

Evidence Brief

Achieving Greater Impact From Investments in Medicine in Canada

17 September 2019



HEALTH FORUM

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Evidence Brief:
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McMaster Health Forum

The McMaster Health Forum's goal is to generate action on the pressing health-system issues of our time, based on the best available research evidence and systematically elicited citizen values and stakeholder insights. We aim to strengthen health systems – locally, nationally, and internationally – and get the right programs, services and drugs to the people who need them.

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KEY MESSAGES

What's the problem?

The focus of many high-profile, national conversations about prescription medicines in Canada has been on whether they are accessible and affordable to the Canadians who need them. One of the key points continually raised is that Canada is the only high-income country that has not established universal coverage for prescription medicines, despite guaranteeing universal access to publicly funded hospital and physician services. There have been numerous calls to include prescription drugs as part of universal coverage since the mid-1960s, with the most recent push for this approach outlined in the final report of the Advisory Council on the Implementation of National Pharmacare. However, to ensure Canadians are getting the most from investments in medicines, there are three related issues of which the first and third receive much less emphasis despite their importance:

- 1) appropriate prescribing, adherence and deprescribing are not currently optimally supported;
- 2) medicines aren't accessible or affordable; and
- 3) reforms in medicines are not being pursued in a manner to optimally support rapid learning and improvement.

What do we know (from systematic reviews) about achieving greater impact from investments in medicine in Canada?

- Element 1 – establish prescriber and patient supports to achieve greater impacts from appropriate medicines
 - This element focuses on: supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies; ensuring patients are aware of the medicines that are most appropriate for managing their condition; and choosing the right mix of promising patient-targeted strategies found to help improve adherence to prescription medicines.
 - We identified 33 reviews, most of which related to sub-elements 1 and 3 and found significant benefits in adherence and in processes of care, however, improvements to patient health outcomes were not consistently reported.
- Element 2 – make sure the right medicines are accessible and affordable
 - This element focuses on: determining how to expand coverage to more Canadians; determining which medicines will be covered; and determining what proportion of costs will be covered.
 - We identified seven reviews, five of which related to determining what proportion of costs will be covered, generally finding that increases in the proportion of costs paid out-of-pocket results in greater use of other health services, however, the quality of the reviews reporting these findings varies.
- Element 3 – adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics
 - This element focuses on: connecting existing assets to leverage existing investments in medicines; using existing tools and decisions to support the identification of medicines to include in an essential medicines list or national formulary; and establishing and fostering assets to fill existing gaps across the seven characteristics at both national and provincial levels.
 - We were unable to find any systematic reviews that directly address the use of rapid-learning health systems related to medicine per se, however, we included two reviews and a series of case studies that related broadly to the characteristics of a rapid-learning health system.

What implementation considerations need to be kept in mind?

- Two barriers to implementation are that: coordinating and planning for medicines across multiple jurisdictions in Canada is quite difficult; and ensuring medicines are used appropriately hinges on behaviour changes among both patients and providers and may be slow to occur.
- The main policy window for implementing the elements is the attention already being given to the issue of prescription medicines in Canada paired with the forthcoming federal election.

REPORT

Prescription medicines are an increasingly vital part of the care provided to Canadian patients. This is widely acknowledged, as are the challenges associated with ensuring prescription medicines are accessible, affordable and used appropriately (by both patients and their providers). The focus of many high-profile national conversations about prescription medicines in Canada has tended to focus on whether they are accessible and affordable for Canadians. For instance, it is frequently pointed out that Canada is the only high-income country that has not established universal coverage for prescription medicines, despite guaranteeing universal access to publicly funded hospital and physician services deemed ‘medically necessary’ through its provincial and territorial health systems.(1; 2) Within this dominant narrative, there have been numerous calls to include prescription drugs as part of universal coverage since the mid-1960s, with the most high profile among these declarations including those made by:

- the 1964 Royal Commission on Health Services (i.e., the Hall Commission);
- the 1997 National Forum on Health;
- the 2002 Royal Commission on the Future of Health Care in Canada (which unlike other reports in this list recommended the implementation of catastrophic coverage);
- the 2018 House of Commons Standing Committee on Health; and
- the Advisory Council on the Implementation of National Pharmacare, which released its final report on 12 June 2019, and explicitly called for the development of a universal, single-payer, public pharmacare program to be established by 2027.

Despite some advancements towards improving access to and affordability of prescription medicines (e.g., the establishment of catastrophic coverage in most provinces), most Canadians continue to rely on a patchwork of private and public mechanisms to cover some – but not all – of the costs of the prescription medicines they need. The range of provincial, federal and private mechanisms in place include:

- provincial public drug programs that provide coverage to select populations, such as:
 - the income-based Fair PharmaCare plan in British Columbia,
 - Alberta Health Benefit for low-income adults, older adults and children,
 - the Ontario Drug Benefit program for older adults and the Trillium Drug Program for those with very high drug costs relative to income in Ontario, and OHIP+ for otherwise uninsured children and youth under 25, and
 - the Quebec Public Prescription Drug Insurance Plan for people without access to a private plan;

Box 1: Background to the evidence brief

This evidence brief mobilizes both global and local research evidence about a problem, three approach elements for addressing the problem, and key implementation considerations. Whenever possible, the evidence brief summarizes research evidence drawn from systematic reviews of the research literature and occasionally from single research studies. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select and appraise research studies and to synthesize data from the included studies. The evidence brief does not contain recommendations, which would have required the authors of the brief to make judgments based on their personal values and preferences, and which could pre-empt important deliberations about whose values and preferences matter in making such judgments.

The preparation of the evidence brief involved five steps:

- 1) convening a Steering Committee comprised of representatives from the partner organizations (and/or key stakeholder groups) and the McMaster Health Forum;
- 2) developing and refining the terms of reference for an evidence brief, particularly the framing of the problem and three viable approach elements for addressing it, in consultation with the Steering Committee and a number of key informants, and with the aid of several conceptual frameworks that organize thinking about ways to approach the issue;
- 3) identifying, selecting, appraising and synthesizing relevant research evidence about the problem, options and implementation considerations;
- 4) drafting the evidence brief in such a way as to present concisely and in accessible language the global and local research evidence; and
- 5) finalizing the evidence brief based on the input of several merit reviewers.

The three approach elements for addressing the problem were not designed to be mutually exclusive. They could be pursued simultaneously or in a sequenced way, and each approach element could be given greater or lesser attention relative to the others.

The evidence brief was prepared to inform a stakeholder dialogue at which research evidence is one of many considerations. Participants’ views and experiences and the tacit knowledge they bring to the issues at hand are also important inputs to the dialogue. One goal of the stakeholder dialogue is to spark insights – insights that can only come about when all of those who will be involved in or affected by future decisions about the issue can work through it together. A second goal of the stakeholder dialogue is to generate action by those who participate in the dialogue and by those who review the dialogue summary and the video interviews with dialogue participants.

- federal public drug programs that provide coverage to select populations, such as:
 - the First Nations and Inuit Health Branch’s Non-Insured Health Benefits program for First Nations peoples and eligible Inuit;
 - the Department of National Defence’s Spectrum of Care program and the Canadian Armed Forces Drug Benefit List for members of the Canadian Forces and their dependents,
 - the Veterans Affairs Canada’s Programs of Choice and Health Care Benefits Program for qualified veterans,
 - the Public Service Health Care Plan for members of the Royal Canadian Mounted Police, and
 - Correctional Service Canada’s Health Services Program for federal offenders; and
- private insurance plans, paid for either in whole or in part by employers as part of work-related extended health-benefits packages, or through premiums paid out-of-pocket by individuals.

Even with these public and private mechanisms in place across the country, many Canadians have access to only catastrophic drug coverage outside of hospitals.(2-4) Furthermore, there have been few attempts to align public provincial and territorial plans or private plans, which has created a largely uncoordinated set of mechanisms that patients rely on to cover the costs of their prescription medicines. While initiatives such as the 2010 establishment of the Pan-Canadian Pharmaceutical Alliance have taken steps to try and ensure prescription medicines are more affordable for Canadians (and the provincial drug plans purchasing some of these medicines on their behalf) through coordinated purchasing arrangements, 5-6% of Canadians still report cost-related non-adherence, suggesting that more could be done.(5)

Given the scope of current and past initiatives outlined above, it is not surprising that particular cost-related challenges and their contributions to the underuse of prescription medicines tend to receive a lot of attention from policymakers in Canada, and considerations about how to address them have largely centred on ensuring access to, and affordability of, prescription medicines. However, these efforts are only partial answers to the question of how to ensure patients in Canada get the most benefit from investments in medicines. In particular, it has also been acknowledged that ensuring appropriateness in the use of medicines more generally – which includes overcoming reasons for underuse of medicines beyond cost, and addressing both overuse and misuse – are also vital components. As such there is a need to expand conversations beyond a singular focus on whether and how health-system financial arrangements can be changed to improve public access to and affordability of medicines, towards one that also considers at least two other issues that get far less ‘air time,’ despite their fundamental importance in achieving greater impacts from investments in medicines:

Box 2: Equity considerations

A problem may disproportionately affect some groups in society. The benefits, harms and costs of approach elements to address the problem may vary across groups. Implementation considerations may also vary across groups.

One way to identify groups warranting particular attention is to use “PROGRESS,” which is an acronym formed by the first letters of the following eight ways that can be used to describe groups†:

- place of residence (e.g., rural and remote populations);
- race/ethnicity/culture (e.g., First Nations and Inuit populations, immigrant populations and linguistic minority populations);
- occupation or labour-market experiences more generally (e.g., those in “precarious work” arrangements);
- gender;
- religion;
- educational level (e.g., health literacy);
- socio-economic status (e.g., economically disadvantaged populations); and
- social capital/social exclusion.

The evidence brief strives to address all Canadians, but (where possible) it also gives particular attention to three groups:

- individuals who only have catastrophic public drug coverage (e.g., those who are self-employed, those without a pension who have retired early, and individuals from particularly vulnerable populations);
- individuals, who despite access to public or private coverage, remain under-insured (e.g., they spend a disproportionate amount of their annual income on medicines); and
- individuals from populations that are at a disproportionately high risk of inappropriately using prescription medicines (e.g., older adults and those with multiple chronic conditions).

Many other groups warrant serious consideration as well, and a similar approach could be adopted for any of them.

† The PROGRESS framework was developed by Tim Evans and Hilary Brown (Evans T, Brown H. Road traffic crashes: operationalizing equity in the context of health sector reform. *Injury Control and Safety Promotion* 2003;10(1-2): 11–12). It is being tested by the Cochrane Collaboration Health Equity Field as a means of evaluating the impact of interventions on health equity.

- how the full range of health-system arrangements can be strengthened to support the appropriate use of medicines across the entire continuum of patient care (e.g., from when diagnoses are made and medicines prescribed, to ensuring patients adhere to their prescriptions, to determining when patients should be taken off medicines prescribed to them through deprescribing); and
- how to facilitate continuous cycles of rapid learning and improvement that can help to ensure health systems are continuously ‘moving the needle’ by improving the impact from investments in prescription medicine.

