement recommendations. These recommendations are completed for federal, provincial, territorial government plan administrators and health policy-makers to aid in their decision-making about the optimal use of, access to, or reimbursement of prescription medicines. • Therapeutic Reviews generate publically available reports including a Science Report (clinical and economic review) and Expert Committee Recommendations and/or Advice Report. • CADTH also provides, as needed, tools and recommendation implementation support to administrators and policy-makers.
Government plan administrators and health policy-makers	• Government plan administrators and health policy-makers review Therapeutic Review reports and may make reimbursement decisions based on the information contained within them. CADTH does not make reimbursement decisions. • Reimbursement decisions may include removal from funding schedules (delisting), partial delisting, risk-sharing with reimbursement only under specific required conditions or additional listing. • The Therapeutic Review process does not specify how reassessment recommendations should be operationalized by government plan administrators or health policy-makers.

Table 2: Summary of Themes and Findings

Theme	Findings
Adoption of a Qualitative Benefit Risk Framework	• HTA agency does not currently employ a defined qualitative decision making framework. • Participants were divided on whether a more structured qualitative B/R framework would improve the HTR process. • CADTH's Therapeutic Review Process was considered to embody the steps found in the UMBRA framework.
Data (Quality and quantity)	• Some participants felt, in general, that available clinical data is not ideal to make HTR recommendations. Resource requirements needed to fully assess all data and gaps in required clinical outcome data make a structured framework more difficult to complete.
Importance of Incorporating Stakeholder Values	• Stakeholder feedback was considered crucial to the HTR process and any framework.
Feasibility of the UMBRA Framework	• The ability to consider comparative effectiveness, clinical relevance and meaningful differences in multiple treatment outcomes was seen as a challenge for HTR and an added complexity to consider in the UMBRA framework. • Ranking or weighing relevant outcomes was considered challenging given the difference in outcomes and stakeholder preferences. • The GRADE and pCODR deliberative frameworks or the ICER were suggested as alternatives for ranking and weighing.

Table 3: Suggestions for HTR UMBRA Revisions

Step 1: Decision Context	
Data Additions: • Utilization data (Interviewee 2) • Economic evaluation (e.g. cost, cost effectiveness, cost minimization, cost utility, budget impact) (Interviewee 2, 3, 4, 6, 7) • Political considerations (Interviewee 3) • Reimbursement history (Interviewee 3) • Public health issues (Interviewee 3) • Prescribing practices (Interviewee 3, 5, 7) • Off-label use (Interviewee 3) • Patient or provider support programs (Interviewee 5) • Research policy question (Interviewee 4, 6) • PICO statement (Interviewee 4, 7)	**Deletions:** • "Submission components" as de novo work such as systematic reviews, economic models are included instead (Interviewee 7)
Additional Stakeholder Input: • Clinician, drug plan jurisdiction, patient input (Interviewee 2, 4, 5, 7) • Expert committee input (Interviewee 2, 4) • Industry input (Interviewee 4)	
Step 2: Building the Value Tree	
Additions: • Focus on outcomes where data exists (Interviewee 4) • Consider adoption and feasibility (Interviewee 6) **Additional Stakeholder Input:** • Patient, clinician (Interviewee 3, 5, 6) • Drug plan jurisdiction (Interviewee 3, 6)	**Deletions:** • Term value not the correct terminology (Interviewee 2, 3) • Modify to "defining the benefits and risks" (Interviewee 2) or "Identify the goals of treatment" (Interviewee 3) **Comments:** • How would you capture /measure a meaningful difference in each outcome and what is the relevance of this difference (Interviewee 3) • No additional stakeholder input in this Step as this input should help "Refine the Value Tree" (Step 3) (Interviewee 7)

<table>
<tr><th colspan="2">Step 3: Refining the Value Tree</th></tr>
<tr><td>Additional Stakeholder Input:
• Patient, clinician (Interviewee 3, 4, 5, 6, 7)
• Drug plan jurisdiction (Interviewee 7)</td><td>Deletions:
• Term value not the correct terminology (Interviewee 2, 3)
• Modify to “refining the benefits and risks” (Interviewee 2) or “Prioritizing your goals” (Interviewee 3)</td></tr>
<tr><th colspan="2">Step 4: Relative Importance of Benefits and Risks</th></tr>
<tr><td>Additions:
• Clinician, public, patient groups to help determine importance as experts (Interviewee 3, 8)
• Focus on whether differences are clinically relevant (Interviewee 4)
• Focus on the values and preferences of stakeholders (as per GRADE) where the evidence exists (as per current process) (Interviewee 4)
• Look at the most homogenous set of data (GRADE framework) (Interviewee 7)
• Bucket/group harms and benefits (refine and group). Split benefits into hard endpoints (Interviewee 7)
• Include everything in the evaluation that is relevant without necessarily ranking or discounting anything (Interviewee 8)</td><td>Comment:
• Challenging to gain consensus (due to the need to have data and reconcile stakeholder differences) to put a discreet weight (or even a ranking) on something (Interviewee 4, 7)
• Also challenging to rank efficacy, safety and economic items (Interviewee 4, 7)
• Challenging to attribute a score to an outcome, what does that score really mean? (Interviewee 6)
• Some harm outcomes would also be ranked first and how would you rank order clinical benefits to these? (Interviewee 7)
• Can’t put weights on aspects that are not objective (Interviewee 8)</td></tr>
<tr><th colspan="2">Step 5: Evaluating the Options</th></tr>
<tr><td>Additions:
• Is there a meaningful difference (meeting a threshold)? How well is that drug achieving that goal in comparison to the others? (Interviewee 3)</td><td>Deletions:
• Remove placebo (Interviewee 2)</td></tr>
</table>

	Comments: • Risk/benefits for economic done via QALY (Interviewee 2) • How do you translate high, medium, low or absent into how meaningful an outcome is (Interviewee 4) • How do you differentiate between comparators for the different outcomes, when there may not be clinically meaningful difference or changes within those outcome measures (Interviewee 7) • If there isn't comparator information lots of uncertainty (Interviewee 7) • Heterogeneity associated with different studies (different times, different populations etc.) makes it challenging to compare across relevant outcomes to make firm recommendation with respect to how looks comparatively. In this case could identify there is a gap (Interviewee 7)
Step 6: Evaluating Uncertainty	
No comments	**Comments:** • Valuable (3, 4, 5, 7)
Step 7: Concise Presentations of Results	
Additions: • Should present the uncertainty (Interviewee 3) • Use GRADE to ensure consistency (with GRADE tables, but may be challenging to create) (Interviewee 7)	**No comments**
Step 8: Expert Judgement and Communication	
No comments	**No comments**

Supplementary Table 1: Data Analysis (21;22)

Analytic Strategy	Details
1. Review of transcript and field notes (note this step has been added to the Miles and Huberman method) (22)	-Each participant's data and any interviewer field notes reviewed shortly after one-on-one interview • Review will encompass reading each participant's transcript to gain an overall flavor of the responses
2. Coding of data	-Interview and field notes: • Reviewed and broken into smaller units • Units coded or named according to the main broad content or emphasis they represent • Peer review of a sample of the coded data
3. Recording insights and reflections on the data	-Interviewer insights and reflections on the data recorded
4. Sorting through the data to determine similar phrase, patterns, themes, sequences and important features	-Develop themes by sorting initial codes into general categories and subcategories • Categorization reflects similarity in regards to process satisfaction
5. Looking for commonalities and differences and extracting for further consideration and analysis	-Themes reviewed for commonalities and differences -Peer review to confirm themes
6. Member checking	-Participants asked to confirm coding and themes developed from their interview
7. Deciding on small group or generalization that hold true for the data	-Themes assessed as a whole to determine which ones most strongly represent the experience of the participants -Peer review to confirm themes
8. Examining these generalizations in light of existing knowledge	-Participants responses reread and categorized into one of the themes to ensure goodness of fit -Peer review
9. Member checking	-Participants granted permission for any direct quotations to be used for publication

Supplementary Table 2. Expressions of Rigour and Enhancement Techniques for a Qualitative Description Design (19;27-28)

Expression of Rigour	Enhancement Technique

Authenticity (Attention to the voice of participants)	• Participants able to speak freely
	  ○ Purposeful sampling
	  ○ Gaining trust
	  ○ Interviews conducted in a neutral location
	  ○ Participant-driven data collection through implementation of a flexible interview guide and flexibility to allow participant to tell their story
	• Participants are heard
	  ○ Promoting richness of data through probing for clarification and depth
	• Participants perceptions represented accurately
	  ○ Accurate transcription confirmed by rereading transcription while listening to tapes and member checking
	  ○ Content analysis (data-driven coding and categorizing themes)

Credibility (How believable are results)	• Capturing and portraying a participants perspective
Criticality (Critical appraisal of every decision made)	• Reflection on the critical appraisal applied to every research decision
Integrity (Ongoing reflection of self-criticality of researcher)	• Reflecting on researcher bias and preventing that bias from influencing participant data • Participant's validation/member checking • Peer review

APPENDIX 1: Material Shared with Study Participants

Invitation to Participate in the Qualitative Study

To be discussed verbally by phone with each potential participant.

Hi <<Name of Potential Participant>>,

My name is Alison Maloney, I am currently a PhD candidate at McMaster University and I am conducting research on qualitative decision frameworks and their use for Health Technology Reassessment. There is no published research to date which has examined this topic with any Health Technology Agency and your contribution to my research would help inform the content of a decision framework for Health Technology Reassessment.

I am conducting a two-phase research study to inform and then gain consensus on the use or modification of a qualitative decision-making framework (called UMBRA). The design of these studies is meant to ensure a Health Technology Reassessment framework addresses decision-making and communication needs of a Health Technology Assessment Agency.

