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Economic Evaluation of Complex Health System Interventions: A Discussion Paper

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ECONOMIC EVALUATION OF COMPLEX HEALTH SYSTEM INTERVENTIONS: A DISCUSSION PAPER

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ABSTRACT

Complex health system interventions have been defined as those with multiple interacting components and may be described based on the presence of several underlying characteristics: (1) number and difficulty of behaviors required by those delivering or receiving the intervention; (2) number of groups or organizational levels targeted by the intervention; (3) number and variability of outcomes; (4) the use of feedback and the degree of flexibility or tailoring of the intervention permitted.

The discussion paper will provide guidance to those tasked with conducting an economic evaluation of complex health system interventions. The guidance will be an elaboration of existing national guidelines for economic evaluation, and serve as a discussion paper to aid investigators conducting economic evaluations of complex health interventions.

This discussion paper is intended to be a starting point for health system and policy researchers who wish to understand some of the fundamentals of economic evaluation and its application to complex health system interventions. There may also be relevance for funders of research as well as knowledge users aiming for a deeper understanding of these issues and value of the results of such analyses. It is also intended to help health system and policy researchers understand some of the fundamentals of economic evaluation and its application. This paper should not be considered an exhaustive treatise on the subject; it will be updated and revised regularly based on user feedback and the changing landscape in evaluation of complex interventions.

Key Words:

Cost-Benefit Analysis/statistics & numerical data*; Cost-Benefit Analysis; Complex Interventions; Canada

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TARGETED SCAN OF THE LITERATURE

Background

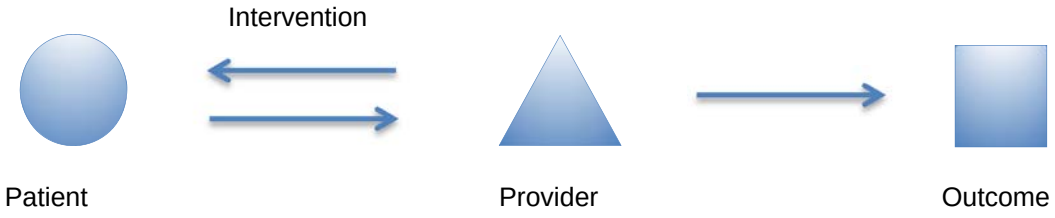
The term 'complex' has been used to describe health interventions that (i) have a number of interacting components, (ii) target groups or organizations rather than or in addition to individuals, (iii) have a variety of intended outcomes, and (iv) are amenable to tailoring or iterative development through adaptation and learning by feedback loops, and (v) where effectiveness is impacted by the behaviors of those delivering or receiving the intervention [1]. Since most health services interventions feature some of these traits, complexity may be considered a relative measure rather than an absolute state.

Interest in complex interventions has stemmed from increasing interest by health care funders and researchers in health system improvement through experimentation and evaluation, as well as a more recent focus on organizational, structural, and policy changes to improve health system delivery. It is now recognized, for example, that health interventions that are observed to be efficacious and cost-effective in the context of highly structured randomized trials may not be effective or cost-effective once they are made available in practice, under less controlled conditions [2].

Complexity can be thought of as a situation that goes beyond a single patient interacting with a single provider. Rather, multiple patients may interact with multiple providers and with each other in a way that can impact relevant patient and health system outcomes, such as measures of health, resource use, and user experience. With some complex interventions, the outcomes themselves can further influence the behaviour of patients and providers. We can illustrate degrees of complexity by examples that show this interaction (Figure 1). For example, a patient/physician shared decision to prescribe a drug to lower high blood pressure with the intent of avoiding future illness is an example of a simple intervention. Another example is use of insulin to avoid future complications from diabetes.

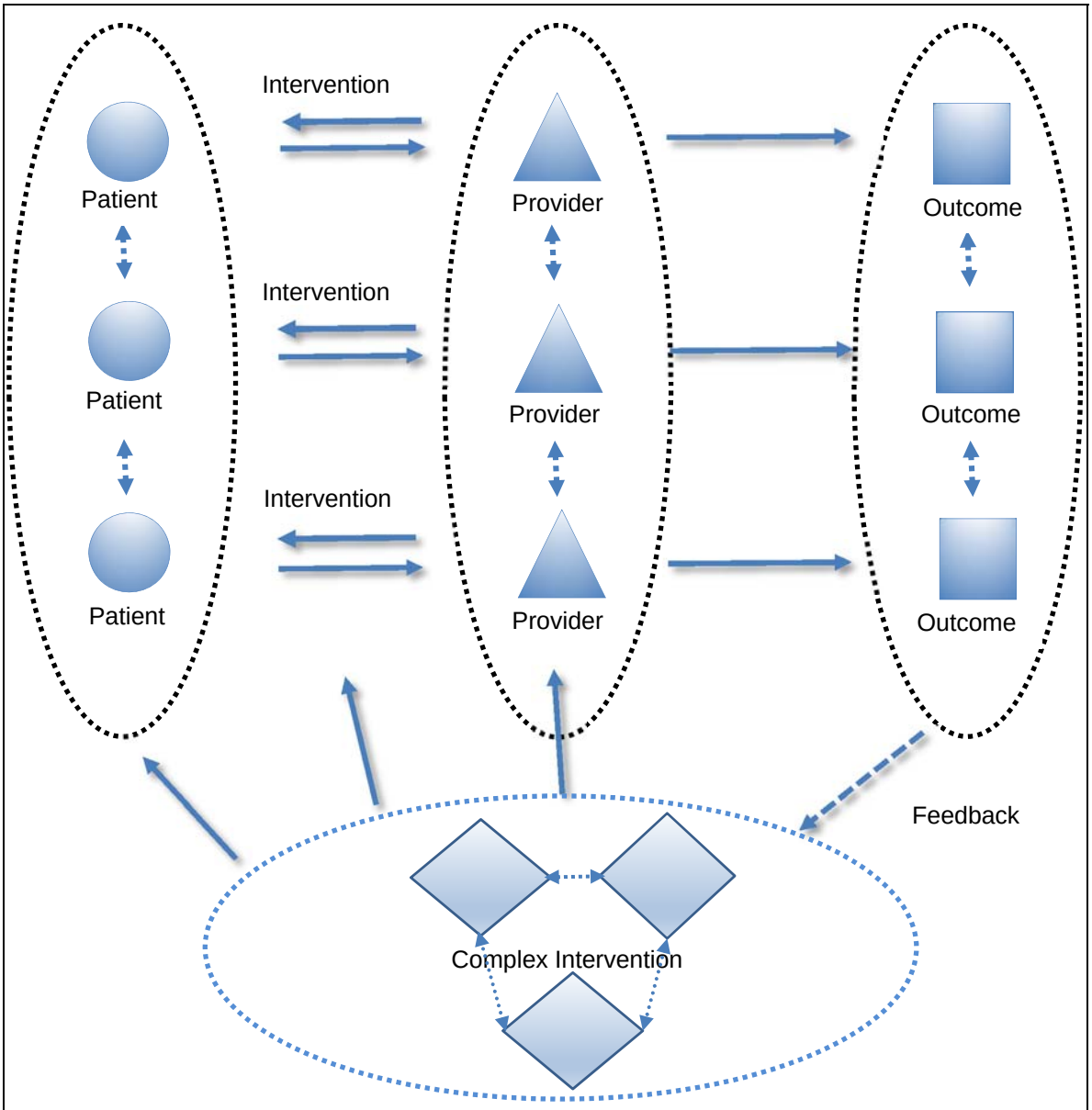
Figure 1: Illustration of simple and complex interventions

Figure 1a: Simple intervention



Simple interventions are delivered from a care provider to a patient after the patient provides some information. The outcome is a result of this interaction and intervention.