These issues are important regardless of how Canada moves forward with the recent recommendations from the Advisory Council for the Implementation of National Pharmacare.

In addition to being timely for the many federal initiatives mentioned above, the dialogue that this evidence brief was developed to inform aligns with the recently published findings from a randomized controlled trial – the Carefully seLected and Easily Accessible at No charge MEDicationS (CLEAN MEDS) trial - which has been designed to identify the effects of free access and appropriate distribution of a set of essential medicine for patients in primary care. The list of essential medicines considered in designing the trial has also been referenced in the recently published report by the Advisory Council on the Implementation of National Pharmacare, which suggests many efforts in the country are converging in numerous ways, creating an opportune window to push the conversation forward in practical ways.

THE PROBLEM

Many Canadians are not taking the medications they need, resulting in a range of challenges, including poor health outcomes and an inefficient use of health services. However, the reasons for this are varied and include at least the three overarching problems:

- 1) appropriate prescribing, adherence and deprescribing are not optimally supported;
- 2) medications are not accessible or affordable; and
- 3) reforms in medicines are not being pursued in a manner that supports rapid learning and improvement.

Below, we elaborate on each of these issues in turn, based on data and evidence we identified from our searches, as well as from insights gained through the 19 key informant interviews we conducted during the preparation of this evidence brief.

Appropriate prescribing, adherence and deprescribing are not optimally supported

Three dimensions of how prescription medicines intersect with the patient-care continuum are important for supporting the appropriate use of medicines: prescribing practices; supporting patient adherence; and deprescribing. However, as outlined in the sections that follow, these dimensions are often not optimally supported across health systems in Canada, which can contribute to the inappropriate use (including underuse, overuse and misuse) of prescription medicines.

Sub-optimal prescribing practices

In 2017, there were 86,644 physicians in Canada making prescribing decisions for their patients, in addition to a number of other providers including dentists, nurse practitioners, and pharmacists whose expanded role in some provinces now allow them to prescribe medications as well.⁽⁶⁾ Ensuring that all of these health providers have up-to-date knowledge and skills related to prescribing (as well as the attitudes conducive to supporting appropriate prescribing) can be challenging. This is borne out in the statistics available on inappropriate prescribing across the country. For example, it is estimated that 40% of the older adults in Canada benefitting from public drug programs receive medications that are potentially inappropriate.⁽⁷⁾ This is concerning for a range of reasons including that inappropriate prescribing is associated with excess morbidity and increased cost. For example, about 17% of hospitalizations in Canada could be prevented with better prescribing and more appropriate use.⁽⁸⁾

However, ensuring the right prescriptions are provided to patients is complicated by five main factors: 1) it is challenging to change established prescriber behaviours and routines; 2) provincial formularies contain thousands of medicines; 3) tools are not always in place to support effective prescribing; 4) there is little coordination between prescribers and dispensers (e.g., physicians and pharmacists); and 5) varied amounts of information or data are collected on the prescribing habits of professionals across provinces.

The first factor complicating efforts to ensure the right prescriptions are provided to patients is that providers – like anyone else – develop habits and often settle into set behaviours and routines that are difficult to change. This includes behaviours related to the types of medicines they are familiar with and routinely

Box 3: Mobilizing research evidence about the problem

The available research evidence about the problem was sought from a range of published and ‘grey’ research literature sources. Published literature that provided a comparative dimension to an understanding of the problem was sought using three health services research ‘hedges’ in MedLine, namely those for appropriateness, processes and outcomes of care (which increase the chances of us identifying administrative database studies and community surveys). Published literature that provided insights into alternative ways of framing the problem was sought using a fourth hedge in MedLine, namely the one for qualitative research. Grey literature was sought by reviewing the websites of a number of domestic and international organizations, such as Health Quality Ontario, the Canadian Institute for Health Information, and the Organisation for Economic Cooperation and Development.

Priority was given to research evidence that was published more recently, that was locally applicable (in the sense of having been conducted in Canada), and that took equity considerations into account.

prescribe to their patients. Features of an individual provider's practice can contribute to engraining these behaviours, and include workload, time pressures or number of patients (which can make it difficult to reflect on and, when appropriate, change established practice habits). Additionally, internal individual factors such as a provider's temperament, desire or willingness to learn can limit their ability to change, as do external factors such as organizational standards, pressure to keep costs contained, and guidelines (which can be operationalized in hospital order sets). A second but interrelated factor is the cumbersome nature of provincial formularies which contain thousands of medicines (and private formularies add additional complexity). It is unrealistic to expect prescribers to be familiar with all of the products and dosages listed, therefore confusion and unfamiliarity may contribute to poor prescribing decisions that aren't the most appropriate or cost-effective. Third, there is a lack of widely available tools in place to support effective prescribing. With the exception of select initiatives such as PrescribeIt in Alberta (run by Canada Health Infoway), there is a paucity of systematically implemented decision-support tools in place to help prescribers to consider the range of options in medicines and make effective and cost-effective decisions. This is particularly true when considering the costs of medicines, which may not be considered and discussed until the patient fills their prescription. Fourth and related to the previous consideration is a lack of communication between prescribers and between prescribers and dispensers. Specifically, pharmacists often have to check medicines with the professionals prescribing them, particularly when there are concerns about the selection of medicines, instructions for dosing or potential interactions with other prescriptions. Without responsive channels for communication, these questions may delay the filling and use of a prescription, a situation that can be further complicated amongst individuals with multiple comorbidities who tend to have multiple prescribers who may each be adjusting an individual patient's medicines. Finally, despite numerous Canadian research reports documenting sub-optimal prescribing, there are varied amounts of capacity and efforts in place across provinces and territories to measure the extent of sub-optimal prescribing across provincial and territorial systems, and even when data are collected it is often at the level of individual practices that would allow feedback to be provided to prescribers.(9)

Sub-optimal supports for patient adherence

Ensuring the right medicines are prescribed is only the first step in managing the treatment of patients with these medicines, since once medicines are prescribed, patients are responsible for taking them appropriately. Unfortunately, poor adherence to medications remains a significant challenge, and it is estimated that each year approximately 30% of prescriptions generated in Canada go unfilled by patients.(10) Given this doesn't include patients who fill their prescriptions but choose not to use the medicines, or who do not adhere to directions of the medicines (e.g., amount to take each day, when/if to finish a course of treatment), the problem is likely larger than even this number suggests. However, it should be noted that some of these prescriptions were never intended to be filled, with providers at times indicating that they should be taken if a condition does not improve. Despite these instances, the issue remains of significant concern given a lack of adherence to medicines has negative consequences for an individual's health, while being a potential cost-driver in health systems that must then deal with the additional costs associated with the complications arising from untreated conditions. Findings from a WHO report illustrate these issues, showing that medication non-adherence accounts for five per cent of Canadian hospital admissions and five per cent of physician visits, resulting in an additional \$4 billion in health-care costs annually.(11) Reasons for non-adherence vary significantly, but in general they include: patient-related factors (such as forgetting to take medicines, denying the condition, mental health or substance-use problems, or cultural or alternative beliefs); treatment-related factors (such as the complexity of the treatment, side effects, inconvenience, cost or time); or problems that arise as a result of a poor practitioner-patient relationship.

In addition to these issues, there are two challenges that can complicate our understanding of (and therefore our ability to address) patients' non-adherence to medicines. The first is that we lack a systematic approach to monitoring the extent to which non-adherence affects an individual patient's care. While some forms of direct and indirect monitoring exist, such as surveys or medication refill rates, these approaches often rely on subjective patient measures that may be skewed by recall or social-desirability bias, or on regular communication between those prescribing and those dispensing medicines (which, as outlined earlier, is rarely

the case across the country). Further, the limited uptake of electronic prescribing (notably in Ontario, which remains one of the only provinces without a central provincial data system in place) restricts our ability to monitor primary and secondary non-adherence. The second challenge is that non-adherence to medicines is frequently framed exclusively as a problem with the patient rather than being indicative of problems with providers' practices, the relationship between providers and patients, or the health system more broadly.(12)

Sub-optimal deprescribing

Finally, the third factor in the appropriate use of medicines is deprescribing, which ensures that the use of medicines evolves alongside patient care, and that the effectiveness and appropriateness of the medicine is continuously re-evaluated by health providers. This key step in patient care is often forgotten given that care tends to be geared towards starting medications, not reducing or stopping them. Deprescribing involves more than identifying inappropriate medicine use, but also requires a full review of the medicines prescribed, and deciding which can be stopped, tapered or reduced. Similar to inappropriate prescribing, the continued use of non-effective medications or more medications than are clinically indicated can be potentially harmful. The use of multiple medicines, if not properly monitored and deprescribed (which includes regularly reviewing and re-assessing an individual's prescriptions), has been associated with a number of negative outcomes, including reduced quality of life, adverse drug reactions, falls, non-adherence, hospitalization and mortality. Conversely studies on appropriate deprescribing have found improvements in clinical outcomes, and in many cases to reduced drug costs.(13)

Beyond the focus of care often being geared towards providing medicines rather than reducing them, three additional barriers limit the extent to which providers are able to deprescribe. First, prescribers experience challenges applying single-disease guidelines to patients with multimorbidity or particularly complex patients (e.g., older adults). Further, decision supports that may assist appropriate prescribing for these complex conditions are not consistently available in all settings or for all types (and combinations) of conditions. Similarly, access to specialists that may be more experienced in prescribing for select complex conditions may also be limited. A second but related challenge is that there may be a number of different providers prescribing medications to individual patients. In particular, complex patients and those with multimorbidities may have numerous medicines prescribed to them by different providers, and some professionals may be wary to challenge the decisions of their colleagues through a deprescription process. One primary study reported that this was particularly important among general practitioners who don't always feel comfortable deprescribing medications that were prescribed by specialists. Finally, the third issue challenging the integration of deprescribing into regular practice is the time available and competing demands that professionals experience. Providers may see deprescribing as being cumbersome and time-consuming, and may limit the number of other patients they are able to see.

While there are challenges to providers routinely engaging in deprescribing, there have been a number of Canadian initiatives that are supporting this work. In particular, the Canadian Deprescribing Network is making headway by engaging a range of policymakers, clinicians, patient advocates and researchers who work together to promote the deprescribing of medications.(14)

Prescription medicines are not accessible or affordable

Prescription medicines in Canada are among the most expensive in the world with \$12 billion spent annually by provincial and territorial governments. Comparatively, Canadians pay about 30% more for the medicines they use compared to other OECD countries,(15) and these prices do not appear to be dropping, with per capita spending on medicines growing by an average 4% per year. This is significantly higher than New Zealand (2.9%) and the U.K. (1.2%).(16) In 2011 per capita costs in Canada were \$771 compared to \$477 in Sweden.(17)

While this is concerning from an economic perspective and points to the potential for achieving better value for money, it is also worrisome from a health-outcomes and health-equity perspective. Existing public programs at the federal and provincial levels only cover select populations or conditions, leaving other Canadians to rely on private insurance coverage through an extended health benefits package provided by employers, or on out-of-pocket payments. Approximately 1.7 million (18) Canadians face cost-related barriers in accessing their prescriptions, which can compromise their ability to benefit from effective treatments and lead to significant complications later in their care process. Further, challenges accessing medicines can lead Canadians to increased use of healthcare services and drive up costs in the system unnecessarily.(15; 19) Importantly, challenges related to the accessibility and affordability of medicines are not only experienced by those who are uninsured, as even those with access to a private plan may be increasingly underinsured as premiums and co-payments continue to increase in order to offset the rapid introduction of high-cost (but often low-value) drugs.