In the first stage of this research I am interviewing [redacted] employees and expert committee members to understand their past experiences with qualitative decision-making frameworks and their insights into how the UMBRA framework could be modified. To understand your past experiences and insights in this first phase of my research, I would like to conduct one telephone interview with you of approximately 30 to 60 minutes in length. This interview will be taped. Following the first interview, I will provide you with a summary of your insights and developed themes. To ensure I have accurately captured your thoughts, I will ask you to confirm your insights and the associated themes by email. I will provide you, by email, the final research findings and confirm your agreement to publish any direct quotes from our discussion in my research. Publication links of this research will be shared with you. Please remember

that your participation in this research is completely voluntary and I will ensure all information that you provide is kept private and confidential by removing your name from all transcripts, any dissertation discussions and published study findings through the use of a coding system. In addition, you will remain anonymous to the other participants throughout this qualitative study.

This Phase 1 research will be approved by the Hamilton Integrated Research Ethics Board prior to commencement of the study.

Your first-phase input will help determine the need for any UMBRA framework modifications. [redacted]

This two-part study has inclusion criteria which I think you might meet, based on an initial discussion and recommendation from [redacted]. The inclusion criteria in this study are as follows:

1. Do you currently work at or for [redacted]?
2. Have you or do you participate in Health Technology Assessments (HTAs) and or Health Technology Reassessment (HTRs) for prescription medicines?
3. Have you participated in any research regarding qualitative decision-making frameworks?

If you answered yes to the first and either second or third questions, you have met the inclusion criteria. Based on this information, would you participate in this study?

If agreement is verbally obtained to participate:

Thank you very much for your agreement to participate. If you have additional questions please e-mail me at alison_maloney@optimum.net or call me at <<[redacted]>>. As a next step, I will email you a Participant Information Sheet and a Consent Form. I will also email you a few dates/times for a first interview. Please review all information provided and, if you are in agreement, email me back your consent as well as the dates and times that would work for you for our first interview.

If no agreement:

Thank you for your time to discuss my research.

Introductory email to Phase 1 Study Participants

To be sent to Phase 1 participants prior to telephone interview.

Re: Study Participation: Health Technology Reassessment: A Decision Framework Phase 1

Dear <<Name of Potential Participant>>,

Further to our telephone discussion and your verbal agreement to participate in research on reassessment decision frameworks, please find attached a participant information sheet and consent form. I have also included below a few dates/times for an interview. Please review the documents provided and, if you are in agreement, return the completed consent form as well as the dates and times that would work for our interview to me via email at alison_maloney@optimum.net. If you have questions or require further information on this study you may contact me at alison_maloney@optimum.net or by phone at [redacted].

Best wishes,

Alison Maloney MFS, MBA

McMaster University Health Sciences

Qualitative Participant Information Sheet

Title of Study: Health Technology Reassessment: A Decision Framework Phase 1

Locally Responsible Investigator and Principal Investigator: Alison Maloney; McMaster University

Co-Investigator(s):

Dr. Lisa Schwartz, Dr. Mitchel Levine and Dr. Daria O'Reilly McMaster University

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You are being invited to participate in a research study conducted by Alison Maloney. In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study, which has already been discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate. Please take your time to make your decision.

What is the purpose of this study?
The purpose of the Phase 1 research is to understand [redacted] past experiences and insights to inform any modifications of a qualitative decision-making framework for HTR.

Why have I been chosen?
You have been asked to take part because you have been identified as being knowledgeable in this area.

Do I have to take part in this study?
It is up to you to decide whether or not to take part and there is no obligation. If you decide to take part you will be asked to sign a consent form. You will receive a signed copy of the consent form via email. If you decide to take part, and then change your mind, you are free to withdraw at any time by contacting Alison Maloney via email at alison_maloney@optimum.net, without giving a reason.

If you decide not to take part in this study, this decision will in no way impact your employment status.

What will my responsibilities be if I take part in this study?

If you volunteer to participate in this study, we will ask you to do the following things:

In the first stage of this research you will take part in:

- one telephone interview of approximately 30 minutes in length which will be taped
- reviewing, by email, a summary of your insights and developed themes and be asked to confirm this information

You will be asked to confirm your agreement to publish any of your direct quotes used. Publication links of this research will be shared with you.

The following points are important for you to remember:

1. Your participation is entirely voluntary
2. You may decide to withdraw from the study at any time
3. You will remain anonymous to other participants throughout this qualitative study and only the researcher will be able to identify your specific answers
4. All records are confidential. Your name will only be recorded on the consent form; it will not be recorded on any transcripts and instead a coding system will be used. This information will only be available to members of the research team. All information will be destroyed (at a maximum) of 5 years after the research is complete
5. Any information that you provide will be confidential and when the results of the study are reported, you will not be identifiable in the findings
6. Following the study research collection, a paper will be sent for publication to a professional journal and will be discussed during a PhD dissertation defense. All details about the people who took part in the study will be kept anonymous
7. You will only have to complete this consent form once as it encompasses the whole Phase 1 qualitative study

What are the potential risks of participating if something goes wrong?
Participants may feel uncomfortable with some of the questions asked. If this is the case, the participant need not respond to any question which makes them uncomfortable. There is a very small risk of confidentiality breach, however, the researchers have taken every precaution (see above information) to ensure that this does not occur.

Will my taking part in this study be kept confidential?
If you consent to take part in this study, your name will not be disclosed and you would not be revealed in any reports or publications resulting from this study. Apart from your consent form, your name will not be recorded on any transcripts. Each participant will be allocated a unique code. You will remain anonymous to the other participants throughout this study and only the researcher will be able to identify your specific answers.

What will happen when the research study stops?
The results of this project will be used to define the hypothesis and item pool of a questionnaire used to further develop a qualitative decision-making framework for use in health technology reassessment. The findings of Phase 1 of this research will be sent for publication in a professional journal and will be discussed in a PhD dissertation defense.

Who is organizing and funding the research?
Alison Maloney is organizing and funding this project.

What are the possible benefits of taking part?
I cannot promise that this study will help you as an individual, but the information that is obtained will help to develop a qualitative decision-making framework for Health Technology Reassessment specific to Health Technology Assessment Agency needs and inform future research on this topic.

If I have any questions or problems, whom can I call?
If you wish to contact someone for further information you can contact the researcher of this study, Alison Maloney, who is a PhD candidate at McMaster University. She may be contacted at alison_maloney@optimum.net or by phone at [redacted].

CONSENT STATEMENT (Phase 1 Qualitative Research)

Participant:

I have read the preceding information thoroughly. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I agree to participate in this study. I understand that I will receive a signed copy of this form.

Name	Signature	Date

Person obtaining consent (principle investigator):

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

Name, Role in Study	Signature	Date

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, Hamilton Integrated Research Ethics Board at 905.521.2100 x 42013.

Consent Form Date: April 17, 2017 Protocol # and version date: 2963 Version #1

Materials Shared with Study Participants: Interview Guide: Phase 1

Text in red will only be verbally discussed with participant.
Text in green will only be provided to participants in advance and not be discussed unless required.
Text in black will be both verbally discussed and provided to participants in advance
Text in blue is only for [AM] as reminders

Interview Guide 1: [redacted] Past Experiences and Insights into Qualitative Frameworks for HTR
Time of Interview:
Date:
Place: Teleconference
Interviewer: Alison Maloney
Participant:
Position of [redacted]:
Introduction to the Research: As we discussed over the phone, I am conducting a two phase research study to inform the use and gain consensus on any modifications of a qualitative decision-making framework (called UMBRA) for Health Technology Reassessment. In the first stage of this research I am interviewing [redacted] to understand their past experiences with qualitative decision frameworks and their insights into how the UMBRA framework could be modified. To understand your past experiences and insights in this first phase of my research, I would like to conduct one telephone interview with you of approximately 30 to 60 minutes in length. This interview will be taped. Following the first interview, I will provide you with a summary of your insights and developed themes by email. To ensure I have accurately captured your thoughts, I will ask you to confirm your insights and the associated themes by email. I will confirm your agreement to publish any direct quotes from our discussion in my research. These quotes would be anonymous. Publication links of this research will be shared with you. Please remember that your participation in this research is completely voluntary and I will ensure all information that you provide is kept private and confidential by removing your name or identifying information from my published study findings or any other discussion of the study results through the use of a coding system. Your first-phase input will help develop any modifications to the UMBRA framework. At a later date, you will be asked to participate in the second stage of this research through questionnaires to gain consensus on any included items of a modified UMBRA framework.
Definitions **Health Technology Reassessment (HTR):**

Interview Guide 1: [redacted] Past Experiences and Insights into Qualitative Frameworks for HTR

Messina and Grainger 2012 definition: A structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives" (1)

This process further enables the reallocation of investments to maximize value for money.

CADTH Current HTR Vehicles: Rapid Responses and Therapeutic Reviews

Qualitative Framework:

Qualitative frameworks frame decision problems through a structured, consistent approach to decision making by "facilitating the selection, organization, summarization, and interpretation of data and preferences relevant to the decision" and aid decision documentation and communication (2).