Figure 1b: Complex intervention



Complex interventions can involve interactions between patients and interactions between providers. The intervention may be directed to populations of patients, providers, or both and may change according to feedback from measured outcomes. The intervention may also serve to mediate the interaction and intervention between providers and patients. The components of the intervention itself may also interact and affect the final outcome.

As further patient/physician/outcome interactions occur, the intervention can be said to be increasingly complex. Truly complex interventions influence or attempt to manage the interaction and information that in turn affects outcomes. For example, a decision to intervene with blood pressure medication may be influenced by further interventions such as public health disease

surveillance and education and awareness programs, along with the interaction the patient has had with other patients at high risk or hospitalized with complications such as heart disease and stroke.

In the second example, outcomes from the decision to use insulin may be optimized by a complex intervention such as case management or facilitated relay of information regarding blood sugar control, dosage and adherence to physicians or patients through an e-health intervention [3]. This complex intervention may involve the use of nurses or pharmacists to educate patients about self-monitoring and insulin dosage adjustment. It may also involve the use of a patient self-management portal or SMS-based technology to facilitate communication. The ultimate health outcomes are a product of the many interactions between patients, providers and other system-wide components.

Several recent analyses have highlighted the importance of the system-wide context in which the intervention is delivered – often complex itself [4,5]. They suggest that the effectiveness of a complex intervention may be very sensitive to where or how it is delivered and adequately measuring and accounting for confounders and influencers during its evaluation has heightened importance. Other commentaries have discussed difficulties in applying standard methods of economic evaluation as many complex interventions may produce benefits beyond health gain [6,7].

There are a number of examples of health interventions that might be viewed as complex. Although the following avenues of investigation in health services and policy research are not distinct categories, these "types" of interventions are more likely to be considered complex and are listed to provide illustrative examples.

Integrated care interventions

Integrated care has been defined as a "coherent set of methods and models on the funding, and the administrative-, organizational-, service delivery-, and clinical levels designed to create connectivity, alignment and collaboration within and between the cure and care sectors.".[8] It also has other definitions,[8] but in principle is concerned with coordinating and joining disparate service delivery organizations within health systems to improve the patient experience through better continuity of care. Integrated care may involve different types of integration including integration of funding, administration, organization of services, and care delivery [9,10]. An important type of integrated care intervention involves the coordination of primary care services or other community-based interventions for chronic disease management (discussed below). Other recent examples of integrated care initiatives in Canada include:

- In Quebec, local community centres, acute hospitals (CHSGS, Centres hospitaliers de soins généraux et spécialisés) and long-term hospitals were merged into 95 health and social services centres (CSSS, Centres de santé et de services sociaux). Four university-based health-care networks (RUIS, réseaux universitaires intégrés de services) were created to coordinate training and research, and provides coverage for 18 regional health authorities.
- In Ontario, 14 Local Health Integration Networks were created in 2006 to provide system-wide coordination and integration of health and social services. These networks have authority over local planning, funding, community engagement and facilitating integration within their region [11].
- Alberta implemented and rigorously evaluated a fully integrated care model with multi-disciplinary teams for hip and knee replacement [12].

Community-based and primary care interventions

The Canadian Institutes of Health research (CIHR) Institute for Health Services and Policy Research (IHSPR) definecommunity-based and primary care interventions as a broad range of primary prevention (including public health) and primary care services outside of community hospitals or tertiary care facilities, including health promotion and disease prevention; the diagnosis, treatment, and management of chronic and episodic illness; rehabilitation support; and end of life care [13]. These interventions are based on integration of hospital-based, community and primary care services and with a community orientation, typically through direct and education of the general population or providers. They are also distinct from policy interventions and do not rely on changes in finance, laws or regulations regarding the organization and delivery of care. Examples of these types of interventions in Canada include:

- A collaborative, multi-pronged, community-based health promotion and prevention programme targeted at older adults and intended to reduce cardiovascular morbidity across 39 mid-sized communities in Ontario [14].
- The virtual ward, a multidisciplinary hospital-based team to optimize medical and social care residing in patients' homes for those at high-risk of re-admission after discharge from hospital (http://clinicaltrials.gov/ct2/show/NCT01108172).
- In Quebec, the CO-ordination Personnes Agées (COPA) model provided integrated primary care with intensive case management for community-dwelling, very frail elderly patients [15].

Guideline and clinical pathway implementation

The use of evidence syntheses to inform clinical practice has led to the development of clinical practice guidelines (CPGs) and clinical pathways (CPs) as a means to make research regarding effective and cost-effective interventions more accessible for care providers. Effective use of these tools requires implementation (i.e., knowledge translation) strategies to facilitate changes in organization and practice behavior. Effective implementation strategies are often complex, providing multiple avenues and overlapping or repetitive approaches to affect behavioural change. Some notable examples include:

- The Canadian Hypertension Education Program (CHEP) creates clinical practice guidelines along with educational materials, manuscripts, clinical summaries, handouts, slide sets, education kits , posters, advertisements, pocket cards, workshops, and education of opinion leaders [16].
- Guideline recommendations for the prevention, diagnosis, and treatment of ventilator-associated pneumonia [17,18] were implemented across Canadian centres using a multifaceted intervention (education, reminders, local opinion leaders, and implementation teams) directed toward the entire multidisciplinary ICU team [19].
- In British Columbia, the effect of the periodic delivery of evidence-based letters on prescribing patterns was assessed [20].

Population and public health interventions

Population health interventions have been defined as "…policy and program interventions that operate within or outside the health sector and have the potential to impact health at the population level." Public health interventions are usually characterized as population- or community-oriented

programs intended to promote, protect or prevent poor health. They are often considered as different from health service or clinical interventions, which are intended to prevent or treat illness in individuals. However, they must often work closely with primary care services as a means to providing early intervention.

Population and public health interventions can be multifaceted and require the use of multidisciplinary teams or coordination across organizations that go beyond the health system. They may also require more extensive mass communication and educational strategies and be iteratively developed. The Federal and provincial governments largely share the responsibility for developing and implementing public health programs, although non-governmental programs do exist. The number of individual programs and services are almost too numerous to mention, however public health programs often provide one or more of the following services: developing standards; surveillance; developing and enforcing laws/regulations; providing direct services to individuals, such as immunization and counseling; providing direct services to populations such as walkable areas, road construction and other prevention-related items; providing incentives/grants, including taxes or fines for risky behaviour; and providing information/education. Examples of public health interventions include:

- Multiple strategies to reduce harm from tobacco use in youth including surveillance, increasing taxes [21] , mass education , introducing legislation regarding advertising and where smoking is permissible, and youth engagement [22].
- A multi-program approach to improving health outcomes associated with substance abuse issues and the mental wellness of First Nations and Inuit that includes training of caregivers and providing community-based services leveraging public health programs such as "building healthy communities" [23].