Taken together, the challenges in accessing appropriate, affordable medicines means that many Canadians are underusing or misusing medications. For example, benzodiazepines are one of the most frequently inappropriately prescribed medicines, in part due to the lack of affordable alternatives to manage mild to moderate anxiety. While organizations such as Choosing Wisely Canada are working to address this, much more would need to be done at a pan-Canadian level, especially if a shift towards national pharmacare is pursued.

Reforms in medicines are not being pursued in a manner that supports rapid learning and improvement

With two (of three) major political parties including national pharmacare as a central piece of their 2019 electoral platform, there has been plenty of discussion about the shape that it may take, however, there has been relatively little acknowledgment that we are unlikely to get reforms exactly right on the first try. There has been even less discussion about how health systems will need to be re-oriented to ensure that commensurate changes in the organization and delivery of care are pursued with the aim of improving the impact from investments in medicines, and how these systems can continuously be improved upon over time. In particular, current approaches to support the development and implementation of next steps related to how Canadians access and use prescription medicines are not actively considering ways to rapidly evaluate and improve where it is necessary to quickly adjust the course. At the level of the individual medicines, one example of where a rapid-learning orientation is missing is in the lack of a post-market pharmacosurveillance system to monitor the safety and comparative effectiveness of drugs. Further, the feedback from any pharmacosurveillance activities that do take place does not feed back into program and service design. These shortfalls occur despite knowing that drugs are often prescribed to populations in which they are not tested and approved, and for conditions for which they were not tested and evaluated.

The interim and final reports from the Advisory Council on the Implementation of National Pharmacare both detailed a number of core principles and foundational elements for successfully implementing national pharmacare regardless of which specific approach is chosen. Many of the principles and elements highlighted in the interim report align with the seven characteristics of a rapid-learning health-system approach (which has been gaining increased traction in Canada and internationally), including:

- an emphasis on the need to ensure any plan is designed and delivered in partnership with patients and citizens, which aligns with the first characteristic of a rapid-learning health-system approach (**engage patients**);
- repeated calls throughout the reports for investing in drug data and information technology (IT) systems, which aligns with the second characteristic of a rapid-learning health-system approach (**digital capture, linkage and timely sharing of data**); and
- the **alignment of governance, financial and delivery arrangements**, the fifth characteristic, through the identified needs for:

- national pharmacare to be founded on strong partnerships between federal, provincial and territorial governments and Indigenous peoples,
- the creation of a national drug agency,
- working with existing national networks, agencies and departments (i.e., Drug Safety and Effectiveness Network, CIHI, CADTH, and Health Canada),
- the provision of prescription drugs based on medical need without financial or other barriers to access,
- portable and consistent coverage across all jurisdictions, and
- the development of a comprehensive, evidence-based national formulary.

While the report was not developed with a rapid-learning orientation in mind, applying this framework has the potential to get us further faster, and supports a clear view of the suggested assets and potential gaps that exist in the pharmacare proposal. As the reports stand, these gaps include:

- the **timely production of research evidence** (the third characteristic), which could include distributed capacity to produce and share research (including evaluations) about the ongoing changes to pharmacare, the capacity to synthesize research evidence in a timely way, and one-stop shops for local evaluations and pre-appraised syntheses;
- the existence of **appropriate decision supports** at all levels with appropriate data, evidence and decision-making frameworks (e.g., for self-management, clinical encounters, program, organizational, and government);
- a **culture supportive of rapid learning and improvement** (the sixth characteristic), which could include explicit mechanisms to develop a culture of teamwork and collaboration across the range of programs and organizations currently involved in medicines in Canada; and
- the **establishment of competencies for rapid learning and improvement** (the seventh characteristic) such as data and research literacy, co-design, leadership competencies and the presence of rapid-learning infrastructure such as a learning collaborative.

Additional equity-related observations about the problem

While the majority of Canadians are covered under some degree of public or private insurance program, there are some individuals who have no coverage at all. However, the scope of this population remains largely unknown, with organizations having released significantly different estimates on the proportion of the population that fall into this category. Some of these estimates include, 5.2 per cent (about 2 million Canadians) from the Conference Board of Canada,(20) while the 2016 Canadian Community Health Survey places this number closer to 19 per cent (or about 7.5 million Canadians).(18) The recent report from the Advisory Council on the Implementation of National Pharmacare suggests that this discrepancy may be the result of including both uninsured and underinsured Canadians (i.e., groups 1 and 2) in the Canadian Community Health Survey or differences in the way in which questions were phrased in each survey. Without insurance, the cost of medications for these groups may become unaffordable, with annual per capita prescription drug expenditure outside of hospitals estimated at \$900 in 2018.(18) While the average out-of-pocket expenditure among those who are uninsured or underinsured is not known, it is likely much higher than the national average of \$452 per year.(18) The inability to pay for the cost of medicines can result in individuals choosing to not fill or adhere to the prescriptions provided, which in turn has been associated with increased morbidity and mortality, as well as increased use of hospital and emergency services, often at more acute stages of morbidity.

In addition to these two groups, we also included individuals who are at a disproportionately high risk of inappropriately using prescription medicines. Potentially inappropriate drug use is a particular concern among seniors and those with multiple chronic conditions who often require numerous types of medications, some of which may be contraindicated. Further, both of these populations (e.g., seniors and those with multiple chronic conditions) seek care from many different providers, which can result in a lack of coordination between prescribers, increasing the risk of adverse drug reactions. Among both

populations, inappropriate drug use has been associated with increased risk of negative outcomes including falls, adverse drug events, increased hospital usage and higher per capita health costs. For seniors alone it was estimated that inappropriate drug use results in additional healthcare costs of \$419 million annually.

Citizens' views about key challenges related to achieving greater impact from investments in medicine in Canada

One citizen panel – which engaged a diverse group of 14 citizens (in terms of age, gender, ethnocultural background and socio-economic status) – was convened in Hamilton (Ontario) on 16 August 2019. The panel consisted of panellists from seven provinces (British Columbia, Alberta, Saskatchewan, Ontario, Quebec, New Brunswick and Nova Scotia). Panellists were provided with a plain-language version of the evidence brief prior to the citizen panel, which served as an input into citizens' deliberations.

During the deliberation about the problem, citizens were asked to share what they perceived to be the main challenges to achieving greater impact from investments in medicine in Canada. They were also asked to identify any challenges that either they encountered personally, or that a member of their family had encountered with respect to: determining whether medicines were right for them (e.g., having discussions about other options such as over-the-counter medicines, having clear explanations why they were prescribed the medicines); affording – or being unable to afford – the medicines they needed; and physically accessing the medicines they needed. Panellists identified six important challenges: 1) patients have unmet informational needs; 2) patients have limited opportunities to have meaningful conversations with their providers about their health and their care; 3) providers are not supported with an interoperable information system; 4) many patients cannot afford the medicines they need; 5) many patients cannot access the medicines they need; and 6) bringing cohesive and sustainable changes across the country will be difficult. These are all summarized in detail in Table 1.

Table 1. Summary of citizens' views about challenges

Challenge	Description
Patients have unmet informational needs	<ul style="list-style-type: none"> • When asked whether they are usually provided with enough information to determine whether medicines are right for them, panellists indicated that their experiences ranged from being provided with not enough information, with too much information, and with conflicting information. <ul style="list-style-type: none"> ○ Not enough information: Most panellists expressed that they did not receive enough information about their conditions and the various treatment options. In some cases, they were provided with instructions that the providers were not fully able to explain (e.g., restricting their consumption of grapefruit/grapefruit juice when taking certain medication). As one panellist said: “No one has been able to explain why, so I am unnecessarily cutting it from my diet with no one being able to explain it to me.” ○ Too much information: A few panellists discussed the challenges of handling the vast amount of information for any single medicine, noting that “[there are] so many side effects listed that there comes a point where you ignore them”, which becomes exacerbated when several medicines are needed. ○ Conflicting information: Some panellists emphasized that they often receive conflicting information about their medicines from their prescriber, the pharmacist, the handouts provided by the pharmacists, and the labels on packages. As one panellist said: “The pharmacist said to take it and then eat right after, while the pamphlet says to take one hour prior to any meal, and finally the prescription said two hours after food.” • Some panellists mentioned that research evidence on medicines is constantly evolving and it's hard to keep up. As one panellist indicated: “[I have been] taking a medicine for

Challenge	Description
	<p>years and all of a sudden there is a warning on it that was never there before; is this new or has this always been the case; if the latter, why now?” A second panellist went further: “[Pharmacists] do explain the stuff to me, but long-term medication, they assume you already understand, but it needs to be discussed again.”</p> <ul style="list-style-type: none"> • Lack of trusted information sources: Many times, patients have to do their own research to obtain information about their medications. For example, one panellist described being explicitly told by his physician to use Google to get information. Several panellists expressed frustration about having to do their own research, and concerns about the quality of information they could find online, stating: “Do you ever believe everything you see online?” Other panellists consulted the websites of disease-specific organizations, provider organizations (e.g., the Mayo Clinic), and the drug manufacturer to find additional information. One panellist indicated that he ran online searches to learn what other patients had to say about specific medicines. • Limited capacity to use health information: Several panellists pointed out that many Canadians have a limited level of health literacy, which may limit their capacity to appropriately use their medication. <ul style="list-style-type: none"> ○ Yet, some panellists indicated that the lack of adherence goes beyond the level of literacy, and that their level of motivation and their complex daily routines may have a further impact. For example, one panellist said “I am fairly well educated but I get busy and just don’t take my medication. I think it’s more laziness over knowledge.”
<p>Patients have limited opportunities to have meaningful conversations with their providers about their treatments</p>	<ul style="list-style-type: none"> • Most panellists emphasized that medical appointments are not conducive to meaningful conversations about their health, the care they receive, or the appropriate use of medicines. These appointments often last a short period of time (estimated by many panellists to be about 10 minutes) and do not allow them to discuss all their health issues. As one panellist said: “We have seven to eight minutes to talk for a year of problems.” A second panellist went further: “The time a doctor spends with a patient is very short. The doctor tries to figure out and prescribe the drug all within one visit, with no follow-up or time to explain how the prescription works.” The limited opportunities to discuss with providers have also been identified as an underlying reason that can exacerbate the inappropriate use of medicines: “[It’s the] physician time and availability that leads to the misuse of medication.” • Another reason why patients and providers do not have meaningful conversations about their treatments may be that many patients share a culture of deference to their providers. While some panellists hoped that patients would be more proactive regarding their own health and their own care (e.g., by asking questions about their conditions and treatment options, and challenging their provider whenever necessary), others highlighted that many patients share a culture of complete deference (and sometimes ‘blind trust’) towards their providers. One panellist wondered if this was a generational issue, referring to her grandmother: “Older people won’t ask a question, there is absolute trust in the doctor. (...) [My grandmother] doesn’t even want to know the name of the medication. She is from an era where you trust the doctor.” A second panellist agreed: “I’m finding it confusing sometimes, but he’s the doctor so we trust them if they prescribe it.”
<p>Providers are not supported with an interoperable information system</p>	<ul style="list-style-type: none"> • Panellists expressed frustration about the absence of an interoperable information system allowing for the timely sharing of patient information across all providers and settings, which contributed to the inappropriate use of medicines. They didn’t understand why health systems in Canada were so slow in the uptake of information and communication technologies that could improve access, affordability and appropriate use of medicines (e.g., patient portals, electronic medical records, computerized decision aids).
<p>Many patients cannot afford the</p>	<ul style="list-style-type: none"> • Panellists expressed concerns about the 1.7 million Canadians facing cost-related barriers to medicines, and many highlighted the high costs of private health insurance. Some self-