Purpose of a Regulatory Qualitative Framework as Highlighted by FDA:

"First, a benefit-risk assessment framework must operate within the applicable legal, regulatory, and policy framework for each regulatory decision. Second, a systematic approach to benefit-risk assessment should support the work of review staff throughout the lifecycle of a drug by capturing the full range of decisions from pre-market review through any regulatory actions that are necessary in the post-market setting. It should facilitate identification of the critical issues regarding benefit and risk and faithfully capture the review team's deliberation on those issues. The approach should also focus discussion and communication on the weighing of those issues, ensuring that benefit and risk considerations are kept in mind throughout review. Finally, a systematic approach should efficiently integrate into a review teams' existing processes and work products." (3)

Interview Questions

1. Can you provide more information about your role at or working with [redacted] specifically:
   a. What is the level of your role [redacted](Director, middle management, individual contributor, other) or working with [redacted]?
   b. Can you describe how you have or are currently participating in [redacted] Health Technology Assessments and/or Health Technology Reassessment for prescription medicines?
   c. Can you describe how you have or are currently participating in any research regarding qualitative benefit-risk frameworks?
2. What Health Technology Reassessment vehicles does [redacted] currently employ? (Probe to understand vehicles and details of the processes as required)
3. Has or is [redacted] working to develop a qualitative decision-making framework for Health Technology Assessment/Health Technology Reassessment for prescription medicines? (Probe to understand past or current [redacted] work and framework details if available)

Interview Guide 1: [redacted] Past Experiences and Insights into Qualitative Frameworks for HTR
3. What types of evidence evaluation and steps are required to complete [redacted] Health Technology Reassessment recommendations and decisions? (Probe to understand experience and details as required)
4. Based on the considerations you highlight in Question 3, would you suggest the UMBRA framework (provided in a separate attachment (see Figure 1 above) requires modification for use in Health Technology Reassessment, and if so, what modifications would you suggest are required to meet decision-making and communication needs? (Probe to understand perspectives and details as required)
5. Do you have any suggestions as to additional [redacted] whom I could talk to that have experience with Health Technology Assessment/Reassessment and/or qualitative decision-making frameworks?
Closing Remarks Thank you for participating in this interview and providing your perspective.

References:

1) Centre for Innovation in Regulatory Science. UMBRA Initiative. http://www.cirsci.org/decision-making-frameworks/umbra-initiative/ (accessed Oct 2016).
2) Hughes D, Waddingham EAD, Mt-Isa S, Goginsky A, Chan E. Downey G, Hallgreen C, Hockley KS, Juhaeri J, Lieftucht A, Metcalfe MA, Noel R, Phillips L, Ashby D, Micaleff A. On behalf of IMI-PROTECT Work Package 5. Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medecines. 2013. http://www.imi-protect.eu/documents/HughesetalRecommendationsforthemethodologyandvisualisationtechniquestobeusedintheassessmento.pdf (accessed October 2016).
3) FDA. Structured approach to benefit-risk assessment in drug regulatory decision-making draft PDUFA V implementation plan - February 2013. Fiscal years 2013-2017. 2013. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf (accessed Jan 2017).

HiREB
Hamilton Integrated Research Ethics Board

April 26 2017

Project Number: 2963

Project Title: Health Technology Reassessment: A Decision Framework

Principal Investigator: Ms. Mary Alison Maloney

This will acknowledge receipt of your letter dated April 17-2017 which enclosed revised copies of the Application, Protocol, the Information Consent Form, and the Recruitment Material along with a response to the additional queries of the Board for the above-named study. These issues were raised by the Hamilton Integrated Research Ethics Board at their meeting held on March 21-2017. Based on this additional information, we wish to advise your study had been given ***final*** approval from the full HiREB.

The following documents have been approved on both ethical and scientific grounds:

Document Name	Document Date	Document Version
consenttemplatephase104172017ver1	Apr-17-2017	2
consenttemplatephase204172017ver1	Apr-17-2017	2
Emailscript20170417Version2	Apr-17-2017	2
Questionnaires20170417Version2	Apr-17-2017	2
ResearchProtocol20170417Version2	Apr-17-2017	2
TelephoneScripts20170417Version2	Apr-17-2017	2

The following documents have been acknowledged:

Document Name	Document Date	Document Version
tcps2_core_certificate	Feb-19-2017	Feb 19, 2017

Please Note: All consent forms and recruitment materials used in this study must be copies of the above referenced documents.

We are pleased to issue final approval for the above-named study for a period of 12 months from the date of the HiREB meeting on March 21-2017. Continuation beyond that date will require further review and renewal of HiREB approval. Any changes or revisions to the original submission must be submitted on a HiREB amendment form for review and approval by the Hamilton Integrated Research Ethics Board.

PLEASE QUOTE THE ABOVE REFERENCED PROJECT NUMBER ON ALL FUTURE CORRESPONDENCE

Sincerely,

Dr. Mark Inman, MD, PhD
Chair, Hamilton Integrated Research Ethics Board

The Hamilton Integrated Research Ethics Board (HiREB) represents the institutions of Hamilton Health Sciences, St. Joseph's Healthcare Hamilton, and the Faculty of Health Sciences at McMaster University and operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; For studies conducted at St. Joseph's Healthcare Hamilton, HIREB complies with the health ethics guide of the Catholic Alliance of Canada

CHAPTER 4: A REFINED FRAMEWORK FOR CANADIAN NATIONAL HEALTH TECHNOLOGY REASSESSMENT RECOMMENDATIONS

Mary Alison Maloney [(a1)] ŧ, Lisa Schwartz [(a2)], Daria O'Reilly [(a3)] and Mitchel Levine [(a3)]

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[(a2)] Department of Health Research Methods, Evidence, and Impact (formerly “Clinical Epidemiology and Biostatistics”) Centre for Health Economics and Policy Analysis, McMaster University

[(a3)] Department of Health Research Methods, Evidence, and Impact (formerly “Clinical Epidemiology and Biostatistics”), McMaster University Programs for Assessment of Technology in Health (PATH) Research Institute, St. Joseph's Healthcare Hamilton

ŧ **Corresponding author**

Cited as: Maloney et al. A refined framework for Canadian national health technology reassessment recommendations. 2018. *Int J Technol Assess Health Care*: in submission

INTRODUCTION

Canadian HTA agency assessors recognized that CADTH's Therapeutic Review process (HTR process) embodied the steps contained within the UMBRA framework (a qualitative benefit risk decision-making framework). Although assessors did not feel that all steps of the UMBRA framework were transferable to the assessment phase of HTR, several research participants did believe that the Therapeutic Review Process could benefit from the inclusion of a deliberative decision-making framework. A deliberative framework could aid CADTH and CADTH's expert committee in decision-making and recommendation dissemination, ultimately progressing the implementation of a recommendation at the jurisdictional level and with various stakeholders.

Given this feedback, Phase 2 of the original Chapter 3 research was not completed and instead, this Chapter focuses on assessment and enhancements to CADTH's HTR Therapeutic Review process. CADTH's Therapeutic Review process was first assessed to determine if it: 1) includes HTR framework process components detailed in Chapter 2 and; 2) embodies the ethical concepts of CADTH's Guiding Principles and the Accountability for Reasonableness Framework. Based on this assessment, Therapeutic Review process enhancements were developed drawing upon a systematic literature search (reported in Chapter 2), qualitative research (reported in Chapter 3) and published literature, frameworks and evaluations. Ultimately, it is hoped that this work can contribute to further stakeholder acceptance and implementation of CADTH's HTR recommendations and be considered for implementation by other HTA agencies.

ABSTRACT

Objectives: The objectives of the research were to: 1) assess, from a health technology reassessment perspective, the Canadian Agency for Drugs and Technologies in Health's (CADTH's) Therapeutic Review Process and 2) based on this assessment, to provide suggested enhancements to this health technology reassessment (HTR) process.

Methods: The CADTH Therapeutic Review process was assessed to determine if it includes HTR framework process components and if it embodies the ethical concepts of CADTH's Guiding Principles and the Accountability for Reasonableness framework. Therapeutic Review process enhancements were developed based on a systematic literature search, qualitative research with Canadian HTA agency assessors and published literature, frameworks and evaluations.

Results: The Therapeutic Review process fully recognizes the importance of stakeholder input, including many patient input opportunities. The process appears to be based on sound clinical and economic evaluation, is well detailed, cost-efficient and streamlined. Three areas for process enhancement were found including the development, documentation and implementation of: 1) Therapeutic Review topic prioritization criteria; 2) a qualitative assessment framework, and; 3) publicly accessible mechanisms for decision monitoring and performance measurement.

Conclusions: Suggested modifications to the CADTH's Therapeutic Review process are meant to enhance transparency, objectiveness and performance measurement. As a next step, modifications could be piloted during a Therapeutic Review reassessment.

Keywords: Health technology assessment, disinvestment, qualitative benefit risk framework, health technology reassessment

MANUSCRIPT: A refined framework for Canadian national health technology reassessment recommendations

Health technology reassessment (HTR) is defined as a "structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives" (1). HTR may result in numerous economic re- or dis- investment outcomes, which include: stopping funding (disinvestment), partial disinvestment (narrowing what is paid for), reinvestment (broadening what is paid for) or no change in use (1). The Canadian Agency for Drugs and Technologies in Health (CADTH) conducts health technology reassessment, in the context of existing coverage policies, for a therapeutic category of drugs or class of drugs through its Therapeutic Review process. Therapeutic Reviews are conducted based on the priorities of federal, provincial and territorial government drug plan administrators (jurisdictions), who use these reports to make formulary-listing decisions and to inform optimization of pharmaceutical drug therapies (2).

Therapeutic Reviews are meant to ensure "that the right drugs are prescribed and used appropriately to improve or maintain optimal Canadian health" (2). To do this, decisions are made to maximize benefits and minimize risks based upon available evidence, costs, patient preferences, societal contexts and resources (2). Therapeutic Reviews result in the publication of two reports. A Science Report (including both a clinical and economical review) is written by CADTH employees in partnership with one or more external clinical experts, two Canadian Drug Expert Committee (CDEC) technical experts and one CDEC public member. The Science Report informs CDEC's deliberation in forming a reimbursement recommendation

(Recommendation Report) or advice for optimal use of drugs (Advice Report) within the publicly funded health care system in Canada (2).

HTR decision making is complex. Health Technology Assessment (HTA) agencies must make judgements by weighing available scientific evidence and considering costs and values. HTR requires a transparent framework that "frames a response to an issue and aids deliberation in producing an answer, through making relevant values, principles or issues explicit" (3). This framework should be a useful and pragmatic aid, which ensures important criteria are considered, integrates various viewpoints and allows for clear communication (3).

The objectives of this paper were to: 1) assess, from a health technology reassessment perspective, CADTH's Therapeutic Review Process and 2) based on this assessment, to provide suggested enhancements to this HTR process to facilitate the selection, organization, summarization and interpretation of data relevant to decisions and to aid decision documentation and communication. It is hoped that the CADTH Therapeutic Review Process and suggested enhancements may inform HTR framework development of other HTA agencies.