Tele-health and e-health interventions

Communications and decision-support media are now being introduced as a means to change the nature of interactions between patients and providers. E-health is a broad term that encompasses the use of digital, telecommunications, and other information technology as a means to improve decision-making, learning, knowledge management, or any number of activities related to health care. Telehealth can be considered a subset of these activities and refers to the delivery of health care facilitated by telecommunications technology. Communication can be further classified as synchronous or asynchronous and may be between patients, patients and providers, or between providers. As e-health is a modality, it may serve as the basis of any number of complex interventions including integrated care, primary care, and public health interventions. Some examples are:

- The use of an online diabetes management portal to promote self-management in patients with diabetes [24].
- The use of home telemonitoring in patients with diabetes and uncontrolled systolic hypertension [25].
- A mobile phone-based system to facilitate management of patients with heart failure [26].

Economic Evaluation and Its Use in Decision-making

Economic evaluations of health interventions have been defined as "the comparative analysis of alternative courses of action in terms of both their costs and their consequences" [27]. All economic evaluations assess costs, but approaches to measuring and valuing the consequences of health interventions differ (see Box 1). Economic evaluations often rely on a combination of mathematical modeling and study information when studies that support the underlying estimates of effectiveness lack key pieces of information.

Economic evaluations are important because "resources - people, time, facilities, equipment and knowledge- are scarce" [27]. They allow those charged with managing resources to either anticipate the potential impact or measure the real impact of any change to the delivery of health care. In the context of health research, they can aid researchers in demonstrating the potential or real economic impact on the health system of a new intervention that can in turn promote its uptake and adoption. For example, one review of telemedicine applications suggested "The absence of a cohesive body of rigorous economic evaluation studies is a key obstacle to the widespread adoption, proliferation, and funding of telemedicine programs" [28].

However, the need to make decisions based on economic evaluations may extend beyond the health system. The effects of public health interventions, for example, may extend into the justice and education systems and require different forms of analysis used in those sectors (e.g., such as cost-benefit analysis). Similarly, economic evaluations may be useful for private sector developers of technology, who must make research and development decisions based on an assumed return on investment [30]. Health system researchers may have to consider the various private and public sector actors that will use an economic evaluation for future decision-making.

Box 1: Forms of economic evaluation

Specific forms of analysis reflect different approaches to evaluating the consequences of health interventions.

- Cost-consequences analyses (CCA) examine costs and consequences, without attempting to isolate a single consequence or aggregate consequences into a single measure.
- Cost minimization analysis (CMA) compare costs only as the consequences are assumed to be equal.
- Cost-effectiveness analysis (CEA) describes consequences in natural units, such as clinical cases detected, or life-years (LYs) gained. A variant of CEA, called cost-utility analysis (CUA) measures consequences in terms of preference-based measures of health, such as disability-adjusted life years (DALYs) or quality-adjusted life-years (QALYs).
- Cost-benefit analysis (CBA) describes consequences in monetary units [27].

Although analysts may choose to use one or more forms of these analyses in their study, they should be aware that each form of analysis might have unique advantages or disadvantages for decision-making. The terms "cost-effectiveness", "cost-benefit" "economic evaluation" are often used interchangeably and, therefore, the term "economic evaluation" is preferred to avoid confusion.

Adapted from [27] and [29]

Economic evaluation has gained more widespread acceptance for decisions regarding new pharmaceuticals and, to a lesser extent, new medical devices and diagnostics [31]. However, the same approach to economic evaluation can be applied to any health intervention, including prevention and promotion programs (such as vaccination and screening), organization of care, rehabilitation, and fiscal policy. Economic evaluation is a principle tool in the world of health technology assessment (HTA), where technology is broadly defined:

> *"The application of scientific or other organized knowledge – including any tool, technique, product, process, method, organization, or system – to practical tasks. In health care, technology includes drugs; diagnostics, indicators and reagents; devices, equipment and supplies; medical and surgical procedures; support systems; and organizational and managerial systems used in prevention, screening, diagnosis, treatment and rehabilitation."* [32]

In Canada, national standards exist for the economic evaluation of health technologies, which can be applied to any complex intervention. They have been developed and maintained by the Canadian Agency for Drugs and Technologies in Health [33]. The guidance is intended to promote consistent evaluation of technology and avoid situations where arbitrary analytic choices can lead to variable findings and analyses that are less useful for decision-making. Consistency is facilitated through the use of a "reference case" analysis -a set of standard approaches that all analysts are required to use (see Box 2). Analysts will then be free to conduct additional analysis according to the decision problem being evaluated. Although this discussion paper refers to the current CADTH guidance (3rd edition), readers should be aware that a new 4th edition of the guideline is now in development. Canada's Treasury board has also developed a generic guidance for the evaluation of regulatory proposals that include health outcomes which may provide supplementary insight [34]. Also

available are guidance for more specific health products including oncology therapies [35] and internationally for vaccines [36].

Box 2: Guidance for the economic evaluation of health technologies: Canada

See - http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

Current guidance for the economic evaluation of health technologies (interventions) is divided into individual categories (called statements) that address various analytic judgments required to conduct rigorous evaluation. These include:

Statement	Description
Study Question	How best to define questions relevant for decision-making
Types of Evaluation	How best to choose the form of analysis, emphasizing the use of cost-utility analysis unless inappropriate
Target Population	Specifying the population affected by the decision and emphasizing analysis of sub-populations if appropriate
Comparators	What the intervention should be compared to and how this should be characterized
Perspective	What costs should be captured, with health system costs required in the reference case
Effectiveness	How health consequences should be estimated, justifying why a single study is appropriate and modifying for real world factors
Time Horizon	Analysts should use a time horizon that captures all relevant costs and consequences
Modelling	Appropriate approaches to modeling based on the nature of the decision
Valuing Outcomes	How outcomes should be valued, particularly for preference-based measures
Resource us and costs	How resources should be identified, estimated and valued
Discounting	Analysts should apply a 5% annual rate of discounting for both health outcomes and costs beyond a year and 0-3% in sensitivity analyses
Variability and uncertainty	How analysts should address both variability and uncertainty of findings
Equity	Equity assumptions used in analysis should be stated – results should be non-weighted for equity in reference case
Generalizability	Analyses that address issues of transferability should be conducted

Adapted from [33]

International standards also exist and are intended to promote rigorous approaches to economic evaluation. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as well as Society for Medical Decision Making (SMDM) have developed and promoted guidance for analysts covering several areas including approaches to estimating costs [37–42], transferring evaluations across jurisdictions [43], and mathematical modeling [44–50,55] (see Box 3). Additionally, checklists have been developed to examine the quality of methods [51] and reporting [29] of these analyses.

Box 3: International standards and guidance for conducting economic evaluation

ISPOR Task Force Reports - http://www.ispor.org/taskforces/tfindex.asp

SMDM Task Force Reports - http://mdm.sagepub.com/content/32/5.toc

Estimating Costs

Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations Task Force Reports I-VI [37–42]**:** These reports cover various aspects of identification, measuring and valuing resources used and across different contexts of decision making.

Transferability of Evaluations

Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report [43]: Good research practices for dealing with aspects of transferability, including strategies based on the analysis of individual patient data and based on decision-analytic modeling.

Modeling

ISPOR-SMDM Modeling Good Research Practices Task Force Reports 1-7 [44–50]**:** Recommendations as to good modeling practices including best approaches for conceptualizing and deciding on model type; best practices in state transition, discrete event, and dynamic transmission modeling; best approaches for estimating model parameters, dealing with uncertainty, validating models and dealing with model transparency.