Challenge	Description
<p>medicines they need</p>	<p>employed panellists indicated that they cannot afford private health-insurance plans, so they do not get them and pay out-of-pocket when necessary.</p> <ul style="list-style-type: none"> • Some panellists pointed out that, when patients face cost-related barriers, they sometimes try to stretch their medications by not taking it as prescribed which can cause additional health problems. • They highlighted that it is not just the cost of the medicines that constitutes a problem. It is also the dispensing fees, the costs of travelling to obtain the medicines, and other costs (e.g., \$50 to transfer paperwork from one provider to another). • Some panellists expressed serious concerns about their providers explicitly asking about their coverage before prescribing medicines. They worried that it may have an impact on the treatment options considered by the provider. As one panellist said: “What is your insurance or coverage is always the first question. I’m worried that could affect the quality of medication I’m receiving.” • From a systems perspective, panellists were surprised to learn that prescription medicines in Canada are among the most expensive in the world (particularly that Canadians pay about 30% more for the medicines they use compared to other OECD countries). They were not aware of the magnitude of the financial problem. • One panellist also emphasized that, as patients, it is not just the cost of the medicine that worried him. It is also the cost to the system of not having timely access to providers, and not enough providers being able to have meaningful conversations with their patients, which exacerbated the inappropriate use of medicines and the broader costs to health systems.
<p>Many patients cannot access the medicines they need</p>	<ul style="list-style-type: none"> • The lack of timely access to a primary-care provider (mostly a family physician) was identified as a critical factor influencing the lack of access to the medicines they need: “The trouble is getting a doctor, so you stick with them even if you don’t agree with their opinion.” • Panellists indicated that they were not familiar with the scope of practice of the different providers (beyond physicians), and who could write prescriptions for what conditions, limiting their ability to access medicines from different avenues.
<p>Bringing cohesive and sustainable change to medicines across the country will be difficult</p>	<ul style="list-style-type: none"> • Panellists indicated that they had limited knowledge about how other provinces and territories are covering medicines. “We don’t necessarily know what’s happening in other provinces” and as a result had difficulty comparing their situation to other Canadians. • Many indicated that the absence of a national pharmacare program (or the absence of similar coverage policies and decisions across jurisdictions) was a source of concern and created inequities across the country. “We need to be under one umbrella.” • But knowing that there are 14 different health systems in the country and that politics often gets in the way, panellists indicated that it would be hard to make changes and achieve consensus on how to move forward. Many panellists indicated that they believed a cultural shift appeared to be the key to any national pharmacare program, because at every level, in every jurisdiction, everyone has an agenda. “To make a huge national shift, it’s going to be hard without a cultural shift.”

THREE ELEMENTS OF A POTENTIALLY COMPREHENSIVE APPROACH FOR ADDRESSING THE PROBLEM

Many approaches could be selected as a starting point for deliberations about an approach for achieving greater impact from investments in medicine in Canada. To promote discussion about the pros and cons of potentially viable approaches, we have selected three elements of a potentially comprehensive approach to achieve greater impacts from investments in medicine. The three elements were developed and refined through consultation with the Steering Committee and key informants who we interviewed during the development of this evidence brief. The elements are:

- 1) establish prescriber and patient supports to achieve greater impacts from appropriate medicines;
- 2) make sure the right medicines are accessible and affordable; and
- 3) adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics.

The elements could be pursued separately or simultaneously, or sub-elements could be drawn from each element to create a new (fourth) element. They are presented separately to foster deliberations about their respective components, the relative importance or priority of each, their interconnectedness and potential of or need for sequencing, and their feasibility.

The principal focus in this section is on what is known about these elements based on findings from systematic reviews. We present the findings from systematic reviews along with an appraisal of whether their methodological quality (using the AMSTAR tool) (9) is high (scores of 8 or higher out of a possible 11), medium (scores of 4-7) or low (scores less than 4) (see the appendix for more details about the quality-appraisal process). We also highlight whether they were conducted recently, which we define as the search being conducted within the last five years. In the next section, the focus turns to the barriers to adopting and implementing these elements, and to possible implementation strategies to address the barriers.

Citizens' values and preferences related to the three elements

We included in the citizen brief the same three elements of a potentially comprehensive approach to address the problem as are included in this evidence brief. For the purpose of the citizen brief, the elements were renamed

Box 4: Mobilizing research evidence about elements for addressing the problem

The available research evidence about elements of a potentially comprehensive approach for addressing the problem was sought primarily from Health Systems Evidence (www.healthsystemsevidence.org), which is a continuously updated database containing more than 8,900 systematic reviews and more than 2,700 economic evaluations of delivery, financial and governance arrangements within health systems. The reviews and economic evaluations were identified by searching the database for reviews addressing features of each of the approach elements.

The authors' conclusions were extracted from the reviews whenever possible. Some reviews contained no studies despite an exhaustive search (i.e., they were 'empty' reviews), while others concluded that there was substantial uncertainty about the approach element based on the identified studies. Where relevant, caveats were introduced about these authors' conclusions based on assessments of the reviews' quality, the local applicability of the reviews' findings, equity considerations, and relevance to the issue. (See the appendices for a complete description of these assessments.)

Being aware of what is not known can be as important as being aware of what is known. When faced with an empty review, substantial uncertainty, or concerns about quality and local applicability or lack of attention to equity considerations, primary research could be commissioned, or an element could be pursued and a monitoring and evaluation plan designed as part of its implementation. When faced with a review that was published many years ago, an updating of the review could be commissioned if time allows.

No additional research evidence was sought beyond what was included in the systematic review. Those interested in pursuing a particular approach element may want to search for a more detailed description of the approach element or for additional research evidence about approach elements.

to be more accessible to a group of citizens. These elements were used as a jumping-off point for the panel deliberations. During the deliberations we identified several values and preferences from citizens in relation to these elements, which we summarize in Table 2.

Table 2. Summary of citizens’ values and preferences related to the three elements

Element	Values expressed	Preferences for how to implement the element
Supporting patients and providers to appropriately use medicines	<ul style="list-style-type: none"> • excellent patient experience • collaboration among patients, providers and organizations within the health system • innovation • competence 	<ul style="list-style-type: none"> • provide patients with more valid and reliable information to inform decisions about the medicines that are most appropriate and support adherence • improve the relationship between patients and providers, thus engaging patients meaningfully in decision-making about their condition and how it is treated • embrace new technologies that could support timely access to care providers, as well as support the appropriate use of medicines • support mandatory professional development of all providers regarding best practices with prescription medicines
Making sure patients can access and afford appropriate medicines	<ul style="list-style-type: none"> • fairness (equity) • choice • stewardship • collaboration between Canadian jurisdictions • trust 	<ul style="list-style-type: none"> • support a publicly-funded, national pharmacare program, with a list of essential medicines that would be available to all people (but have the capacity to choose additional plans that they could pay for to expand the list of covered medicines) • mitigate tension between a desire to have a centralized authority making decisions about public coverage for medicines, and a desire to decentralize coverage decisions to be tailored to unique populations • support greater collaboration among Canadian jurisdictions to combine their negotiation in order to bring the costs of prescription medicine down
Enabling decision-makers to make small yet rapid changes to support the appropriate use of accessible and affordable medicines	<ul style="list-style-type: none"> • continuously improving (quality) • based on data and evidence (evidence-informed care and policy) • accountability • stewardship 	<ul style="list-style-type: none"> • support health systems to commit to making small and rapid improvements to the way in which medicines are prescribed, paid for and provided • support for rapid changes that are evidence-based • support the creation of an arm’s-length organization that would steward these changes

Element 1 – Establish prescriber and patient supports to achieve greater impacts from appropriate medicines

This element focuses primarily on ensuring the appropriate use of prescription medicines (rather than access or affordability) and would include efforts to ensure appropriate prescribing (and deprescribing) by providers based on the best available evidence, and informed expectations among patients about the medicines prescribed to them. Sub-elements could include:

- supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies:
 - education (materials, meetings, outreach),
 - local opinion leaders,

- local consensus processes,
- peer review,
- audit and feedback,
- reminders and prompts,
- tailored interventions,
- patient-mediated interventions,
- multi-faceted interventions;
- ensuring patients are aware of the medicines that are most appropriate for managing their condition, align their demand for them based on this awareness (e.g., through patient-education initiatives), and engage them in decision-making in their condition; and
- choosing the right mix of promising patient-targeted strategies found to help improve adherence to prescription medicines, including:
 - tailored ongoing support from allied health professionals,
 - education,
 - counselling (including motivation interviewing or cognitive behavioural therapy),
 - daily treatment support,
 - support from family or peers.

Key findings from the citizen panel

There were four main values-related themes that emerged during the discussion about element 1:

- 1) excellent patient experience;
- 2) collaboration among patients, providers and organizations within the health system;
- 3) innovation; and
- 4) competence.

The first values-related theme emerging from the panel focused on improving the patient experience. Panellists indicated that providing patients with more valid and reliable information was fundamental to helping them to make informed decisions about the medicines that are most appropriate for managing their conditions, and helping them adhere to them.

A second values-related theme was collaboration among patients, providers and organizations within the health system. Panellists emphasized the need to improve the relationship between patients and providers, thus engaging patients meaningfully in decision-making about their condition and how it is treated. Many indicated that patients should be part of a cohesive care team. They should be engaged in developing a holistic treatment plan, so they could have a greater investment in (and adherence to) the plan. To achieve this, panellists pointed out the need for longer medical appointments (and thus more time for conversations), and frequent follow-ups to establish a rapport with the care team (which could be facilitated by a nurse care coordinator who could do proactive follow-up, especially for the first week of any new treatment plan).