METHODS

The current CADTH Therapeutic Review Process (2) (Figure 1) was assessed to determine if it: 1) includes HTR framework process components as per a recent systematic literature review (4); and, 2) embodies the ethical concepts of CADTH's Guiding Principles (5) and the Accountability for Reasonableness framework (6) (Table 1). To establish the legitimacy and

fairness of resource allocation decisions in a public health care system, CADTH's Therapeutic Review Process is guided by eight underlying ethical principles (based on previous work done within the pan-Canadian Oncology Drug Review (pCODR) organization). Principles included are governance, representation, evaluation, excellence, evidence-based, ethical framework, efficient and effective, health system focus (5). The second standard for assessment was whether the framework met the four conditions (publicity, relevance, revision and appeals; regulative) of the Accountability for Reasonableness framework (6). Accountability for Reasonableness, an ethical decision-making framework for fair policy setting, was chosen as a standard as it is long standing, devised for a policy and a health care setting, and focused on limit setting decisions under resource constraints (6).

Based on the ethical concept assessment, three Therapeutic Review Process enhancements were developed. Prioritization criteria (Enhancement 1) selection was guided by a systematic search, which identified the most prevalent HTR identification and prioritization criteria in the literature (4). However, almost all criteria found focused on the concept of disinvestment or obsolescence, therefore some modification to the criteria are suggested to include the possibility of the concept of reinvestment.

To develop a deliberative qualitative framework (Enhancement 2), two steps were considered, first, the development of a process and second, a set of recommendation considerations (including criteria/sub-criteria and a dashboard) that would guide deliberations. Through the review of past CADTH Therapeutic Reviews (7) and three previously published process frameworks (8-10), a deliberative qualitative assessment process was developed. Published

process frameworks were compared based on feedback gathered from participants during qualitative research with Canadian HTA agency assessors conducted by M.A. Maloney (unpublished data, 2018) (Table 2). These included the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework (8); Grill and Dawson's ethical framework (9) and; the GRADE Evidence to Decision (EtD) Framework (10). Similarly, to develop the CADTH Recommendation Considerations, published frameworks were analyzed based on feedback gathered during qualitative research with Canadian HTA agency assessors conducted by M.A. Maloney (unpublished data, 2018). CADTH already uses criteria/sub-criteria within its pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee Deliberative Framework (11). This pCODR framework as well as the Ontario Health Technology Advisory Committee (OHTAC) (12) and GRADE EtD framework criteria (10) were considered when developing Therapeutic Review decision criteria, sub-criteria and a dashboard. The proposed CADTH Therapeutic Review Recommendation Consideration framework encompasses elements from each of these frameworks (Table 3).

To analyze publicly accessible mechanisms for decision monitoring and performance measurement and to provide recommendations (Enhancement 3), an evaluation of the CADTH organization by Science-Metrix (13) was reviewed and the CADTH website searched.

RESULTS

Guiding Principles and Ethical Elements

An assessment of the Therapeutic Review Process (2) confirmed that it includes and can be mapped to all common HTR framework components of: 1) identification and prioritization

criteria and methods; 2) assessment processes (including interpretation, organization, summarization of data and evidence); and, 3) dissemination strategies (4) (Figure 1).

It was also found that CADTH's HTR process incorporates many of CADTH's guiding principles (5) and Accountability for Reasonableness ethical standards (6) (Table 1). The process fully recognizes the importance to public health policy of open, transparent and collaborative interactions with key stakeholders through many touchpoints and feedback mechanisms. Numerous stakeholders are involved, including individual patients, caregivers, family members, patient groups, individual clinicians, professional organizations, pharmaceutical companies, industry groups, health regions, and ministries of health. HTR decisions involve complex scientific and economic evidence; this is recognized in CADTH's Guiding Principles and embodied in the Therapeutic Review Process through a focus on health outcomes and economic impact analysis and rigorous and consistent evidence-based clinical and pharmacoeconomic reviews. Finally, the Therapeutic Review Process appears cost-efficient and streamlined.

CADTH's Guiding Principles indicate an openness to continuous process improvement through incorporation of best practices (5). In this regard, a framework should make relevant values, principles and issues explicit to frame and communicate a decision. Recent CADTH stakeholder feedback also indicated a desire for more transparency in the context and content of CADTH discussions that occur during drug review processes (13). To ensure the Therapeutic Review process is considered fair, transparent, relevant and objective, as per the ethics frameworks reviewed (Table 1), additional refinement to this process is suggested as

follows: 1) transparent prioritization criteria for Therapeutic Review topic selection; and 2) publication of a deliberative, responsive and transparent framework to guide both CADTH's scientific and economic reports and CEDEC recommendations/advice.

One of CADTH's Guiding Principles called "Evaluation" indicates that a review process should have the capacity for ongoing evaluation (decision monitoring/performance measurement) to support continuous process improvements, as well as, the capacity for health outcomes and economic impact analysis to support decision-making and planning (Table 1) (5). Although CADTH does not issue decisions following a Therapeutic Review, it does issue recommendations/advice whose outcomes are publicly transparent. This leads to the suggestion of a third Therapeutic Review process enhancement of: 3) publicly accessible mechanisms for decision monitoring and performance measurement. The Accountability for Reasonableness framework includes a "Revision and Appeals Condition where there must be a mechanism for challenge and dispute resolution regarding limit-setting decisions and, more broadly decisions should be revisable in light of new evidence and arguments" (6). Given the Therapeutic Review Process is not directly linked to HTR decision issuance (limiting or otherwise); there need not be further modification to this process to include additional challenge mechanisms (other than currently included stakeholder feedback mechanisms) or a dispute resolution process. However, these mechanisms should be in place for any jurisdiction that is making reimbursement-based decisions because of a CADTH HTR or any other recommendation. Therapeutic Review decisions are revisable through existing mechanisms when new evidence or arguments surface.

Following review of CADTH's Guiding Principles, one revision is suggested to remove CADTH's "Health System Focus" principle which reads: "Cancer treatment drugs are evaluated within a review process and decision-making framework consistent with those used for drugs for other diseases" (Table 1)(5). This principle is not applicable for the Therapeutic Review process, as it does not encompass oncology drug review nor are CADTH review processes or decision-making frameworks currently consistent across all technology assessment categories.

DISCUSSION

An Enhanced Framework

Three proposed enhancements for CADTH's Therapeutic Review process are described below.

Enhancement 1: Prioritization Criteria for Therapeutic Review Topic Selection

The decision to conduct a Therapeutic Review can be made by CADTH or a jurisdiction through one of three well-documented identification criteria: 1) When two or more drugs with the same or similar indication are expected for future submissions to the Common Drug Review 2) When a CDEC "reimburse" or "reimburse with criteria" recommendation triggers a coverage policy review of existing drugs (i.e., reimbursement policies); and, 3) If a previous CDEC Recommendation suggests a Therapeutic Review of drugs in a class (2). There is no need to revise these criteria other than to note that CADTH's criteria differ from the published definitions of HTR (1) as CADTH includes emerging drugs or drugs with a new indication in the Therapeutic Review Process.

It is unclear whether the Formulary Working Group (FWG) considers specific prioritization criteria to rank identified health technology reassessment topics for Therapeutic Review. These criteria should be developed and shared publicly by including them in the Therapeutic Review Process (Figure 1) to ensure transparency in prioritization setting. Suggestions for clearly stated health technology prioritization criteria, include: high budget and/or low cost effectiveness; impact to public health (effectiveness or safety changes); frequency of disease or use of technology; burden of disease; conflict with clinical practice guidelines, clinical college position statements, and/or Cochrane Review recommendations (4).

Enhancement 2: Qualitative Assessment Framework

CADTH's Therapeutic Review process does not include a transparent qualitative framework to aid CADTH and CEDEC in decision-making and recommendation dissemination. However, CEDEC does deliberate and consider evidence as their Recommendation/Advice report includes the reasons for recommendation that was made, the CDEC values and preferences, patient preferences, the evidence discussed and the research gaps (2). Integrating a qualitative framework into the Therapeutic Review Process would aid deliberations to produce a recommendation, ensure specific criteria are considered, provide consistency in considerations, and frame recommendations through a concise summary of the evidence considered and judgments made (10).

To develop a deliberative qualitative framework, both a process (Table 2) and a set of guiding deliberation criteria are suggested (Table 3). A deliberative qualitative assessment process is proposed, based on comparison of three frameworks (8-10) and feedback gathered from

Canadian HTA agency assessors conducted by M.A. Maloney (unpublished data, 2018). A study of CADTH past Therapeutic Reviews (7) confirms that CADTH has incorporated elements of each of these three frameworks into their decision-making process. A common process methodology between CADTH Therapeutic Reviews is also evident but not clearly outlined in the Therapeutic Review process.

The proposed qualitative assessment process includes three main steps to move from evidence to decision (Table 2). The first step, which is referred to as the "Question and Input Identification", explicitly captures CADTH's current process and based off of the GRADE EtD framework (10) (but also encompasses the UMBRA (8) and Grill *et al* (9) ethical framework concepts. This step does not include any new process components but merely provides the details of CADTH's current Therapeutic Review process (Table 2). Components include: Objectives (why recommendation is needed); policy/research questions (includes populations, interventions, comparisons, outcomes); relevant subgroups; review perspective to address question; and, a plan to capture key background information to understand/answer the question.