Reporting Quality Checklist

Consolidated Health Economic Evaluation Reporting Standards (CHEERS)-Explanation and Elaboration [29]: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force: Best approaches to reporting for purposes of journal publication.

Methodological Quality Checklists

Best Practices for Conducting Economic Evaluations in Health Care [51]: A Systematic Review of Quality Assessment Tools: Agency for Health Research and Quality synthesis report about available checklists including the more commonly used Drummond/BMJ[52], Quality of Health Economic Studies (QHES)[53] and Consensus on Health Economic Criteria (CHEC)[54] checklists.

PURPOSE OF DISCUSSION PAPER

The purpose of this discussion paper is to consider the potential issues that arise when existing guidelines for economic evaluations are used to evaluate complex health system interventions. The issues raised in this paper will be particularly relevant to current and future CIHR-IHSPR priorities for research investment; for instance, in the areas of community-based primary healthcare and e-health innovation for high system users. Likewise, there may be relevance for investigators

working in this area, other funders of research, as well as knowledge users aiming for a deeper understanding of these issues and value of the results of such analyses.

The intent of this report is not to create guidelines for those performing economic evaluation of complex interventions but to provide an exploration of the issues that analysts might encounter when attempting to apply current guidance. It is also intended to help health system and policy researchers understand some of the fundamentals of economic evaluation and its application. By elaborating on issues not addressed by existing guidelines in regards to complex interventions, the intent is to reduce variation in methods of economic evaluation and ultimately to improve the health care decisions they are intended to inform.

Although there is a recognized need for new methods in this area and some are suggested at the end of each of the illustrative examples [56], developing and testing new methods is beyond the scope of this paper. Similarly, several authors have promoted the need for entirely new approaches to the economic evaluation of these interventions [57,58]. This paper is not intended to refute these proposals, However, in the absence of a widely accepted alternative approach, it does rely on current and conventional methods for the economic evaluation of health programs. In some cases, we will provide specific recommendations or guidance for what to do in specific circumstances, however much of this document is intended to identify and discuss issues so that analysts can make informed decisions about the judgments they apply and assumptions they use when conducting economic evaluations.

Economic evaluation is intended to link costs with consequences relevant for decision-making. Conducting an economic evaluation does not remove the underlying challenges of *evaluating the consequences of any complex intervention* including difficulties in *attribution of cause and effect and using study designs within natural settings that allow for adequate measurement and valuation*. Those conducting economic evaluation therefore have a common challenge with those tasked with a clinical evaluation of the complex intervention. Economic evaluation may exacerbate some of the challenges with data and information as more data (on resource use) and analysis (such as extrapolation of short-term outcomes) may be required. Economic evaluations often rely on a combination of mathematical modeling and study information when studies that support the underlying estimates of effectiveness lack key pieces of information.

This paper, therefore, highlights additional issues encountered by conducting economic evaluation and does not attempt to tackle some of the more fundamental issues that may be encountered when evaluating complex interventions in general. The common issues between evaluation and economic evaluation should also highlight the need and importance of designing protocols for evaluation in collaboration between those conducting evaluation and economic evaluation.

HOW TO USE THIS DOCUMENT

Readers of this document should at first familiarize themselves with existing CADTH guidance for the economic evaluation of health technologies [33]. The next section will elaborate on some of the issues that may be encountered when using this guidance for the economic evaluation of complex interventions in general. More specific illustrative examples are given in further sections in the areas of (1) Integrated care or system interventions; (2) Community-based primary care interventions; (3) Guideline implementation interventions; (4) Public health interventions; and (5) Telehealth and e-health interventions.

Issues for the Economic Evaluation of Complex Interventions

General issues

Complex interventions may introduce some particular issues across different fields of inquiry (e.g., e-health or public health) that require special consideration. These include:

1) **Type of evaluation and valuing outcomes:** Not all complex interventions are intended to improve length and health-related quality of life and there may be multiple outcomes relevant to decision-making. Therefore, although conducting cost-utility analysis may still be feasible in the reference case, other forms of analysis may be useful to inform decisions. For comparability, analysts should still be encouraged to use cost-utility analysis whenever possible and as per current guidelines.

2) **Comparators:** Analysts face a challenge of deciding whether they are comparing (i) a complex intervention to the lack of the intervention; (ii) various components of the intervention to each other, (iii) sequence in which components are introduced, or (iv) one or all of these. It may be a particular challenge for analysts to identify *a priori* the full set of relevant simple and complex interventions being compared. In the reference case, analysts should be encouraged to compare the complex intervention with a counterfactual condition of no complex intervention. Analysts should then consider additional analysis that compares the economic impact of one or more of the individual component parts of the complex intervention if this information is available. The complex intervention must also be clearly defined so as to allow for reproducibility by other investigators and interpretation by decision-makers [59].

3) **Perspective:** Current guidelines suggest in the reference case, the publicly funded health system should be the perspective used; that is, analysts should examine costs to the publicly funded health system first and use an alternate perspective only if it appears relevant [33]. As complex interventions may often impact costs outside of the health system, analysts should be prepared to conduct secondary analyses using different perspectives to capture additional relevant costs.

4) **Effectiveness:** Current guidelines suggest using a systematic review to estimate the magnitude of effectiveness and adjust for "real-world" factors. However, outcomes from complex interventions may be more sensitive to the context in which they are delivered than is seen with simple interventions [60,61]. Analysts may also have to rely on non-randomized studies of effectiveness to a greater extent, which creates challenges when trying to combine studies (e.g., through meta-analysis), to create overall estimates of effectiveness. Analysts should pay particular attention to recent guidance that attempts to address challenges with estimating effectiveness from complex interventions through the use of systematic reviews [62].

5) **Resource use and costs:** It may be more difficult to measure the resource levels (e.g., such as human resource requirements or consumables) associated with the individual components of a complex intervention. Investigators may need to be prepared to develop original cost algorithms if they are non-existent. They must also consider the additional study size or need for record linkage that may be required to analyze the economic impact of complex interventions.

6) **Modeling –** Conventional approaches to economic modeling are generally used for simple interventions with single decision problems that exist within a broader continuum of care. To better understand the influence of the various components of a complex intervention, mathematical models that incorporate a broader spectrum of care pathways may be required. One such approach has been termed "whole disease modeling" and is based on using discrete event simulation models that can capture both interventions and the context (processes, pathways and sequence) in which they are delivered [63–65].

Some of these same issues have been described in the UK Medical Research Council (MRC) guidance for the development, evaluation and implementation of complex interventions to improve health [1]. The authors highlight that in addition to conventional problems with the evaluation of any health intervention, additional problems can be encountered with complex interventions that "relate to the difficulty of standardising the design and delivery of the interventions, their sensitivity to features of the local context, the organisational and logistical difficulty of applying experimental methods to service or policy change, and the length and complexity of the causal chains linking intervention with outcome." The MRC guidance also cites specific issues of comparators, clearly defining the intervention and primary outcome, resource use and perspective as primary issues, and borrowing from previous challenges identified with economic evaluation in the field of social welfare [66].