The third values-related theme was innovation. Panellists indicated that health systems should embrace new technologies that could support timely access to care providers (e.g., online bookings and virtual appointments), as well as support the appropriate use of medicines (e.g., innovative blister packs and specialized pill boxes to organize all the medication taken by a patient) as well as novel ways to ensure patients and providers can discuss medicines, side effects and interactions while they are being taken appropriately (e.g., two-way text or phone apps prompting users to report any adverse reactions, worrying side effects, that also serve as a reminder for timely use of their medicines).

The fourth values-related theme was competence. Panellists called for mandatory professional development of all providers regarding best practices with prescription medicines. They also briefly discussed how we could optimally leverage the core competencies of all providers in the care team. For example, while physicians may be better equipped to provide information about diagnosis and the pros and cons of different treatment options, pharmacists may be best positioned to provide in-depth information about medicines.

Key findings from the literature

We identified 33 reviews relating to element 1 and its sub-elements listed above. The majority of this literature related to the first sub-element of supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies.

For sub-element 1 (supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies), there is a significant amount of literature that exists, but for the purposes of this brief, we have chosen to focus on those that relate specifically to medicines and improving appropriate prescribing. Readers interested in what is known from synthesized research evidence about provider-targeted strategies more generally can consult an overview of systematic reviews or two previous evidence briefs prepared by the Forum which summarize the results of this overview.(21-23) With respect to medicines and improving appropriate prescribing, we identified evidence on a range of approaches for provider-targeted strategies including: education; audit and feedback; medication reviews and case conferencing; patient-mediated interventions (e.g., supporting the patient to use decision aids); tailored interventions; and computer-mediated interventions. Positive results in care processes (e.g., improved prescribing, adherence to best practices in medicines, quality of care), were generally found for educational outreach visits, audit and feedback, medication reviews and case conferencing, and for select computer-mediated interventions including computerized reminders, computerized drug dosage advice, and barcode administration system.(24-34) However, the effectiveness of these interventions varied significantly in their effect sizes. Only one review on computerized drug dosage advice reported improved health outcomes as a result of the intervention, which included a reduction in the time to therapeutic stabilization and reduced risk of toxic drug levels among patients.(31) A number of reviews also reported no or uncertain effects when comparing provider interventions to comparators. One recent medium-quality review found no significant effect from patient-mediated interventions on health professionals' adherence to recommended practice.(35) There were no clear messages in the identified reviews about the effectiveness of printed educational materials, tailored interventions, or computerized prescribing.(30; 33; 36-38)

For the second sub-element (ensuring patients are aware of the medicines that are most appropriate for managing their condition and align their demand for them based on this awareness), one recent medium-quality review found that education intervention delivered by multi-disciplinary teams resulted in higher adherence to medicines than patients receiving usual care.(39) However, the review found no improvement in adherence from the use of decision aids or shared decision-making.(39) The same review and one older medium-quality review found that augmented pharmacy services, including face-to-face education, pharmacist-led multicomponent interventions, and case-management interventions, improved medication adherence.(39)

Finally, for sub-element 3 (choosing the right mix of promising patient-targeted strategies found to help improve adherence to prescription medicines), the reviews we found examined training health professionals to identify barriers to adherence, the use of reminder packaging, case management, financial reinforcement to support adherence and non-medicinal prescriptions. One recent medium-quality review found that training for health professionals to increase patient adherence was most successful when combined with additional interventions to improve adherence.(40) Two reviews, one older high-quality and one recent medium-quality, found reminder packaging increased adherence to medicines compared to normal packaging, however another older high-quality review found little evidence to support the use of calendar blister packaging.(41; 42) One medium-quality review found some evidence to support the use of eHealth interventions such as web-based monitoring and telemedicine, while another recent medium-quality review found two-way text messaging reminders significantly improved medication adherence.(43; 44)

A summary of the key findings from the synthesized research evidence is provided in Table 1. For those who want to know more about the systematic reviews contained in Table 1 (or obtain citations for the reviews), a fuller description of the systematic reviews is provided in Appendix 1.

Table 1: Summary of key findings from systematic reviews relevant to Element 1 – Establish prescriber and patient supports to achieve greater impacts from appropriate medicines

Category of finding	Summary of key findings
Benefits	<p>Supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies</p> <ul style="list-style-type: none"> • One older high-quality review found that audit and feedback led to small but important improvements in professional practice, finding a median adjusted increase of 4.3% in desired practice. <ul style="list-style-type: none"> ○ The same review found that feedback tends to be more effective when baseline performance is low, when the source is a supervisor or colleague, when it is provided more than once, when it is given in both verbal and written formats, and when it includes both explicit targets and an action plan.(24) ○ However, one recent medium-quality and one older medium-quality review found physician feedback led to little or no difference in medication adherence, patient outcomes or health-resource use, but was found to result in small improvements in processes of care including making medication changes and creating open dialogue with patients.(25; 26) • One recent high-quality review and two older medium-quality reviews found that educational-outreach visits alone, or when combined with other interventions such as patient-mediated interventions, provider-targeted information, or computerized prompts, had small but relatively consistent effects on improving appropriate prescribing.(27; 28) • One older high-quality review and one recent high-quality review found that the use of computer reminders generally improved the quality of care being provided, with the older review estimating a median 3.3% improvement in appropriate medication ordering.(29; 30) • One older high-quality review found that computerized drug-dosage advice improved the appropriateness of the initial dose of medications, increased serum concentrations, reduced the time to therapeutic stabilization, reduced the risk of toxic drug level, and reduced the length of hospital stay.(31) • Two recent high-quality reviews found that on average interventions to optimize prescribing for older people in care homes (i.e., medication review, case-conferencing, and professional education) improved medication appropriateness and identification and resolution of medication-related problems, however their effects on costs, hospital admissions, adverse drug events or mortality remain uncertain.(45; 46) <ul style="list-style-type: none"> ○ Similarly, one recent high-quality review found medication reconciliation reduced the presence of medication discrepancies but had no effect on healthcare utilization, medication adherence, unplanned readmission rates, and adverse effects of medications.(47) • One older medium-quality review found that multifaceted interventions that involved combinations of physician, patient and public education were the most successful in reducing antibiotic prescribing for inappropriate indications.(26) <ul style="list-style-type: none"> ○ The review noted that the effectiveness of interventions is strongly dependent on the particular prescribing behaviours and characteristics of a particular community. • One recent high-quality review found that both restrictive interventions (those that apply rules to help physicians prescribe properly) and enablement techniques (which provide advice or feedback to help physicians prescribe properly) successfully increased the number of hospital inpatients treated according to antibiotic prescribing policy.(32) • One recent high-quality review found that implementing a barcode administration system significantly reduced medication errors, but the effect on harm reduction remains unclear.(33) • One recent overview of reviews found promising results from: medication reviews when conducted by pharmacists; pharmaceutical interventions; computerized interventions; and educational interventions to reduce the use of inappropriate medications.(34) • One recent medium-quality review found that patient-mediated interventions including patient-reported health information, patient education interventions, and patient decision aids had little effect on professionals’ adherence to recommended practice.(35)

	<p>Choosing the right mix of promising patient-targeted strategies found to help improve adherence to prescription medicines</p> <ul style="list-style-type: none"> • One recent medium-quality review found skills training for health professionals to increase patient adherence were most successful when combined with other interventions. <ul style="list-style-type: none"> ○ Skills taught included methods to uncover patients’ barriers to adherence, methods to find solutions to barriers, methods to teach patients about adherence, and the availability of standardized adherence treatment checklists.(40) • One older high-quality review and one recent medium-quality review found that reminder packaging increased the percentage of pills taken compared to normal packaging,(48) with the medium-quality review suggesting it was most effective when included as part of a multifaceted strategy. <ul style="list-style-type: none"> ○ However, another older high-quality review found little evidence to support the use of calendar blister packaging or pill organizers.(41; 42) • One older medium-quality review found interventions that included elements of case management, face-to-face education with pharmacists, and pharmacist-led multicomponent interventions improved medication-adherence outcomes for hypertension, heart failure, depression and asthma.(49) • One medium-quality review found some evidence to support the use of electronic health interventions such as web-based monitoring, customized educational and monitoring websites, telemedicine and internet-based self-monitoring to improve medication adherence.(43) <ul style="list-style-type: none"> ○ Similarly, one recent medium-quality review found two-way text message reminders significantly improved medication adherence.(44) • One recent medium-quality review found education interventions delivered by multidisciplinary teams resulted in higher adherence rates than patients receiving usual care. <ul style="list-style-type: none"> ○ The review found mixed effects for the use of augmented pharmacy services for medically complex patients, but suggested that positive improvements were observed more often than negative or non-significant changes. ○ However the review found that decision aids and shared decision-making did not result in improvements to adherence or other outcomes.(39) • One older medium-quality review found financial reinforcement interventions generally improved adherence rates of medication.(50) • One recent high-quality review found comparable results from the use of non-medicinal prescriptions for managing chronic health conditions in primary care.(51) • Two studies included in one recent high-quality review found mixed effects of discharge planning on medication errors, with one study reporting a significant difference while the other found no difference between the intervention and control groups.(52)
Potential harms	<ul style="list-style-type: none"> • No harms were identified
Costs and/or cost-effectiveness in relation to the status quo	<ul style="list-style-type: none"> • No cost-related reviews were found
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<ul style="list-style-type: none"> • Supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies <ul style="list-style-type: none"> ○ One older high-quality review found that while printed education materials had small beneficial effects on professional practice, there was insufficient information included in the studies to determine the effect on patient outcomes. <ul style="list-style-type: none"> ▪ Further, the review found that the effectiveness of printed material varies considerably based on: the source of information; tailoring; purpose; level of evidence; and format.(36) ○ One recent high-quality review found that while tailored interventions (strategies to improve professional practice that are planned and take account of prospectively identified determinants of practice) to improve professional practice are more effective than no intervention or the dissemination of guidelines, it remains uncertain whether tailored interventions are more effective than non-tailored interventions such as audit and feedback or educational outreach.(37) ○ One recent high-quality review was unable to determine whether computer-generated reminders, alone or coupled with co-interventions, improved patient outcomes given the

	<p>heterogeneity of reminders in included studies.(30)</p> <ul style="list-style-type: none"> ○ One recent high-quality review was unable to determine whether pharmaceutical-care-based approaches (e.g., promoting the correct use of medicines by identifying, preventing and resolving medication-related problems) resulted in clinically significant improvements in polypharmacy.(53) ○ One recent high-quality review was unable to determine whether professional (e.g., health information technology to identify individuals at risk of medication problems, electronic systems notifying dose changes) or organizational (e.g., medication reviews by pharmacists, nurses or physicians or clinician-led clinics or home visits) interventions for reducing preventable medication errors had an effect on the number of people admitted to hospitals, emergency-department visits or mortality.(38) ○ One recent high-quality review found the use of a computerized prescribing system and check and control checklist did not have conclusive results about their effects.(33) <ul style="list-style-type: none"> ● Choosing the right mix of promising patient-targeted strategies found to help improve adherence to prescription medicines <ul style="list-style-type: none"> ○ One recent high-quality review was unable to delineate the effective components of interventions to improve medication adherence given the heterogeneity in patients, treatments and intervention types.(54)
<p>Key elements of the policy option if it was tried elsewhere</p>	<p>Supporting appropriate prescribing by choosing the right mix of promising provider-targeted strategies</p> <ul style="list-style-type: none"> ● One recent overview of reviews found that while computerized systems may support a reduction in inappropriate medicines, computer systems may not capture the full picture of a patient’s medication use if they purchase drugs from non-participating pharmacies or take over-the-counter medicines.(34)
<p>Stakeholders’ views and experience</p>	<ul style="list-style-type: none"> ● No reviews were found that focused on stakeholders’ views and experience.