Step 2, called "Assessing the Evidence" of a proposed qualitative assessment process, provides further transparency and direction to staff and CEDEC members during the detailed scoping, protocol and research, and recommendation phases of the Therapeutic Review. This step includes two previous undetailed activities. First, it is necessary to confirm that all the relevant comparative outcomes (e.g. efficacy and harm outcomes) have been identified through a systematic literature search (clinical and economic), ethical, patient perspective,

environmental, review of unpublished data, and stakeholder feedback (including Project Scope, Protocol, and Science Report). All identified outcomes are then included in CADTH analyses and evidence for recommendations (Table 3). The discovery of outcomes can occur throughout three specific phases of the Therapeutic Review process (see spotted boxes in Figure 1) and, at times, could necessitate revision to completed analyses in the case that an outcome was missed. Both the CADTH team drafting the Science Report and CEDEC members compiling the Recommendations should complete this outcome confirmation step. Should an additional outcome be identified by CEDEC, which would necessitate modification of analyses and/or the Science Report, necessary revisions would be included in the Recommendation Phase before the Science Report is finalized.

The second proposed new activity is that CADTH and CEDEC use criteria and sub-criteria (Table 3) to assess the evidence leading to CEDEC recommendations/advice. Table 3 includes four proposed criteria and sub-criteria and Supplementary Table 1 provides a dashboard, which can be used for CADTH's Therapeutic Review recommendation/advice considerations. Criteria include overall clinical benefits and harms; cost effectiveness; alignment with societal, patient and ethical values; and, feasibility of adoption. Table 3 also includes definitions of both criteria and sub-criteria as well as data sources used for evidence compilation. These criteria, sub-criteria and dashboard are meant to act as a tool for producing recommendations based on heterogeneous evidence. The tool is to be used by the CADTH team and CEDEC at two specific points of the Therapeutic Review process, during the Protocol and Research Phase (as CADTH is drafting the Science Paper) and during the Recommendation Phase (as CEDEC is forming its final recommendations/advice). Grey

shaded boxes within Figure 1 depict the points that the proposed criteria and sub-criteria should be considered. The use of the tool allows for relevant comparative outcomes (bucketed within criteria) to be judged in respect to all other criteria. The tool is meant to allow for the consideration of all data source outcomes. It provides a framework to organize outcomes/evidence within criteria/sub-criteria and to facilitate and focus discussion. Dashboard questions per criteria allow for multiple values to be weighed against each other in a reviewer's, and then review team's, mind(s) in response to a specific Therapeutic Review. However, no formal weighing of criteria is proposed for criteria/sub-criteria, as there ought to be no presumption that any particular value is always prioritized over another (3).

The last step, Step 3, involves documenting the Therapeutic Review recommendations and is called "Documenting the Recommendation". This step ensures relevant values, principles and issues are made explicit to frame and communicate a decision. The Criteria Dashboard (Supplementary Table 1) requires responses to specific questions as outlined in Table 3. In responding to these questions, reviewers should consider the magnitude of evidence, degree of certainty regarding the evidence, and quality of evidence. The Criteria Dashboard should be drafted as the CADTH team completes their clinical, economic and stakeholder input analysis. This draft is then presented to CEDEC during the first step of the Therapeutic Review Recommendation Phase. CEDEC deliberates, considering all available evidence and finalizes the Criteria Dashboard graphical display to be included in the draft Recommendation/Advice Report. Please see Supplementary Table 1 for the Criteria Dashboard Template. The Criteria Dashboard can be further updated following stakeholder feedback and is published in the completed Recommendation Report. Based on the Criteria Dashboard, CEDEC draws

conclusions and explicitly states the rationale for the final recommendation. CEDEC also highlights any outstanding issues or other significant information pertaining to the recommendation, including how to address gaps and if there is a need for further studies.

Enhancement 3: Publicly Accessible Mechanisms for Decision Monitoring and Performance Measurement

CADTH's Therapeutic Review recommendations are meant to inform jurisdictional stakeholder listing decisions, based on effectiveness, safety and/or resource use concerns (i.e. inappropriate utilization of drugs). While the evaluation of CADTH activities by Science-Metrix (13) indicates individual CADTH units are collecting data and reporting on performance, this information is not easily accessible to the public. This evaluation found that "there was no centralized repository or system for storing, retrieving, processing and quality assurance of performance data at CADTH" (13). The report also found that systems are available which can track some aspects of CADTH's contribution to long-term outcomes (e.g., awareness outcomes, policy and clinical decision-making outcomes etc.); (13). Given these findings, two recommendations, one short-term and one long-term should be considered. First, CADTH should continue to monitor jurisdictional policy change or lack thereof resulting from published Therapeutic Reviews. This summary of jurisdiction decisions should be linked to individual Therapeutic Reviews and published on CADTH's website. Second, the long-term impact of jurisdictional policy change (based on adopting a CADTH recommendation) should be qualified and quantified, documented and posted with the summary of jurisdiction decisions. To do so, CADTH should work with their jurisdictional stakeholders to determine appropriate outcomes for measurement (e.g., health, economic and societal outcomes) and how to capture CADTH's

Therapeutic Review recommendation contribution relative to other factors that may have had an influence on the specific outcome (e.g. timeliness of a review, stakeholder buy-in and support, new data or Health Canada decision and prevalence of a disease state).

LIMITATIONS

Revisions to the Therapeutic Review Process were based on ethical/priority review, qualitative study and literature assessment. The acceptance, practical application and validity of this modified Therapeutic Review Process framework requires further evaluation and implementation in practical situations (such as use in a future Therapeutic Review). For instance, the addition of further process to assess evidence through recommendation considerations could increase complexity of the CADTH/CEDEC review compared to the current process. However, Therapeutic Reviews are complex and require a balance between simplicity and transparency. The use of recommendation consideration criteria/sub-criteria and a dashboard will require familiarization, resourcing and, at times, may be incomplete due to lack of available data. An important next step would be to pilot this enhanced Therapeutic Review process, modifying any step that does not meet CADTH and stakeholder expectations.

CONCLUSIONS

By assessing the HTR Therapeutic Review Framework using, as a standard, both CADTH's Guiding Principles and the Accountability for Reasonableness ethical framework, three areas for framework enhancement were discovered. Enhancements are meant to promote transparency, objectiveness and performance measurement (through health outcomes and economic impact analysis). The application of transparent prioritization criteria to select a

Therapeutic Review should also improve consistency, as the same set of explicit criteria will be considered in each prioritization decision. A deliberative qualitative framework provides the ability: to capture all outcomes/values relevant to a decision; for structured reflection, organizing outcomes/evidence into criteria and encouraging value discussion; and, documentation of criteria dashboard questions. The trustworthiness of recommendation/advice should also be increased, as it will be easier for stakeholders to appraise the basis of a recommendation/advice. Finally, publicly accessible mechanisms for decision monitoring and performance measurement provide HTA agencies with feedback on the relevance of this work and opportunities for further enhancement. The suggested CADTH Therapeutic Review framework and suggested enhancements may also be considered for use by other HTA agencies to develop and present high quality health technology reassessment recommendations.

SUPPLEMENTARY MATERIAL

Supplementary Table 1: Criteria Dashboard Template www.journals.cambridge.org/

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CONFLICT OF INTEREST

This work has been completed in partial fulfillment of the requirements for Mary Alison Maloney's PhD degree in Health Research Methodology at McMaster University. In addition, Mary Alison Maloney works full-time as the Vice-President of North America Consumer Health

Regulatory Affairs for Bayer US LLC. This work was done independently of any affiliation or information exchange with Bayer. Dr. Lisa Schwartz's Arnold L. Johnson Chair in Health Care Ethics is funded through a private endowment; Dr. Schwartz was a member of an Expert Review Panel for CADTH until April 2017. Dr. Mitchel Levine and Dr. Daria O'Reilly have no potential conflicts of interest. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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Figure 1: CADTH Optimal Use Program: Therapeutic Review Process (2)

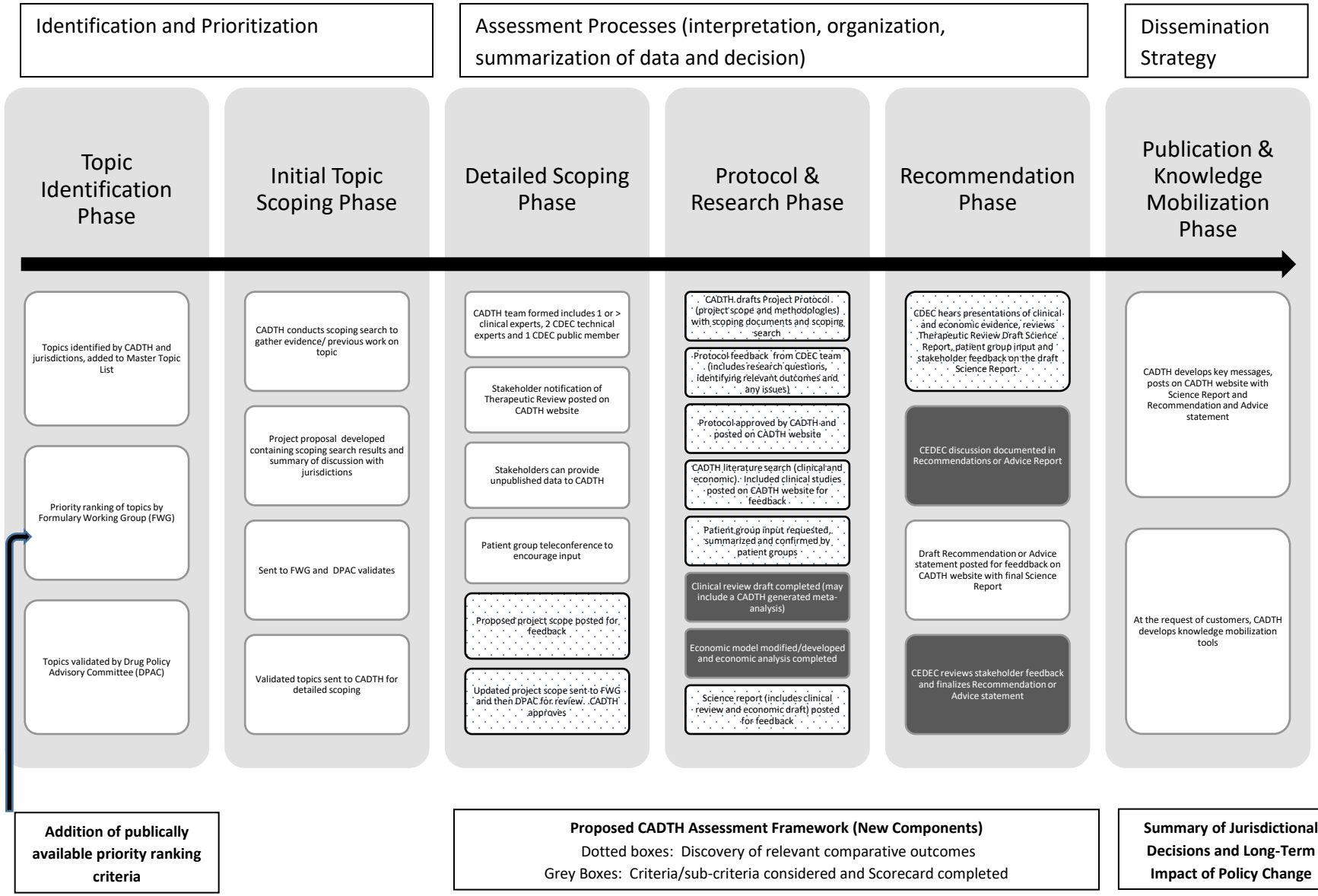

Table 1: CADTH Guiding Principles and Accountability for Reasonableness Ethics Framework