Other issues

There may be other issues worth considering that are peripheral to these main challenges. Some issues associated with the conduct of economic evaluation of complex interventions have been identified through previous reviews and include: (1) study questions (i.e., decision problems) not adequately defined [67]; (2) analysts using forms of analysis that do not allow for comparability across programs (e.g., using cost-consequences analyses instead of cost-utility analyses) [68]; (3) study populations may be ill-defined [69]; (4) outcomes may be inappropriately valued, for example using patient satisfaction [68,70]; and (5) discounting may be inappropriately conducted [71]. Importantly, although these issues have been empirically shown to be associated with the conduct and reporting of economic evaluation for complex interventions, they are not necessarily caused by the complexity of the intervention. They could simply reflect other factors, such as lack of training and awareness of use of appropriate methods by investigators in their respective fields.

Elaboration of issues with examples

Example 1: Integrated delivery systems or networks

Joint replacement is a cost-effective treatment for severe osteoarthritis in the hip and knee [72]. To address long waiting periods and variability in service access and outcomes the Alberta Orthopaedic Society began with a comprehensive analysis of hip and knee replacement services, followed by the design of a new model of care to increase efficiency in the public health system.

Based on results from the economic evaluation as well as other quality metrics, Alberta Health encouraged the provincial implementation of this new model of care. The Alberta Bone and Joint Health Institute was asked to help the Health Regions in Alberta translate what was learned in the pilot study to routine practice. Knowledge translation was a critical feature of the pilot project and remains central to the ongoing efforts to implement the new path of care. This has led to new organizational arrangements and broad awareness by practicing clinicians. Most of the orthopedic

surgeons in Alberta who do joint replacement surgery have adopted the new path of care in their practices.

One of the issues related to conducting an economic evaluation of this new program is:

1) **Effectiveness and Valuing Outcomes:** *Determining the relative effectiveness of the new care pathway:* A partnership of surgeons, affiliated healthcare providers and decision support researchers designed and implemented a new evidence-informed clinical pathway for patients requiring total hip or knee replacement and compared the clinical outcomes of that approach to standard care using a randomized controlled trial. Quality-of-care outcomes were measured using a defined measurement framework adapted from the Institute of Medicine by the Alberta Health Care Quality Council [73]. Although some of these outcomes reflected patient health outcomes (such as 'effectiveness' and 'safety') that could be directly applied to economic evaluation, other, outcomes reflected broader system outcomes (such as accessibility). Once a cost-utility analysis is conducted, analysts can consider reporting these additional outcomes using a secondary cost-consequence analysis approach.

Suggestions for moving forward: This evaluation highlights the importance of outcomes that may be associated with complex interventions that are not accounted for in standard health-preference-based measures and reflect wider social values. Further opportunities for advancing methods in this area may relate to using enhanced measures of benefit that incorporate these metrics, such as is currently being explored with approaches such as MCDA or equity-weighted QALYs [6,74].

Example 2 – Community-based interventions - selection of the optimal chronic disease management strategy within Alberta's primary care networks

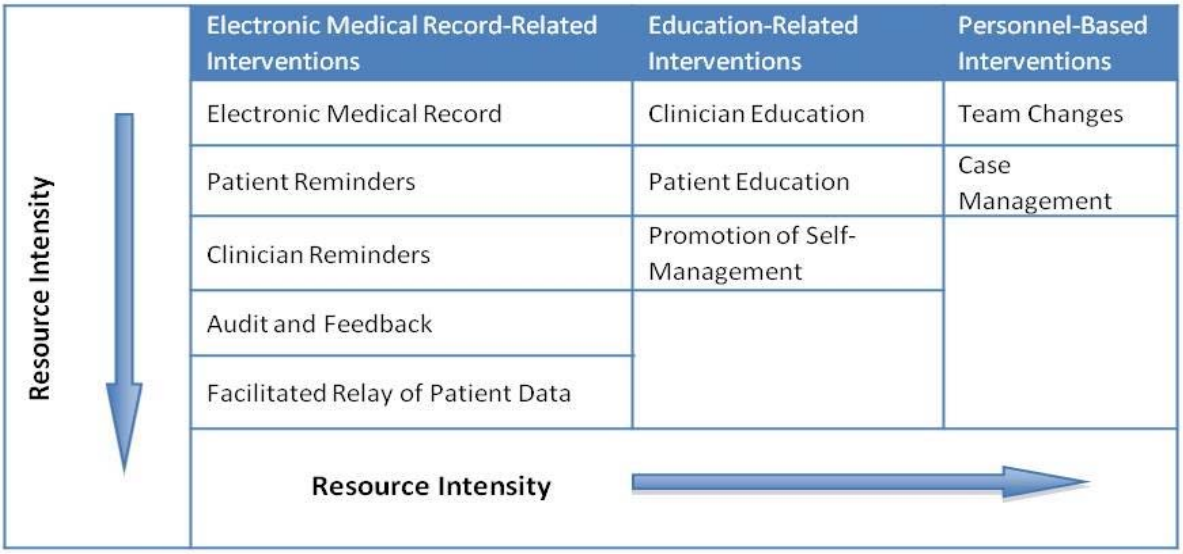
The Alberta Primary Care Networks (PCNs) are an example of a primary care model in which groups of family practices hold a budget to supplement care for their patients outside the usual fee-for-service model [75]. Nearly 80% of eligible family physicians in Alberta currently participate in a PCN. Additional funding of $62 per enrolled patient per year is provided to PCNs to support activities which fall outside the typical physician-based fee-for-service model but are in accordance with specified objectives: improving access to primary care; improving coordination of care; and increasing the emphasis on health promotion and chronic disease management. Consequently, a hypothetical group of 20 family doctors, each caring for an average of 1200 rostered patients, will be allocated nearly $1.5 million in additional funds annually [76].

PCNs must decide how to allocate resources to best meet the needs of their patients, considering their priorities and those of the provincial health ministry. While PCNs have several priorities, they will likely need to consider the type of chronic disease management programs to provide to optimize care for patients with chronic diseases such as diabetes or cardiovascular disease. Previous work showed PCNs have had a small and variable impact on the care and outcomes of patients with diabetes [75], and that PCNs studied funded a wide variety of different chronic disease management programs, presumably based on their impression of effectiveness, what was feasible to implement given the availability of allied health personnel locally, and what other health system chronic disease management programs were available to patients in that geographic area.

Given that additional primary care networks are being established, and expanded, to inform subsequent decisions regarding choice of chronic disease management strategies, consideration was given to conducting an economic evaluation to determine the cost-effectiveness of the various chronic disease management strategies available, each of which varies by relative effectiveness [3],

and by resource intensity [76] (Figure 2). Since one of the important objectives for a PCN is to maximize the health gains for their patient population using a fixed sum of money, conducting a systematic comparison of the relative costs and health effects of candidate programs seems highly relevant. To date, this work has not been completed, largely due to some of the specific issues associated with conducting economic evaluation of these complex interventions:

Figure 2: Resource intensity of chronic disease management strategies (Source: McBrien [77] and Tricco [3])



1) **Target population and variability:** When understanding the effectiveness of a chronic disease management strategy, it's important to consider the patient population within which was studied. A previous review examining the effectiveness of these strategies [3] was conducted in patients with diabetes. However, it's likely that chronic disease management strategies established by primary care networks will be used by other types of patients with chronic diseases. The effectiveness of the different interventions may differ across patient populations, and this is a challenge that requires consideration during an economic evaluation. Acknowledging this, given that the interventions generally seek to optimize lifestyle management, self-management strategies, and use of appropriate medications, it's equally possible that the interventions may have similar effects in different chronic diseases. Investigators will need to consider whether the effectiveness and cost-effectiveness is likely to vary across the types of patients in whom the intervention may be used in practice.