Element 2 – Make sure the right medicines are accessible and affordable

The element focuses on providing a set of key considerations that are required – many of which have been discussed extensively in Canada – to ensure prescription medicines are accessible and affordable when they are prescribed. Sub-elements of this element include:

- determining how to expand coverage to more Canadians
 - e.g., filling existing gaps between public and private by including Canadians who aren't covered within existing plans or by a private plan,
 - e.g., establishing universal access for every Canadian;
- determining which medicines will be covered
 - e.g., cover the entire list of essential medicines,
 - e.g., cover a sub-set of the list of essential medicines; and
 - determining what proportion of costs will be covered.

One approach to ensuring the accessibility and affordability of medicines could be to implement essential medicines lists that are based on the health needs of the populations, which would require careful decisions in each of the sub-elements above.

Key findings from the citizen panel

The discussion about element 2 focused on determining how to expand coverage to more Canadians and decide which medicines will be covered and what proportion of costs will be publicly covered. There were five main values-related themes that emerged during the discussion about element 2:

- 1) fairness (equity);
- 2) choice;
- 3) stewardship;
- 4) collaboration between Canadian jurisdictions; and
- 5) trust.

The first values-related theme that emerged was fairness (equity). This theme emerged when discussing how to expand coverage to more Canadians and which medicines should be covered. Panellists generally agreed about the need to provide public coverage for a list of essential medicines for everyone.

The second values-related theme focused on choice. Panellists generally agreed with the idea of a publicly funded, national pharmacare program, with a list of essential medicines that would be available to all people. Yet, they want people to have the capacity to choose additional plans that they could pay for to expand the list of covered medicines.

The third values-related theme was stewardship. It emerged during a discussion about the need for leadership when making coverage policies and coverage decisions. The discussions highlighted some tension among the panellists between a desire to have a central authority making decisions about coverage of drug policies, and a desire to decentralize coverage decisions. Several panellists indicated that coverage decisions regarding medicines should be managed at a more regional/local level, to get close to your priority populations, while still being consistent with coverage policies established at the national level. As one panellist said: “[We need a] centralized authority combined with grassroots [actions] to remove the chaos that can occur.”

The last two values-related themes that emerged during the discussion of element 2 were collaboration among Canadian jurisdictions and trust. Panellists mentioned again their concerns that prescription medicines in Canada are amongst the most expensive in the world. They supported greater collaboration among Canadian jurisdictions to combine their negotiation power to bring down the costs of prescription medicine. This discussion also revealed a certain level of mistrust towards the pharmaceutical industry, which many panellists perceived as resisting efforts to lower drug prices and threatening governments that it would lead to reduced

research and development investments, less innovation in Canada, and fewer jobs in our life sciences sector. As one panellist said: “We are held hostage by pharmaceutical companies.”

Key findings from the literature

We identified seven systematic reviews related to the three sub-elements.

For the first sub-element (determining how to expand coverage to more Canadians) we identified one recent medium-quality review which found that expanding prescription-drug insurance can play a crucial role in decreasing the use of other healthcare services, while contributing positively to patients’ health outcomes.(55) However, we did not identify any reviews related to mechanisms to expand coverage.(55)

With regards to the second sub-element (determining which medicines will be covered), we identified one older high-quality review which found the use of prior authorization policies reduced older adults’ unnecessary use of gastric-acid suppressants and non-steroid anti-inflammatory drugs, as well as resulted in savings for up to two years. However, results differed substantially across categories of drugs.(56)

Finally, we found the most evidence relating to sub-element 3 (determining what proportion of costs will be covered) specifically examining different pricing policies including out-of-pocket payments, fixed co-payments and caps on medicines, reference and index pricing. One recent medium-quality review found that increased out-of-pocket payments for medicines led to increased demand for select health services including outpatient and inpatient services, hospitalization, and emergency-room visits.(57) Similarly, two recent high-quality reviews and one older medium-quality review found that while restrictive caps on medicine, fixed co-payments and pharmaceutical budget caps reduced the amount paid by insurers, they increased the utilization of other health services.(58-60) Finally, one older high-quality review found a reduction in the cumulative drug expenditures for insurers on both reference and cost-share drugs in the first year after reference pricing was introduced, however, there was significant heterogeneity across the proportion of savings.(61) The same review found an increase in the use of generic drugs through index pricing and a reduction in the use of brand-named drugs.(61)

A summary of the key findings from the synthesized research evidence is provided in Table 2. For those who want to know more about the systematic reviews contained in Table 2 (or obtain citations for the reviews), a fuller description of the systematic reviews is provided in Appendix 2.

Table 2: Summary of key findings from systematic reviews relevant to Element 2 – Make sure the right medicines are accessible and affordable

Category of finding	Summary of key findings
Benefits	<p>Determining how to expand coverage to more Canadians</p> <ul style="list-style-type: none"> • One recent medium-quality review found that expanding prescription-drug insurance can play a crucial role in decreasing the use of other healthcare services, while contributing positively to patients’ health outcomes.(55) <p>Determining which medicines will be covered</p> <ul style="list-style-type: none"> • One older high-quality review found the use of prior-authorization policies reduced older adults’ unnecessary use of gastric-acid suppressants and non-steroid anti-inflammatory drugs, as well as resulted in savings for up to two years.(56) <p>Determining what portion of costs will be covered</p> <ul style="list-style-type: none"> • One recent medium-quality review found that reducing out-of-pocket payments may enhance the health status of patients, with improvement in subjective health ratings, a reduction in cardiovascular events and a decrease in mortality being reported.(57) • One older low-quality review found that the implementation of pricing policies across European countries resulted in appreciable decreases in the price of select generic drugs and enhanced ability to pay for increases in the utilization of proton-pump inhibitors and statins.

	<ul style="list-style-type: none"> ○ However, the review included a broad range of pricing policies reducing the generalizability or conclusiveness of findings.(62)
Potential harms	<p>Determining what portion of costs will be covered</p> <ul style="list-style-type: none"> ● One recent high-quality review found that restrictive caps on medicines and fixed co-payments limited use of medication. <ul style="list-style-type: none"> ○ The same review found that effects of a combined ceiling and co-insurance marginally decreased medicine use and short-term expenditure for insurers, while continuing to increase health-service utilization.(58) ● One recent high-quality review found that while pharmaceutical budget caps or targets may decrease medication costs and prescriptions, they may result in poorer health outcomes.(59) ● One older high-quality review found that prior authorization policies for second generation anti-psychotic drugs resulted in an increase in both treatment discontinuity and usage of other health services.(56) ● One recent medium-quality review found that increasing out-of-pocket payments resulted in increased demand for outpatient and inpatient services, hospitalization, and emergency-room visits.(57) ● One older medium-quality review found increased odds of non-adherence when people were required to co-pay for their medications.(60)
Costs and/or cost-effectiveness in relation to the status quo	<p>Determine what portion of costs will be covered</p> <ul style="list-style-type: none"> ● One older high-quality review found a reduction in the cumulative drug expenditures for insurers on both reference and cost-share drugs in the first year after reference pricing was introduced, however there was significant heterogeneity across the proportion of savings. <ul style="list-style-type: none"> ○ Similarly, the same review found an increase in the use of generic drugs through index pricing and a reduction in the use of brand-named drugs(61)
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<ul style="list-style-type: none"> ● Uncertainty because no studies were identified despite an exhaustive search as part of a systematic review <ul style="list-style-type: none"> ○ No empty reviews were found ● No clear message from studies included in a systematic review <ul style="list-style-type: none"> ○ One recent high-quality review could not determine the effects of restrictive caps on medicine usage or costs.(58) ○ One recent high-quality review found inconclusive evidence on pay-for-performance policies and reimbursement rate policies for prescribers.(59)
Key elements of the policy option if it was tried elsewhere	<ul style="list-style-type: none"> ● No reviews found
Stakeholders' views and experience	<ul style="list-style-type: none"> ● No reviews found

Element 3 – Adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics of a rapid-learning health systems

This element focuses on adopting a rapid-learning approach to build on the existing investments in medicines by connecting existing assets in the system, and to prepare provincial systems for any changes pursued at the federal level. A rapid-learning health system has seven characteristics within which related assets can be developed and subsequently ‘linked up’ to support iterative cycles of learning and improvement. These are:

- 1) engaged patients;
- 2) digital capture, linkage and timely sharing of relevant data (which corresponds to ‘data and analytics’);
- 3) timely production of research evidence (which corresponds to ‘support to grow and share best practices’);
- 4) appropriate decision supports (which corresponds to ‘tools and templates’ and ‘digital health supports’);
- 5) aligned governance, financial and delivery arrangements (which corresponds to ‘incentives’ and ‘legislative, regulatory and policy or other enablers’);
- 6) culture of rapid learning and improvement; and
- 7) competencies for rapid learning and improvement (which corresponds to ‘change-management support’).(63)

With these characteristics in mind, sub-elements could include:

- connect existing assets to leverage existing investments in medicines, including, for example:
 - creating formal links between the Advisory Council on the Implementation of National Pharmacare and CIHR to take advantage of data collected from, for example, the International Pharmacosurveillance Research Network, and
 - using existing tools and decision aids, such as those created by the Canadian Deprescribing Network, Patented Medicines Prices Review Board and CADTH’s Common Drug Review, to support the identification of medicines to include in an essential medicines list/national formulary; and
- establish and foster assets to fill existing gaps across the seven characteristics at both national and provincial levels (notably on those left out of initial recommendations from the Advisory Council), including:
 - engaging patients and citizens in setting and regularly adjusting targets relevant to access to use of medicines (characteristic 1),
 - co-design reforms to existing (or new) programs and services with patients and citizens (characteristic 1),
 - invest in systems to produce, synthesize, curate and share research evidence about the problem, policy options, and implementation considerations (characteristic 3),
 - establish explicit mechanisms within the proposed national drug agency to promote a culture of team work and to collaborate with the full range of partners needed to support rapid learning and improvement (characteristic 6), and
 - establish regular public reporting and foster the necessary competencies to support rapid learning and improvement, such as the physician learning program in Alberta (characteristic 7).

Key findings from the citizen panel

The discussion around element 3 focused on how to support health systems to try new approaches and to make small yet rapid changes to the way in which medicines are prescribed, paid for and provided. There were four main values-related themes that emerged during this discussion:

- 1) continuously improving (quality);
- 2) based on data and evidence (evidence-informed care and policy);
- 3) accountability; and
- 4) stewardship.