CADTH Guiding Principles (5)	**Accountability for Reasonableness Ethical Framework (6)**
Governance: A review process with governance structures that are fair, **objective, transparent,** and accountable to patients, health care funders, and the public.	Publicity Condition: Decisions must be publicly accessible **(fully transparent) about the grounds for the decisions.**
Representation: A review process that is multidisciplinary, cross-jurisdictional, and collaborative in nature, and includes appropriate input from key stakeholders and links to other key national initiatives.	Relevance Condition: **Decisions must rest on reasons that stakeholders can agree are relevant**.
Evaluation: A review process with capacity for data capture and ongoing evaluation (**decision monitoring/performance measurement**) to support continuous process improvements, as well as the capacity for health outcomes and economic impact analysis to support decision-making and planning.	Revision and Appeals Condition: Must be a mechanism for challenge and **dispute resolution regarding limit-setting decisions**, and, more broadly decisions should be revisable in light of new evidence and arguments.
Excellence: A review process that reflects an ongoing commitment to excellence through incorporation of best practices in a spirit of continuous quality improvement.	Regulative Condition: Either voluntary or public regulation of the process to ensure that conditions 1-3 met.
Evidence-Based: A review process with capacity for rigorous and consistent evidence-based clinical and pharmacoeconomic reviews to support evidence-based decision-making.	
Ethical Framework: A review process that includes an ethical framework.	

CADTH Guiding Principles (5)	**Accountability for Reasonableness Ethical Framework (6)**
Efficient and Effective: A review process that is cost-efficient, effective, and streamlined (i.e., reduced duplication) to support timely decision-making.	
Health System Focus: **Cancer treatment drugs** are evaluated within a review process and decision-making framework consistent with those used for **drugs for other diseases. Suggest removing this Guiding Principle.**	

Bolded items are those not currently fully captured in the CADTH Therapeutic Review Process

Table 2: Comparison and Proposed Deliberative Qualitative Decision Framework Processes

Frameworks	Assessment Processes (Interpretation, Organization, Summarization of Data and Decision)							
UMBRA Framework (8)	**Step 1 Decision Context:** Input components included in assessment	**Step 2 Building the Value Tree:** Identify and select all relevant outcomes and create value tree	**Step 3 Refining the Value Tree:** Which benefits/ risks justified to be included in assessment and provide rationale. Modify value tree	**Step 4 Relative Importance of Benefits and Risks:** Reviewers provide expert judgement to rank or weigh benefits/ risks, according to perspective of decision-makers	**Step 5 Evaluating the Options:** Score/ assess the outcome of benefits and risks against comparators. Provide either qualitative or quantitative values for each benefit/risk	**Step 6 Evaluating Uncertainty:** Conduct sensitivity analyses to assess the impact of uncertainty in data sources/ evidence. Describe variability between studies. Consider how balance of benefits/risks affected by uncertainty	**Step 7 Concise Presentation of Results:** Summarize the data in tabular and graphical displays to aid review and interpretation	**Step 8 Expert Judgement and Communication:** Expert judgement provides overall outcome and whether the benefit-risk balance is positive or negative. Describe any outstanding issues and other significant information and how they will be addressed and if need for further studies. Clear recommendation should be provided
Ethical Framework (Value-based Pluralist Approach) (9)	**Step 1: Identification:** Identify relevant alternatives	**Step 2: Distinguishing:** Distinguish relevant empirical differences between alternatives, including contingencies		**Step 3: Ranking:** Rank, as far as possible, alternatives from best to worst	**Step 4: Evaluation:** Make explicit, as far as possible, in what sense some alternatives are better than others			**Step 5: Documentation:** Submit the result of the evaluation to a designated oversight institution
GRADE Evidence to Decision (EtD) (10)	**Formulating the question** -Details of question (Problem, Intervention, Comparison, Outcomes)	**Making assessments:** Criteria to assess interventions/options for coverage decisions: -Judgment made by a panel for each criterion -Research evidence and additional considerations used to inform each judgment				**Drawing conclusions** Panel reviews judgments they have made for all criteria in their assessment and considers implications of judgements for the recommendation. Based on their assessments, panel draws conclusions about the strength of the recommendation. Conclusion includes relevant considerations (e.g. subgroups, implementation,		

Frameworks	Assessment Processes (Interpretation, Organization, Summarization of Data and Decision)		
	-Perspective to address question -Relevant subgroups -Key background information for understanding question -Why recommendation needed		monitoring and evaluation, and research priorities for uncertainties or gaps) Presentation: Framework layered: Present key messages top layer with links to more detailed information (e.g. summary of findings table and then to a systemic review). Helps structure discussions for expert committees
Proposed CADTH Assessment Framework	**Step 1: Question and Input Identification** -Objectives (why recommendation needed) -Policy/research questions (Includes Populations, Interventions, Comparisons, Outcomes) -Relevant subgroups -Perspective to address question -Plan what key background information is needed to understand/ answer question	**Step 2: Assessing the Evidence** -Confirm all relevant comparative outcomes (e.g. efficacy and harms outcomes) have been identified and included in analyses and evidence for recommendations -CADTH and CEDEC use criteria and sub-criteria (Table 3) to review evidence for recommendations	**Step 3: Documenting the Recommendation** -Criteria Dashboard drafted by CADTH and publically posted in draft Recommendation Summary to document findings. Updated as necessary based on stakeholder input -Based on the Criteria Dashboard CEDEC draws conclusions and makes the rationale for the final recommendation explicit -Any outstanding issues or other significant information described, including how this should be addressed and if there is a need for further studies -Graphical representation of Criteria Dashboard included in CEDEC final Recommendation Report

Table 3: CADTH Therapeutic Review Recommendation Considerations Framework

Criteria for Recommendation	Definition of Criteria	Criteria Dashboard	Subcriteria/Evidence for Recommendation and (Data Sources)	Definition of Sub-Criteria
Overall Clinical Benefits and Harms	A measure of the comparable meaningful differences in (overall) health benefit and harms to diagnose or manage a health care condition or health care related issue The overall comparable meaningful differences in clinical benefit and harms should be determined after evaluating the effectiveness and safety, burden of disease and need associated with each health technology	Benefits and harms: Are there any comparable meaningful differences in overall clinical benefit and harms between comparators? (Yes or No Describe response including: 1) how subcriteria contribute to the assessment, and 2) the magnitude and quality of evidence) Outcome importance: Is there important uncertainty about or variability in how much people value the main outcomes? (Yes or No and Describe) Certainty of evidence: Describe any data gaps	Effectiveness (CADTH Systematic review, unpublished data, CADTH meta-analysis (direct and indirect) and stakeholder input)	Potential health impact of technology compared to other drug and non-drug alternatives measured in terms of relevant patient outcomes (mortality, morbidity, quality of life). Magnitude, direction and uncertainty of effect should be considered
			Safety (CADTH Systematic review, unpublished data and stakeholder input)	Frequency and severity of adverse effects associated with the technology compared to other drug and non-drug alternatives
			Burden of illness (Patient group/other stakeholder input)	Incidence, prevalence or other measure of disease burden on the population
			Need (CADTH Scoping report, patient group/other stakeholder input)	Availability of an effective alternative to the technology(ies)
Cost Effectiveness	A measure of the net efficiency of the technology, including consideration of uncertainty, compared to available alternatives	Efficiency: Are there any meaningful differences in efficiency between comparators? (Yes or no and describe including the magnitude and quality of evidence)	Economic evaluation: • Costs, cost per QALY, cost per life year gained, cost per clinical event avoided. Uncertainty of results considered	See Definition of Criteria

Criteria for Recommendation	Definition of Criteria	Criteria Dashboard	Subcriteria/Evidence for Recommendation and (Data Sources)	Definition of Sub-Criteria
		Certainty of evidence: Data gaps? (Describe any data gaps)	(CADTH Systematic review and Economic model(s))	
Alignment with Societal, Patient and Ethical Values	Balanced judgement made after considering reasonable sources of societal and patient preferences and ethical principles relevant to the use of the technologies	Have societal, patient and ethical values been considered? (Describe considerations) Will the adoption of reimbursement recommendations be congruent with societal/patient and ethical values? (CEDEC only) (Describe)	Societal, patient and ethical values (patient group/other stakeholder input)	Societal, patient and ethical based values, which bear on the appropriate use and impact of the recommendation.
Feasibility of Adoption	An assessment of the feasibility of adopting, maintaining or modifying reimbursement criteria for one or more health technologies into/in the health system	How feasible is it to adopt, maintain or modify reimbursement criteria into/in the health system? (Highly feasible, moderately feasible, low feasibility, uncertain Explain response) (CEDEC only)	Economic feasibility: Budget Impact Assessment comparison (Budget Impact Assessments)	The net budget impact of a technology on other drug and health system spending
			Organizational feasibility (Formulary Working Group, Drug Policy Advisory Group and Other Stakeholders as necessary)	Ease with which reimbursement recommendations can be adopted/modified, with an assessment of health system enablers and barriers to implementation (including operational, capital, human resources, legislative and regulatory requirements)