2) **Effectiveness and comparators:** Notwithstanding the fact that the relative effectiveness of nearly a dozen different interventions, some of which are complementary, and some of which are alternatives, would be challenging to assess, there are additional complexities to consider. Most studies that have assessed the effectiveness of these interventions have examined the impact of combinations of different types of interventions such as patient education, provider education, case management, audit and feedback, facilitated relay of information and others [3]. Systematic reviewers acknowledged difficulties in categorizing the strategies into consistent categories and often-relevant details on the intervention itself were left out, making it challenging for someone to replicate the intervention [3]. The different combinations of interventions also raises methodological issues about how best to

assess the impact of each individual strategy, as well as what might be the optimal combinations of interventions [62]. Innovative methodological approaches are being assessed to quantify the individual impact of the interventions, which may overcome this difficulty [78].

Suggestions for moving forward: Acknowledging the challenges of conducting an economic evaluation of all possible chronic disease management strategies across the range of patient populations that they might be used in, PCN leaders must still make and justify their decisions regarding use of chronic disease management strategies, and consideration of the costs and relative effectiveness of the interventions remains important. In the short term, discussions with stakeholders from primary care networks to identify the most feasible interventions that could be implemented would limit the list of interventions to be assessed. Although future implementation of CDM programs could be supported by systematic reviews of available clinical data and a full economic evaluation, analysts should focus on strategies to get this information in a timely fashion to those who are going to make decisions.

Example 3 - Cost-effectiveness of strategies for promoting the uptake and implementation of clinical guidance and other health interventions

This section discusses the use of cost-effectiveness analysis in making decisions about the allocation and efficiency of resources to implementation strategies, which are intended to improve care by inducing lower-level decision makers or actors (including health professionals and patients) to change their behaviors and practices. These complex interventions are being increasingly considered by policy-level decision-makers for improving health care quality and outcomes.

One specific example is considered here: the use of audit & feedback (A&F) to Dutch primary care physicians to enhance intensive control of blood glucose in patients with type 2 diabetes [79]. This intervention is intended to improve control of blood glucose through more frequent medical check-ups and earlier intervention with blood-glucose lowering medication. Although promoted in a local clinical practice guideline, the dissemination of this guideline alone appeared insufficient to induce Dutch primary care physicians to change their behaviors and practice: only 64% of patients with type 2 diabetes received intensive glycemic control after the guideline was distributed. This despite that intensifying treatment to control blood glucose levels in type 2 diabetes is of proven clinical benefit—and these benefits have been shown to justify the costs.

An A&F intervention requires systematic monitoring of clinical performance and the provision of feedback to primary care physicians - although this can be expected to improve quality of care, it requires a share of the limited resources available for improvements in health care to implement—whether within a particular health care organization or health insurer, or within a larger health system such as a nation.

Committing resources to an A&F implementation strategy implies a trade-off against the benefits expected from changes in the uptake and coordination of care due to implementation efforts and the net return derivable from alternative uses of these resources. Thus, it is imperative that decisions about the allocation and efficiency of implementation strategies are informed by a type of analysis that assesses the added improvement in health outcomes relative to cost. This can be accomplished through conducting a cost-effectiveness analysis. Previous reviews in this area have suggested a hybrid approach that uses evaluations of behaviour change coupled with modeling of component effectiveness might be most practical in this area [80–82].

The next section sets out the reasons why implementation strategies such as A&F can be viewed as complex interventions to improve health care; the following section illustrates how an economic evaluation of A&F in the management of type 2 diabetes in primary care may be approached. This section concludes with general directions for the advancement of methods for assessing the allocation and efficiency of resources to implementation strategies.

Audit & Feedback as a Complex Intervention

Audit & feedback can be considered complex in many different ways, two of which are especially relevant to its evaluation:

(1) Multiplicity and Interdependence of Components of Audit & Feedback

When evaluating the efficiency of allocating resources from implementation strategies such as A&F, analysts cannot take the simplistic viewpoint that the intervention is independent of the underlying choice of intervention and aspects of care. This is because the outcome from the implementation strategy is actually a function of (a) the differences in efficiency between medical interventions for implementation and (b) the degree to which health professionals and patients consider or perceive the time and other resources they are to invest in implementation activities (e.g., taking part in clinical audits and using feedback to enhance performance) as worthwhile. Additionally, decisions to commit resources to implementation and coordination of care are usually only considered if and only if a decision maker considers or perceives current practice(s) as suboptimal. So, the overall efficiency of implementation strategies like those of other complex interventions in health is a function of multiple components that act both independently and interdependently and can lead to a wide variation in findings.

(2) Continuous Development of Audit & Feedback

Another common assumption in economic evaluation is that any given intervention is static – its performance is consistent and does not change after a decision to adopt it. Decision-makers are therefore asked to make a binary decision as to whether an intervention is worthwhile given the information on outcomes and costs available.

Like many complex interventions, A&F may lead to variable outcomes that change or are modified depending on how clinical performance in diabetes type 2 is audited and in how primary care physicians are provided with feedback over several cycles. Information or knowledge about how A&F performs is used in customizing any given strategy for implementation to maximize quality improvement and efficiency—with many actors having influence on the modifications and outcomes.

Economic evaluation of the use of Audit & Feedback to primary care providers to enhance intensive control of blood glucose in patients with type 2 diabetes

An economic evaluation of A&F suggested that—from a health system perspective—implementing this strategy for changing diabetes practice represents an efficient allocation of resources for health care improvement. With an 18% increase in type 2 diabetic patients receiving intensive glycemic control at an expected expense of €100 per patient annually, A&F was expected to lead to a 0.16 QALY-increase at an added cost to the system of €4232 as compared with "usual care". The incremental cost-effectiveness ratio for A&F, €25,640 per QALY, is under the threshold value of €30,000 per QALY decision makers commonly use in the UK to consider an intervention in the UK (and the Netherlands) National Health System as cost-effective [83].

1) **Variability and uncertainty:** Whether actually implementing an A&F program is efficient is an open question, however. Standard approaches to economic evaluation usually consider A&F in isolation and provide an estimate of uncertainty surrounding the ICER that only reflects incomplete information or sampling error from research inputs. This includes uncertainty related to estimates (or predictions) of change in intensive glycemic control by primary care physicians due to feedback, uncertainty as to the QALY gains by increased control of blood glucose in type 2 diabetic patients who did not receive such treatment prior, and uncertainty about the expenditures on A&F. But if we view A&F as a complex intervention whose efficiency cannot be independent of other choices or aspects in care, uncertainty in estimates of cost-effectiveness should also reflect other important aspects including the change in primary care physicians' practices in the treatment of type 2 diabetes that may go beyond intensive glycemic control and other medical practices and the fact that the approach to delivering A&F may vary during the process of its implementation. Properly informing decisions from economic evaluation will require a broader view and consideration of these potential sources of uncertainty. This will avoid situations where economic evaluations produced to inform decisions are unhelpful for improving diabetes care.