The first two values-related themes that emerged were continuously improving (quality) and based on data and evidence (evidence-informed care and policy). Panellists generally agreed that health systems in Canada

should commit to making small and rapid improvements to the way in which medicines are prescribed, paid for and provided. However, they indicated decision-makers should commit to these rapid changes as long as there are standards around the quality of the research evidence to support such changes.

The last two values-related themes focused on accountability and stewardship. The panellists generally agreed about the need for a leadership and governance structure that would ensure the stewardship of these small, yet rapid changes.

Some panellists proposed various arm's-length organizations that could oversee these changes, for instance the 'Director of Change' within each province and territory, who would be accountable to a 'National Director of Change'. They also envisioned a national body that would oversee the costs of medicines and the list of essential medicines publicly covered for all (based on the best available statistical data, research evidence, and best practices around the world). While a leadership body was seen as essential to embrace making these small and rapid changes, a few panellists remain skeptical about the feasibility of such an approach: "We need a clear vision from leadership but there are too many agendas to make it feasible."

Key findings from the literature

We identified two systematic reviews and one series of descriptive case studies that were deemed to be most relevant to adopting a rapid-learning and improvement approach. While they relate broadly to the characteristics of a rapid-learning health system, they do not address its development to support medicines. In addition, the McMaster Health Forum also recently completed two rapid syntheses and a provincial stakeholder dialogue (including the development of an evidence brief), which we used to inform this element.(63-65) The first rapid synthesis and stakeholder dialogue focused on creating a rapid-learning health system in Ontario, and the other rapid synthesis focused on creating rapid-learning health systems in Canada.

The most recent rapid synthesis (from December 2018) was focused on creating rapid-learning health systems in Canada.(65) While the findings are too detailed to report in full here, three high-level points, directly from the report, are worth noting here:

- the list of assets is remarkably rich for the health system as a whole and for the primary-care sector and elderly population specifically, even in small jurisdictions, but there are a number of notable gaps across a number of jurisdictions, such as data about patient experiences often not being linked and shared in a timely way to inform rapid learning and improvement;
- some other sectors (e.g., home and community care) and populations (e.g., Indigenous peoples), many conditions (e.g., mental health and addictions) and some 'treatments' (e.g. surgery) have been or will be the focus of sustained efforts to create rapid-learning health systems in some jurisdictions; and
- some strong connections have been made among assets, although frequently the connections among sets linked to a single characteristic of rapid-learning health systems (not among assets linked to many different characteristics), and rarely were the connections made explicitly to support rapid learning and improvement.

Three findings are notable for achieving greater impact from investments in medicines specifically the rich array of assets available across the country, the cross-cutting nature of medicines to other rapid-learning initiatives (e.g., for problems, in some geographic areas, or in some sectors), and the lack of connections explicitly made among the many different organizations working in the area of medicines.(65) Figure 1 below provides an example of what potential connections could look like at the federal, national or pan-Canadian level.(65)

We also identified two recent low-quality systematic reviews related to rapid learning. The first review examined attempts to adopt the rapid-learning health-system paradigm, with an emphasis on implementation and evaluating the impact on current medical practices.(66) The review identified three main themes to adopting a rapid-learning health system:

- clinical data reuse (i.e., building learning health-systems by extracting knowledge from geographically distributed data collected in daily clinical practice);
- patient-reported outcome measures (i.e. using patient reporting mechanisms for collecting health-related quality indicators); and
- collaborative learning (i.e., using peer specialists for both capturing the indicators of healthcare delivery and encouraging changes through support and pressure).(66)

The second review focused on the ethical issues that can arise in a rapid-learning health system and grouped 67 ethical issues within four phases of rapid learning:

- designing activities: the risk of negative outcomes (e.g., reducing the quality and usability of results) from designing learning activities less rigorously so they are not classified as research, and the risk of inadequate engagement of stakeholders (which can affect the success of the learning activity due to a lack of established trust and support);
- ethical oversight of activities: the conflict between current oversight regulations and a learning health system, which can delay or even prevent learning activities from being conducted due to confusion regarding which learning activities require ethical oversight, and an inconsistent and burdensome oversight process;
- conducting activities: risks of misguided judgments regarding when and how participants should be notified and asked for consent, and the conflict between current data-management practices and regulations and the goals of a learning health system; and
- implementing learning: difficulties with changing practice in a timely manner (e.g., due to conflict with the current research infrastructure or current financial incentives), issue of transparency (e.g., due to underperforming providers or commercial interests), and unintended negative consequences from implementation (e.g., widening health disparities or increasing the risk of liability).(67)

The same review identified the following strategies to address these issues:

- establishing clear and systematic policies and procedures to determine which learning health-system activities require ethical review, how data sharing and data protection should be handled, and how to inform patients in routine and systematic ways about the learning system;
- training and guidance for ethics committee members to learn how to apply ethical principles in the context of learning health-system activities and for researchers to learn about ethics guidelines; and
- simplified ethical review and consent process to make it easier for learning health-system activities to be conducted, including implementing a dedicated ethical-review process and streamlining the consent process.

The descriptive case studies showcased various rapid-learning health systems, including for a health system as a whole, as well as some implemented in specific organizations (e.g., academic health centres) and sectors (e.g., specialty care), and for specific categories of treatment (e.g., surgery and palliative care) and populations (e.g., children and youth). The case studies showed a number of key factors influencing successful implementation of rapid-learning health systems, including:

- meaningful stakeholder engagement, partnership and co-production being key pillars in the development and implementation of rapid-learning health systems;
- robust data infrastructure being a central component (e.g., data needs to be systematically and consistently captured, readily available, and shared);
- leadership-instilled culture of learning;
- strategic and operational assistance required to support the development of core competencies; and
- a clear set of performance and quality measures required to evaluate the development and implementation of rapid learning (including public reporting on performance and quality).(65)

A summary of the key findings from the synthesized research evidence is provided in Table 3. For those who want to know more about the systematic reviews contained in Table 3 (or obtain citations for the reviews), a fuller description of the systematic reviews is provided in Appendix 3.

Figure 1. Potential connections among assets at the federal, national or pan-Canadian level to support rapid learning and improvement in the coverage and use of prescription drugs

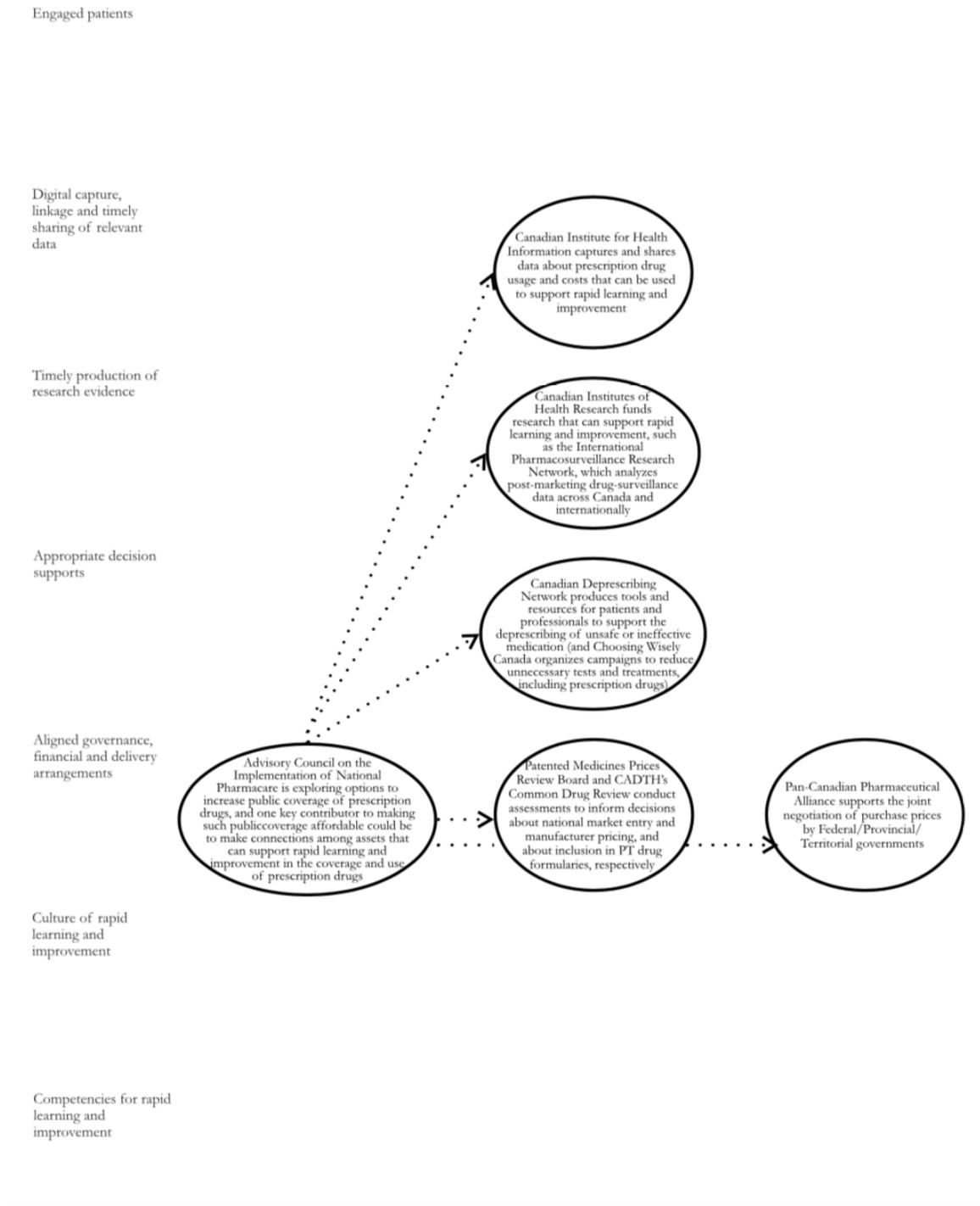


Table 3: Summary of key findings from systematic reviews relevant to Element 3 – Adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics

Category of finding	Summary of key findings
Benefits	<ul style="list-style-type: none"> No evaluations of benefits to a rapid-learning approach were explicitly identified in included systematic reviews
Potential harms	<ul style="list-style-type: none"> One recent low-quality review identified 67 ethical issues that can arise in a rapid-learning health system within the following four phases: 1) risk of negative outcomes as a result of designing activities; 2) ethical oversight of activities can lead to a conflict between current oversight regulations and learning systems; 3) in conducting activities there is the risk of misguided judgments regarding when and how participants should be notified and asked for consent; and 4) implementing learning can create challenges in timeliness, transparency and unintended negative consequences from implementation.(66)
Costs and/or cost-effectiveness in relation to the status quo	<ul style="list-style-type: none"> No cost-related information was identified
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<ul style="list-style-type: none"> No evaluations were identified
Key elements of the policy option if it was tried elsewhere	<ul style="list-style-type: none"> A series of case studies summarized in one of the rapid syntheses documenting the implementation of rapid-learning health systems showed a number of key factors influencing implementation, including: meaningful stakeholder engagement, partnership and co-production; robust data infrastructure; leadership-instilled culture of learning; strategic and operation assistance required to support the development of care competencies; and a clear set of performance and quality measures required to evaluate the development and implementation of rapid learning.(65)
Stakeholders' views and experience	<ul style="list-style-type: none"> One low-quality systematic review examined attempts to adopt the learning health-system approach, with an emphasis on implementation and evaluating the impact on current medical practices, and found minimal focus on evaluating impacts on healthcare delivery.(67)