Red font: concept found in OHTAC framework (12)
Black font: concept found in pCODR Deliberative Framework (11)
Blue font: concept found in GRADE EtD Framework (10)
Purple font: new wording

Supplementary Table 1: Criteria Dashboard

Criteria for Recommendation	Questions	CADTH or CEDEC Summary
Overall Clinical Benefits and Harms	Benefits and Harms: Are there any comparable meaningful differences in overall clinical benefit and harms between comparators?	*Yes or No* *Describe response including:* *1) how subcriteria contribute to the assessment, and* *2) the magnitude and quality of evidence*
	Outcome Importance: Is there important uncertainty about or variability in how much people value the main outcomes?	*Yes or No* *Describe*
	Certainty of evidence: Data gaps?	*Describe any data gaps*
Cost Effectiveness	Efficiency: Are there any meaningful differences in efficiency between comparators?	*Yes or No* *Describe including the magnitude and quality of evidence*
	Certainty of evidence: Data gaps?	*Describe any data gaps*
Alignment with Societal, Patient and Ethical Values	Have societal, patient and ethical values been considered?	*Describe considerations*
	Will the adoption of reimbursement recommendations be congruent with societal/patient and ethical values? (CEDEC only)	*Describe*
Feasibility of Adoption	How feasible is it to adopt, maintain or modify reimbursement criteria into/in the health system? (CEDEC only)	Highly feasible, moderately feasible, low feasibility, uncertain Explain response

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 SUMMARY AND MAJOR CONTRIBUTIONS

Strained economies have resulted in limited health care budgets. To maximize every dollar, governments, HTA agencies, policy makers and academics are exploring frameworks and processes that value marketed drug products with the premise of identifying and disinvesting in "low-value" technologies and theoretically reinvesting savings, at least in part, in "high-value" drug technologies. The author of this thesis chose the study of health technology reassessment (HTR) frameworks as the process of health technology disinvestment (or reassessment) is not widely practiced and seemed to be fraught with challenges. The objectives of this research were to: 1) identify overarching and qualitative decision-making reassessment framework challenges and methodological gaps; and 2) develop and/or modify a reassessment framework to address challenges/gaps.

Three studies were performed consecutively to meet these objectives. First, a systematic literature review was conducted to retrieve published drug technology disinvestment (or reassessment) framework information including terms and definitions, framework components, as well as, challenges and solutions to HTA disinvestment. This review highlighted a common foundational need of Regulatory Authorities and HTA Agencies, that is to assess a wide-variety of data and, based on that assessment, to make subjective decisions pertinent to many stakeholders. The retrieved literature also confirmed that qualitative benefit-risk frameworks had been developed and were in use to facilitate prescription drug regulatory decision-making[1-2]. These findings suggested an opportunity to assess whether a qualitative benefit-risk framework (i.e. the UMBRA framework) could be used or modified to further enable

prescription medicine reassessment. To answer this question, a qualitative descriptive study was conducted to understand Canadian HTA agency assessors' experiences with the UMBRA framework and to collect their insights on the use and or modification of this framework to aid HTR. For the purpose of relevance, assessors were asked to compare the UMBRA framework to an existing Canadian HTR framework (CADTH's Therapeutic Review). Surprisingly, HTA agency assessors were divided on the utility of the UMBRA framework and felt that CADTH's Therapeutic Review process generally encompassed the UMBRA process steps. However, participants recognized that CADTH's Therapeutic Review assessment process does not include a transparent, deliberative qualitative framework. Given these findings, the last study focused on CADTH's Therapeutic Review process and whether this reassessment framework could be modified to address identified challenges and gaps. The specific objectives were to assess, from a health technology reassessment perspective, CADTH's Therapeutic Review Process and, based on this assessment, suggest enhancements to meet stakeholder needs.

Disinvestment Challenges

Disinvestment challenges proved prevalent during the conduct of this research while documented solutions were broad and hypothetical. For the purpose of this summary, only those challenges where a potential solution is proposed are described below.

1. *Lack of evidence/data*: In conducting a HTR, many treatments and associated outcome data may need to be compared. However, this data may be either non-existent or not comparable given difference in study design[3-7]. Data gaps or lack of the ability to compare data creates a level of uncertainty when forming recommendations.

2. *Complexity/too much data*: HTA assessors felt it challenging to consider comparative effectiveness, clinical relevance and meaningful differences in multiple treatment outcomes. The number of different endpoints (efficacy, safety, economic, societal) and attributed stakeholder values was seen as a challenge to confirming an endpoint's rank or weight.
3. *Stakeholder resistance to delisting or decreasing funding for established prescription medications:* Stakeholders will resist losing access to a particular medication for numerous reasons. These include: entrenchment in the perception or fact that a medication still provides value to some patients due to clinical training, practice paradigms, and ensuring option availability[4-5, 7-12], loss aversion and entitlement[6, 13-14]; inertia due to the lack of political, clinical, and administrative will to support disinvestment[4, 8-12] in part due to competing clinical, patient and political interests[4-5] and; disinvestment success not being evident[15-16].
4. *Lack of HTR frameworks and administrative mechanisms:* Many countries do not have the resources or required knowledge to develop HTR frameworks or the administrative mechanisms necessary to implement such frameworks[4, 7, 8-10].

To combat these challenges, health technology reassessments should be robust, transparent and practical. This research has shown that HTR frameworks must incorporate: the informational needs of the decision-makers; clear and transparent mechanisms to identify and prioritize medications for reassessment; mechanisms for involving multiple stakeholders throughout the HTR process; a transparent qualitative decision-making framework to guide assessment and recommendations; appropriate dissemination strategies to ensure stakeholder understanding of recommendations and; an assessment of jurisdictional uptake and impact.

Terminology: Reassessment Instead of Disinvestment

The term chosen to describe the optimal use of a drug technology in comparison to its alternatives may influence stakeholder engagement. Initiatives focused on "disinvestment" could immediately infer a foregone process conclusion or loss to stakeholders, including rationing and or budgetary cuts[17]. A more neutral term, such as reassessment, is recommended for this process as it suggests the possibility of broader outcomes including reinvestment. This terminology change may decrease stakeholder process and recommendation resistance and increase the will to form partnerships to address data and methodological gaps. This thesis employed MacKean *et al.*'s definition of HTR: "A structured, evidence-based assessment of the clinical, social, ethical and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives"[17]. This definition of reassessment[17] and all other reassessment definitions[11, 18] found during the systematic literature review (Chapter 2) do not reference the possibility that a comparator could include an emerging technology. However, CADTH's HTR processes include identification criteria also encompassing emerging drugs and/or their associated indications[19]. It is therefore suggested that MacKean *et al.*'s reassessment definition be modified to include the possibility of comparators including emerging technologies as follows: "A structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology currently used in the health care system, to inform optimal use of that technology in comparison to its alternatives **which may include emerging technologies**". This definition more accurately reflects real-world practice and the possibility of including emerging drug technologies in HTR.

Identification and Prioritization of Drug Technologies for HTR

The systematic literature search documented in Chapter 2 highlights the lack of clear differentiation criteria for identifying or prioritizing a drug for disinvestment/reassessment as often the same criteria could be found as an indicator for identification, prioritization or both. Identification of a technology for disinvestment/reassessment involves distinguishing which technologies may require a coverage policy review while prioritization ranks these technologies for review. One future solution to this problem is to remove the need for drug technology identification and prioritization through HTA agencies adoption of fixed HTR time periods in a drug's lifecycle or specific criteria (e.g. new efficacy or safety finding) as to when to conduct a HTR. This could incentivize invested stakeholders (e.g. drug manufacturers) to generate additional research to fill data gaps or collect and contextualize data[3, 4, 12, 20]. However, this solution may be too resource intensive for some HTA agencies. Alternatively, clearly differentiated, efficient and transparent identification and prioritization criteria and methods should be included in a HTR framework.

An assessment of CADTH's Therapeutic Review Framework[19] found CADTH to employ transparent identification criteria as follows:

- When two or more drugs with similar indications are expected for future submission to the Common Drug Review;
- When a CDEC recommendation triggers a coverage policy review of existing drugs (i.e., reimbursement policies);

- If a CDEC recommendation suggests that a therapeutic review should be conducted to evaluate the comparative clinical effectiveness and cost-effectiveness of drugs in a particular therapeutic area.

CADTH's Therapeutic Review Framework did not clearly indicate how the Drug Policy Advisory Committee Formulary Working Group considers specific prioritization criteria to rank identified HTR topics. CADTH has stated "Topics selected are based on CADTH's customers' needs and requests. Social, legal, ethical, environmental, political, entrepreneurial, and research (innovation) issues may be factors considered"[19]. CADTH has recognized that topic prioritization criteria could be more transparent and has demonstrated an open-mindedness to increase transparency in the future[19]. Prioritization criteria should be included in an overarching HTR framework to ensure transparency in priority setting and to increase stakeholder buy-in to the need for a reassessment. Chapter 4 provides specific prioritization criteria as suggested additions to the Therapeutic Review Framework. These criteria were developed, in part, based on the systematic literature search findings in Chapter 2. However, disinvestment identification and prioritization criteria identified in the literature search were almost all developed based on the concept of disinvestment or obsolescence, and therefore, focused on the risk to the patient (safety concerns) or lack of improvement to health coupled with a high budget impact or failure to show cost-effectiveness. There was therefore a need to modify these criteria to include the possibility of the concept of reinvestment. Differentiated prioritization criteria suggested for CADTH's Therapeutic Review Framework were: high budget and/or low cost; effectiveness; impact to public health (effectiveness or safety changes); frequency of disease or use of technology; burden of disease; conflict with clinical

practice guidelines, clinical college position statements, and/or Cochrane Review recommendations.