Suggestions for Moving Forward

The challenges of making economic evaluation of A&F useful for decision-making suggest three directions for the advancement of methods:

Valuing outcomes

Implementing a quantitative approach to priority setting and design of complex interventions through value-of-implementation analysis: Before investing in an A&F implementation strategy or other mechanism to improve the uptake and coordination of proven medical interventions, it seems imperative that a decision maker has some notion of the returns in benefits expected. This can be estimated through an analysis of the value-of-implementation [84,85]. Not only can value-of-implementation analysis help identify problems of implementation and coordination as priorities for improvement, but this type of analysis can aid in the efficient design of complex interventions in priority areas. Once a decision is made to implement the strategy, a decision-maker may still choose to collect appropriate data inputs and re-evaluate the intervention. Conducting value-of-implementation analysis requires: (1) some estimate (or prediction) of the change in implementation and coordination of care expected from implementation strategies, and (2) some estimate (or valuation) of the monetary value of added improvement in health outcomes.

Comparators

Informing the choices of components of complex interventions according to integral analysis of outcomes: decision-makers face two sets of choices: 1) decisions about medical interventions (the choice of items, services, or procedures to use in preventing, diagnosing or treating particular diseases or conditions, that is); and 2) decisions about implementation strategies and other mechanisms of promoting the uptake and coordination of care if this is considered or perceived to be necessary. Two approaches to the analysis of such conceptually distinct but related decisions can be adopted: sequential analysis and integral analysis.

In a sequential approach, decisions about mechanisms for promoting the uptake and coordination of care follow on the decisions about medical interventions. The efficiency of resource allocation is evaluated separately for each addition or substitution to the existing mix of interventions—and the

choices of intervention components are made in a serial, one-at-a-time fashion. Such a sequential approach is in line with the continuous, incremental process to health care improvement decision makers commonly employ—and was implicit in evaluating the use of A&F in Dutch primary care.

An integral approach implies choices of components of a complex intervention to improve health care (both medical interventions and the mechanisms to enhance implementation and coordination of care) are made simultaneously—by comparing the overall efficiency in resource allocation for all possible configurations of components for intervention, now and in the future. Treatment alternatives and other interventions for patient management can often be expected to differ both in their efficiency as well as in their cost of implementation—that is, the expenses on time and other resources to make sure that the medical intervention of choice gets implemented into practice and that patients receive coordinated care. Under these conditions, an integral approach to economic evaluation offers decision-makers advantages over sequential analysis: more efficient allocation of resources and more comprehensive assessment of uncertainty in decision-making [86]. However, many questions remain as to how to incorporate integral analysis effectively into the process of evaluating and making choices about the allocation of resource to interventions more complex than those usually considered for improving health care. Perhaps the most obviously important question is how to develop meaningful priors concerning the level of implementation of medical interventions and the level of care coordination—without any investment in effort to change these—and meaningful priors concerning the costs of implementation strategies or other mechanisms to realize desired change in uptake and coordination of care.

Reporting

Reporting measures of efficiency of complex interventions that incorporate differences in perspectives and differences in levels of decision making: Whether spending on implementation and coordination as part of a complex intervention to improve health care achieves an allocation of resources more efficiently than usual care depends critically on the degree to which expenditures are perceived by the actors other than the decision makers at policy-level (including health professionals and patients) forming part of such intervention as good value for the money. Different actors at different decision-making levels will have different perspectives on cost-effectiveness; they will each value the returns expected from the (perceived) resources (including time) they are to invest for the complex intervention to improve care and outcomes in a different fashion.

The ratio of the expected overall cost to expected overall benefit, as traditional CEAs commonly report, sums up all information relevant for a decision maker at policy-level to determine whether a complex intervention leads to more efficient use of health care resources in the aggregate. But reporting of aggregate ratios alone need not meet the needs for information by all the decision-makers and actors that are needed to deliver the various components of the intervention. The question is how to report these perspectives so that this is most informative and most influential in the processes of making decisions about the efficient allocation of health care resources. Analysts might need to consider disaggregating information about the efficiency in a complex implementation intervention by the component interventions and across actors at different decision-making levels, thereby accounting for potential differences in information needs and perspectives on cost-effectiveness.

Example 4 – Public health interventions

Numerous reviews and published opinions have highlighted the challenges of conducting economic evaluation for public health interventions [87–93]. A recent Canadian review of the literature on the intersection of the fields of health economics (focusing mainly on economic evaluation) and public health was conducted to inform broader discussion by the CIHR Institute of Population and Public Health and other Public Health partners, including the National Collaborating Centres for Public Health (NCCPH), the Canadian Population Health Initiative of the Canadian Institute for Health Information (CPHI-CIHI) and the Public Health Agency of Canada (PHAC) [88]. The subsequent proceedings of the workshop report stated:

> *"Most public health professionals are not trained in economics and most economists are not familiar with the field of public health. Public health researchers need to broaden their understanding of the discipline of economics so that dialogue is more productive and helps enlist the efforts of economists in PPH work. To this end, we must understand how to incorporate the field of Economics into research beyond studies in 'health economics' or specialized sub-areas, like 'economic evaluation.'"[94]*

Population and public health interventions are directed at communities or individuals and communities simultaneously and through a number of interacting components, such as education, behavioral interventions, screening, and health technologies (like a vaccine, laboratory test, or medicine). They are often intended to generate costs and benefits beyond the health system and may rely more heavily on data sources outside of randomized trials for evaluation. Public health interventions are also often implemented as a means to reduce social inequalities, both in terms of health and other metrics. Analysts must be aware that economic evaluations do not capture impacts on how health is distributed (i.e., equity) but rather how health can be maximized over an entire population. Several challenges relating to the complexity of public health interventions have been identified:

1) **Effectiveness:** Economic evaluations require robust estimates of effectiveness, typically from systematic reviews of randomized trials. Given the nature of population-based and public health interventions, RCTs may not be feasible. This is not a challenge specific to economic evaluation but an underlying challenge of evaluation in general [95]. Analysts will then be faced with the challenge of using observational studies gathered from data sources such as electronic medical records, registries or administrative databases [96]. Since many population and public health interventions are intended to have long-term effects, statistical extrapolation techniques or mathematical modeling may need to be employed to estimate long-term outcomes using short term studies. It will be important for analysts to report these analytic assumptions in a clear and transparent manner to allow for replication and further exploration of the findings [29].
2) **Valuing outcomes:** There have been suggestions by some that QALYs may be less appropriate in public health interventions "designed to address health behaviours and inequities in health"[88]. Payne and colleagues describe an attempt to identify relevant outcomes from providing a clinical genetic service that includes a population-based screening program [6]. Through a review and nominal group technique, six outcome domains were identified that included non-health benefits related to providing a clinical genetic service. These are described in Figure 3. As with the previous example in integrated care, analysts may need to consider reporting additional consequences in a secondary analysis

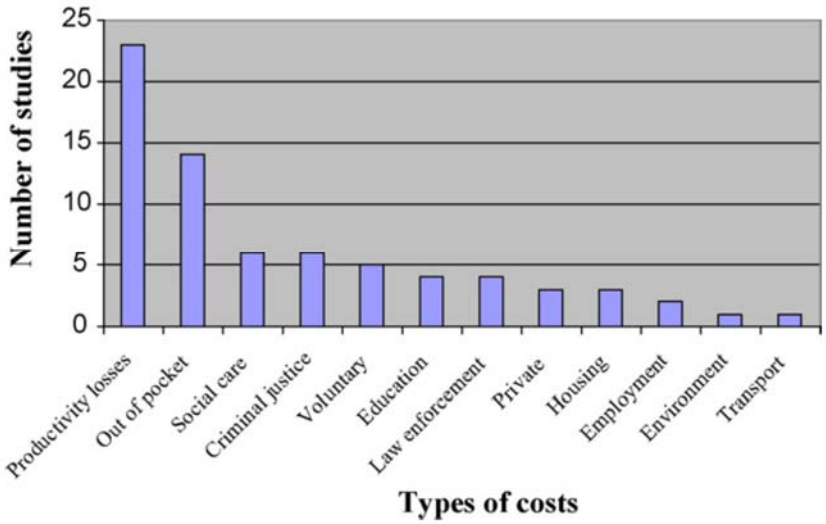
(such as a cost-consequences analysis) taking great care not to double-count outcomes within health-preference-based measures (such as QALYs) that appear in a reference case analysis.