Stakeholder Involvement

Politicians, clinicians, patients, patient groups, caregivers, family members, specialty societies, health system leaders (including drug plan personnel), and industry are critical components of a reassessment process. Qualitative descriptive research participants (Chapter 3) considered stakeholder input and feedback to be crucial to an HTR process while the literature search detailed in Chapter 2 also identified the need for a transparent engagement and consultation process[3]. Increased stakeholder involvement throughout an HTR process can help capture and improve the real-world value and applicability of HTRs. CADTH's Therapeutic Review Framework recognizes the importance of open and transparent stakeholder involvement throughout the process incorporating many touchpoints and feedback mechanisms.

Qualitative Deliberative Framework

CADTH Therapeutic Review Framework and processes are standardized, clear and comprehensive. However, this Framework does not include a transparent, deliberative qualitative framework to aid CADTH and their expert committee in decision-making and recommendation dissemination. It appears recommendations are made intuitively, after extensive data collection, calls for stakeholder input, CADTH analysis of the data and discussion amongst experts. Assessment of overall benefits and risks occur without a transparent and precise review of the value structure and trade-offs of a recommendation. CADTH uses processes, written reports, briefings, committee discussions and expert advice to

determine a recommendation. CADTH also has a responsibility to publicly communicate the benefits and risks of their HTR recommendations in a clear and understandable way to inform listing decisions and to ensure transparency of the reasons and rationales to their recommendations. CADTH does publish Therapeutic Review reports including a summary of the data submitted and the conclusions reached. However, transparent communication about CADTH and expert committee perspectives, value judgements and trade-offs between the key benefits and risks is lacking.

Integrating a qualitative deliberative framework process into the assessment phase of the Therapeutic Review Framework could solve this challenge. The valuation of drugs requires a process that is tailored to the assessment, adaptable, transparent and makes reasoning explicit but also identifies limitations and uncertainty of the evidence, and has a structured approach to decision dissemination and implementation[5-7, 10, 16, 21]. A qualitative deliberation framework should "facilitate the selection, organization, summarization, and interpretation of data and preferences relevant to the decision"[17]. Qualitative deliberative frameworks can enhance the clarity of the decision-making process by helping to set internal standards and consistency for decision-making, encouraging appropriate documentation, ensuring each benefit and risk is articulated including their relative importance, and providing a standardized way to communicate benefits and risks to various stakeholders[22].

To develop a deliberative qualitative framework for HTR, it is believed that both a process and a set of recommendation considerations (including criteria and a dashboard) are required to guide HTA assessors and expert committee deliberations and recommendations. This

framework must be developed to align and support any underlying HTA agency ethical concepts, values and principles. A framework should encompass existing HTR processes without disrupting current effective flows of information and be flexible to accommodate any quantitative methods[23].

Chapter 4 provides development details of a qualitative deliberative framework to complement CADTH's Therapeutic Review processes. Three steps are included in this framework: Step 1 Question and Input Identification, Step 2 Assessing the Evidence and, Step 3 Documenting the Recommendation. Given the challenge of data complexity, Step 2 has specifically included a reiterative (if necessary) process to confirm that HTA assessors and experts are identifying and considering all relevant comparative outcomes. This Step also incorporates a Recommendation Consideration Framework, which includes specific criteria and sub-criteria to be used by HTA assessors and experts to produce recommendations. The Recommendation Consideration Framework groups relevant comparative outcomes by four criteria: 1) Overall Clinical Benefits and Harms 2) Cost Effectiveness 3) Alignment with Societal, Patient and Ethical Values and 4) Feasibility of Adoption. This framework is meant to enable the organization of evidence to facilitate the review and discussion of recommendation value structures and trade-offs without the use of formal weighing or ranking. Step 3 includes a Criteria Dashboard, which is to be completed by assessors and experts while working through the recommendation consideration framework. The dashboard was developed to ensure that relevant values, principles and issues are made explicit to frame and communicate the decision. The magnitude of evidence, degree of certainty regarding the evidence and quality

of evidence should be documented in the dashboard to help stakeholders understand a decision.

Decision Monitoring and Performance Measurement

It is important to evaluate the implementation of HTR recommendations[24]. Evaluation should include an assessment of whether a jurisdictional policy change occurred given an HTR recommendation and, if so, the long-term effect of that change.

Evaluation closes the feedback loop from policy development to post-policy implementation. The goal is to assess the efficiency and effectiveness of an HTR recommendation during and after its implementation in order to:

- Identify if a policy change is achieving its desired results;
- Determine whether benefits and costs are meeting expectations;
- Uncover any unintended consequences; and
- Inform future HTR recommendation development[25].

CADTH does monitor jurisdictional policy change decisions and does conduct some performance measurement through clinical and economic impact analysis of a jurisdictional change following the publication of a Therapeutic Review recommendation[26]. However, CADTH's decision monitoring and performance measurement activities and outcomes are not transparent. Evaluation of decision outcomes and performance measurement require CADTH to transparently pre-specify methods, targets, and timelines for evaluation and to communicate findings to the public. These evaluations can identify lack of recommendation uptake, unintended consequences or unproven clinical and/or cost effectiveness outcomes. Such

post-policy evaluations are necessary to optimize the HTR process and to proactively inform further Therapeutic Review Framework modifications[25].

5.2 FUTURE AREAS OF RESEARCH

This work has identified numerous HTR framework challenges and methodological gaps with a focus on CADTH's Therapeutic Review Framework. Framework enhancements are hypothesized to provide solutions to identified challenges and gaps. Suggested enhancements include:

- The use of the term reassessment instead of disinvestment;
- A modified definition of the term reassessment to include, within the definition of alternative technologies, emerging drug technologies;
- Ensure ethical concepts, values and guiding principles have set the scope and outlined boundaries for an overarching HTR framework and embedded qualitative deliberative process (if present);
- If resources permit, adoption of fixed HTR time periods in a drug's lifecycle or specific criteria (e.g. new efficacy or safety finding) as to when to conduct an HTR eliminating the future need for identification and prioritization criteria and methods;
- Clear differentiation between the criteria used to identify and prioritize a drug for reassessment;
- Revised HTR identification and prioritization criteria to ensure the concept of "reinvestment" is captured;

- The implementation of a qualitative deliberative framework process within the assessment phase, including recommendation criteria and a publicly available criteria dashboard;
- The requirement for transparent, pre-specified methods, targets and timelines for HTR recommendation decision outcomes and performance measurement and for these results to be communicated publicly.

These findings are important as, if implemented: they could increase the quality of HTR recommendations and improve stakeholder acceptance and uptake ultimately helping to ensure the financial and institutional sustainability of the Canadian public health care system. The acceptance, practical application and validity of these proposed HTR framework modifications do require further evaluation through implementation in real-world situations. It is suggested that these modifications be further tested by first calling for broad stakeholder feedback and then, following any necessary revisions, implementing these changes, either individually or in combination, in an upcoming CADTH Therapeutic Review. This would allow for both theoretical and hands-on feedback from Canadian stakeholders further progressing a sense of stakeholder ownership and a validated overarching and qualitative deliberative framework.

It is unclear whether these HTR recommended enhancements can be extrapolated across geographical areas and social contexts. HTR is one component of broader health care decision-making processes, and as such, HTR frameworks typically reflect a health system's history, values and key policy objectives[27]. For instance, country-specific complexities of

decentralized health care structures, variability in insurance services, purchasing processes for drugs and lack of agreed HTR frameworks makes international methodological uptake difficult[8, 11, 12-14]. Future research is necessary to assess which of the above methodological enhancements could be adopted by other jurisdictions and which must be tempered for local contextual and system realities.

5.3 CONCLUSION

This thesis highlights the lack of publicly available research pertaining to disinvestment or reassessment frameworks, partly due to the lack of publication and/or to a discrepancy in terminology of policy-maker disinvestment initiatives. Given this relatively underdeveloped field of research, the objectives of this thesis were to identify overarching and qualitative decision-making reassessment framework challenges and methodological gaps and to develop and/or modify a Canadian reassessment framework to address these challenges/gaps.

The ultimate goal of an overarching reassessment framework is to generate useful recommendations to inform the optimal use of drug technologies thereby improving the efficiency and quality of care within a public health care system. This research confirms that common HTR framework components already exist including identification and prioritization criteria and methods, assessment processes (interpretation, organization, summarization of data and evidence) and dissemination strategies. While component criteria, methods and processes varied between frameworks, this research has identified some framework enhancements, which are hypothesized to address HTR challenges. First, framework terminology is important to ensure stakeholder engagement. Overarching and qualitative reassessment frameworks should be based on underlying HTA agency ethical concepts,

values and guiding principles. If identification and prioritization criteria exist they need to be clearly differentiated and encompass the concept of reinvestment. The reassessment process must involve input from key stakeholders including buy-in and commitment from the users (payers) of HTR recommendations. Process and decision transparency is also paramount throughout the reassessment and decision-making process. A qualitative deliberative framework applied during the assessment phase and tailored to reassessment, provides a transparent, structured, consistent approach to decision-making, makes reasoning explicit while identifying limitations and uncertainty to evidence and aids in decision documentation and communication. Finally, transparent HTA agency decision monitoring and performance measurement activities and outcomes are important to inform further HTR recommendations.

Health care budgets are not infinite and as such, the goal of optimizing value for money has become important. HTR is required to support evidenced-informed drug technology reimbursement decisions throughout a medications' lifespan to ensure the sustainability of the health care system. To move this field forward, research must continue to build on these research findings with a focus on developing HTR framework methodological approaches, which provide solutions to barriers of implementation.

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