Figure 3: Identified domains with their description and examples of outcome measures, adapted from Payne [6]

Domain	Description Used in Delphi	Examples of Outcome Measure Containing the Domain
Knowledge of the genetic condition	Knowledge about the genetic condition in the person who attended the clinic. The aspects of knowledge measured include knowledge about the risks of the condition to them and other members of their family.	Breast Cancer Genetic Counselling Knowledge Questionnaire Genetic Knowledge Index Knowledge about genetic risk for breast cancer
Anxiety	Whether using the service had changed how anxious the person felt.	Cancer Anxiety and Helplessness Scale General Health Questionnaire Hopkins Symptom Checklist
Depression	Whether using the service had changed how depressed the person felt.	Beck Depression Inventory Hospital Anxiety and Depression Scale Self-Rating Depression Scale
Worry	Whether using the service had changed how worried the person felt.	Worry Interference Scale Breast Cancer Worry
Health status	Whether using the service had changed the health of the patient. The aspects of health measured include ability to care for oneself, ability to perform day-to-day activities, pain, ability to get around, anxiety and depression.	Medical Outcomes Short-Form Survey (SF-36; SF-12)
Quality of life	Whether using the service had changed the quality of life of the patient. The aspects of quality of life measured include physical and mental well-being, social and family relationships and attitudes to the future.	Subjective Quality of Life Profile Functional Assessment of Cancer Therapy-General

3) **Resource use and cost:** Complex public health interventions are likely to have an effect on many resource use categories outside of the health sector. Weatherly reports the types of costs outside of health system costs identified in a review of economic evaluations of public health interventions (Figure 4). These costs include productivity losses to society due to missed work, out of pocket costs, social care costs, and costs to the criminal justice, education, housing, environment, and transport sectors. Although there may be compelling economic arguments for applying different discount rates to costs outside of health [97], current guidelines suggest applying a standard rate.

Figure 4: Types of resource use categories that may require consideration in economic evaluations of public health (outside of health), from Weatherley [87]



4) **Equity:** Incorporating equity considerations into decision-making is a central theme in public health and has been an ongoing challenge in the field of economic evaluation for decades [88]. Current guidance suggests using equal equity weights in the Reference Case analysis and then encourages analysts to state the implications of the intervention on equity and for identifiable subgroups [33]. Weatherly suggests analysts should consider explicitly identifying equity considerations by conducting "a narrative review of the equity considerations at stake". Analysts are encouraged to consider approaches to explicitly identifying equity considerations in public health that have been described by Cookson and Drummond [74].

Example 5 – Telehealth and e-health interventions - coupling an interactive patient portal with telehealth and case management

In their formative stages of development, telehealth interventions might have been considered as complex interventions. This was due to the several interacting components required that contributed to the effectiveness of the intervention including the travelled distance between care provider and patient and the presence of a separate capital structure that was the communications network. As economic researchers soon discovered, these characteristics of complexity could be handled with traditional economic concepts [28,98].

Telehealth and e-health interventions have now become more mainstream with useful application in primary and community-based interventions – often for purposes of better managing chronic disease or other conditions associated with considerable economic burden. For example, numerous e-health interventions combine case management with the use of patient web-based portals or SMS-based technology as a means to empower patients to individualize care and self-manage their conditions. At its core, efficient e-health applications reduce health human resource burden through automation. These complex interventions harbor a number of challenges for analysts, specifically:

1) **Perspective:** Depending on the perspective taken when conducting an economic evaluation, the patient's personal time may become a relevant variable and must be factored into the

analysis. If patients have to travel to the care providers (which was the alternative situation to using telehealth) then travel costs could be used as a measure of the value of patient's resources used. For an e-health intervention, the travel costs are opportunity costs: e-health helps patients avoid the travel and lost time from work (or leisure) that is associated with the intervention. Longer-term absences from work may translate into larger societal productivity costs. Analysts must take care to use appropriate techniques to value avoided travel and caregiver time.

2) **Valuing Outcomes:** In all the cases, the outcomes are standard measures that are used in economic evaluations. In his review of telehealth practices, Roine (2001) documented a number of telemedicine applications in which standard outcomes were used [98]. While it is true, in the case of telemedicine, that the circumstances underlying the patient/doctor interaction are more complex than in the case where there is a personal contact. But the economic principles are not at all different, and standard economic evaluation techniques are used.

Suggestions for moving forward: Telehealth and e-health interventions are likely to affect resources within the health system and outside the health system (e.g., travel costs for patients) and analysts will need to be prepared to additionally use a societal perspective when conducting economic evaluation. There may also be costs to stakeholders outside of patients and providers that need to be accounted for [28]. There may be additional issues related to e-health interventions when they are used for chronic disease management. For example, a systematic review of the health economic impact of disease management programs for COPD revealed most studies (82%) did not report detailed characteristics of institution(s) or region in which the intervention is implemented, e.g. size of the region and rural or urban environment. Only one study (of 11) reported a plan to avoid contamination by other interventions and only three (of 11) studies clearly provided details of the comparator [99]. A similar review of self-management programs in asthma found that few economic evaluations incorporated a form of analysis that allowed for comparability (e.g., such as CUA or CEA) [100]. Rather than developing new methods, this suggests analysts in this area may really want to ensure they are accurately applying existing ones, to ensure comparability of evaluations.

CONCLUDING REMARKS

We hope this discussion paper will aid analysts in understanding and consistently applying a framework for the economic evaluation of complex health system interventions. Although analysts may encounter additional challenges not identified in this paper, we hope some of those discussed will better prepare them in areas where complex interventions are used. Consistent analysis is important to allow comparisons of the relative impact of interventions and to support knowledge translation and decision-making.

This paper is intended to only be a starting point for health system and policy researchers who wish to understand some of the fundamentals of economic evaluation and its application complex interventions. There may also be relevance for funders of research as well as knowledge users aiming for a deeper understanding of these issues and value of the results of such analyses. It is also intended to help health system and policy researchers understand some of the fundamentals of economic evaluation and its application. This paper should not be considered an exhaustive treatise

on the subject; it will be updated and revised regularly based on user feedback and the changing landscape in evaluation of complex interventions.

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This discussion paper has been produced in response to a request from *CIHR Institute of Health Services and Policy Research (CIHR IHSPR)*. The discussion paper will provide guidance to those tasked with conducting an economic evaluation of complex health system interventions. The guidance will be an elaboration of existing National guidelines for economic evaluation, and serve as a discussion paper to aid investigators conducting economic evaluations of complex health interventions. This paper is intended to be a starting point for health system and policy researchers who wish to understand some of the fundamentals of economic evaluation and its application complex interventions.

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