Additional equity-related observations about the three approach elements

We identified three systematic reviews relating to the first and second elements for the prioritized populations (i.e., individuals not currently covered by the patchwork of public programs or employer insurance; individuals, who despite access to public or private coverage, remain under-insured; and individuals from populations who are at a disproportionately high risk of inappropriately using prescription medicines). Two reviews addressed non-adherence among vulnerable populations. The first review, which was recent and medium quality, found non-adherence rates among Indigenous Australians to be significantly higher than among non-Indigenous Australians.(68) The review found a number of barriers to medication use including: missing cultural competencies; distance to travel; cost; stopping medications when feeling better; medication issues when at home; and cultural or religious beliefs.(68) Facilitators to medication adherence included: dose administration aids; establishing good patient-provider relationships; patient and community education sessions; and family support.(68) A second older medium-quality review found that combined facilitators to medication adherence included: dose administration aids; establishing good patient-provider relationships; patient and community education sessions; and family support. A second older medium-quality review found that combined patient-provider strategies improved adherence to medications among lower socio-economic populations. These included: multidisciplinary disease-management services; patient education; continuing medical education for providers; and telephone follow-up.(69)

Finally, one recent medium-quality systematic review relating to element 2 identified strategies to broaden coverage on health insurance for vulnerable populations including the elderly, low-income individuals, immigrants and children. The review found that providing information, application forms and support to complete these were more likely to register for health insurance. However, this review only included two studies which differ significantly from each other and therefore limit the generalizability of findings, notably because residents of the U.S. (where the two studies took place) must register for health insurance rather than having a universal model in place.(70)

IMPLEMENTATION CONSIDERATIONS

A number of barriers might hinder implementation of the three elements of a potentially comprehensive approach to achieving greater impact from investments in medicine, which needs to be factored into any decision about whether and how to pursue any given element (Table 4). While potential barriers exist at the levels of patients, providers, organizations and systems, perhaps the biggest barriers lie in both the extent to which the proposed elements require coordination and planning across multiple jurisdictions in Canada (and, in the case of element 2, agreement about how to proceed with changing health-system financial arrangements knowing that any approach will create both winners and losers), and in the extent to which ensuring medicines are used appropriately hinges on behaviour changes among both patients and providers. Despite these barriers, Table 5 identifies a number of potential windows of opportunity that could facilitate the implementation of the elements, with the most important being the attention already being given to the issue of prescription medicines in Canada paired with the forthcoming federal election.

Table 4: Potential barriers to implementing the options

Levels	Element 1 – Establish prescriber and patient supports to achieve greater impacts from appropriate medicines	Element 2 – Make sure the right medicines are accessible and affordable	Element 3 – Adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics
Patient/individual	<ul style="list-style-type: none"> • Patients’ preferences for and decisions about the medicines they take (and subsequently whether or not they adhere to prescriptions) may be influenced by sources of information external to the health professionals prescribing medicines to them (e.g., the media or advertising) • Patients who are already at risk for not adhering to their prescriptions may be difficult to engage in ongoing support efforts that are additional components to their regular package of care 	<ul style="list-style-type: none"> • Patients may oppose the introduction of additional targeted programs designed to fill coverage gaps if they are not direct beneficiaries and when there are associated with increases in the amount of tax dollars governments need to allocate to fund these programs • Patients may oppose any changes to the list of publicly covered prescription medicines if it will result in them losing coverage (or having reduced coverage) 	<ul style="list-style-type: none"> • Patient engagement requires significant inputs from patients (e.g., time and other resources), which can be challenging given an individual’s health state
Care provider	<ul style="list-style-type: none"> • Providers may resist efforts that are perceived to be an evaluation of how they practice and/or prescriptive of how they should practice • Providers may not have the time and/or resources to integrate additional patient-engagement efforts into their routine care processes 	<ul style="list-style-type: none"> • Providers may not shift prescribing practices to align with a new list of covered medicines and/or changes to the extent to which certain medicines are covered for patients in ways that will benefit them most 	<ul style="list-style-type: none"> • Professionals who are already overburdened with work may have limited time to engage in rapid learning and improvement
Organization	<ul style="list-style-type: none"> • Organizations may not have the appropriate structures in place to support certain provider-targeted strategies 	<ul style="list-style-type: none"> • Organizations such as hospitals may have long-standing bulk-purchasing agreements in place with 	<ul style="list-style-type: none"> • Organizations could view this element as one that requires substantial investment in terms of

	(e.g., audit and feedback, reminders and prompts) and patient-targeted strategies for which they'd play a significant role (e.g., tailored ongoing support)	pharmaceutical suppliers that could make it difficult to adjust the medicines available and prescribed to patients in these settings in the short and medium term (and subsequently the prescriptions patients expect to take with them when transitioning to a different care setting such as primary care)	infrastructure and analytic capacity
System	<ul style="list-style-type: none"> • Fragmented health systems characterized by sectors that are not fully integrated and that have challenges with ensuring smooth patient transitions across different providers and settings may struggle to ensure their efforts engage all relevant care providers (particularly for patients with multiple conditions and complex needs who engage with many potential prescribers in several settings) • Few systems have a natural focal point that can both lead efforts to ensure appropriate prescribing and adherence, and establish accountability for the appropriate use of prescription medicines 	<ul style="list-style-type: none"> • Decision-making authority over the health-system financial arrangements required to change who is covered, what is covered and what proportion is covered, rests with provincial governments, creating a significant coordination challenge if such changes were to be pursued across Canada • The exclusion of prescription medicines from the list of publicly covered 'medically necessary' services in most jurisdictions in Canada has resulted in the establishment of a strong private insurance market and associated interest groups, which may resist any changes that directly affect their profitability 	<ul style="list-style-type: none"> • Many jurisdictions lack the resources (e.g., technology, infrastructure and personnel) for timely data collection and system monitoring • Information around personal health information may restrict the sharing of information and data collection

Table 5: Potential windows of opportunity for implementing the elements

Type	Element 1 – Establish prescriber and patient supports to achieve greater impacts from appropriate medicines	Element 2 – Make sure the right medicines are accessible and affordable	Element 3 – Adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics
General	<ul style="list-style-type: none"> • Significant political and public attention continues to be placed on the issue of prescription medicines in Canada – and particularly on the issue of national pharmacare with the release of the final report by the Committee on the Implementation of National Pharmacare – creating ongoing opportunities to consider not only how to make the right medicines accessible and affordable, but also about how to ensure they’re used appropriately, and within an orientation that will enable health systems to continually learn and improve how this is approached • The forthcoming federal election in the fall of 2019 will create new opportunities for policymakers and stakeholders to consider how these elements can be integrated into proposed plans for reform 		
Element-specific	<ul style="list-style-type: none"> • Initiatives such as ‘Choosing Wisely’ have gained momentum throughout Canada, providing a framework upon which efforts to improve patient and provider decision-making can be built 	<ul style="list-style-type: none"> • Several existing initiatives – including the CLEANMeds trial and the essential medicines list – are helping to provide valuable insights about the best options for making the right medicines accessible and affordable 	<ul style="list-style-type: none"> • Recent developments have created an opportunity for a dramatic scale-up in rapid learning and improvement: <ul style="list-style-type: none"> ○ Canada-wide moves to this framework in provincial and territorial health systems (and hopefully through whatever pan-Canadian health organizations and national pharmacare plan emerge after the next federal election) ○ provincial, national and international work led by the McMaster Health Forum and its partners to inform this movement towards rapid-learning health (and social) systems (including a Canada-wide rapid synthesis and Ontario-focused rapid synthesis and stakeholder dialogue on the topic, and a 14-country rapid-learning and improvement network)

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APPENDICES

The following tables provide detailed information about the systematic reviews identified for each option. Each row in a table corresponds to a particular systematic review and the reviews are organized by element (first column). The focus of the review is described in the second column. Key findings from the review that relate to the option are listed in the third column, while the fourth column records the last year the literature was searched as part of the review.

The fifth column presents a rating of the overall quality of the review. The quality of each review has been assessed using AMSTAR (A Measurement Tool to Assess Reviews), which rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial, or governance arrangements within health systems. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered “high scores.” A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8.

The last three columns convey information about the utility of the review in terms of local applicability, applicability concerning prioritized groups, and issue applicability. The third-from-last column notes the proportion of studies that were conducted in Canada, while the second-from-last column shows the proportion of studies included in the review that deal explicitly with one of the prioritized groups. The last column indicates the review’s issue applicability in terms of the proportion of studies focused on: individuals who only have catastrophic public drug coverage (e.g., those who are self-employed, those without a pension who have retired early, individuals from particularly vulnerable populations); individuals, who despite access to public or private coverage, remain under-insured (e.g., spend a disproportionate amount of their annual income on medicines); and individuals from populations who are at a disproportionately high risk of inappropriately using prescription medicines (e.g., older adults and those with multiple chronic conditions). Similarly, for each economic evaluation and costing study, the last three columns note whether the country focus is Canada, if it deals explicitly with one of the prioritized groups and if it focuses on achieving greater impact from investments in medicines in Canada.

All of the information provided in the appendices was taken into account by the evidence brief’s authors in compiling Tables 1-3 in the main text of the brief.

Appendix 1: Systematic reviews and economic evaluations relevant to Element 1 – Establish prescriber and patient supports to achieve greater impacts from medicines

Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
Provider-targeted strategies	Examining the effects of audit and feedback on professional practice and healthcare outcomes (24)	<p>A review of 140 papers examined the effects of audit and feedback on professional practice and healthcare outcomes.</p> <p>Audit and feedback involves the measure and comparison of an individual's professional practice or performance against established professional standards. Most studies included in this review measured the effect of audit and feedback on doctors' proper usage of treatments, laboratory tests, or improving the overall management of patients with chronic disease.</p> <p>Results from the study indicated that feedback tends to be more effective when baseline performance is low, when the source is a supervisor or colleague, when it is provided more than once, when it is given in both verbal and written formats, and when it includes both explicit targets and an action plan.</p> <p>Overall, it was found that audit and feedback generally leads to small but potentially important improvements in professional practice. Quantitatively, the median adjusted risk difference of compliance with desired practice was a 4.3% absolute increase in desired practice when considering any trial comparing audit and feedback against no intervention.</p>	2012	8/11 (AMSTAR rating from McMaster Health Forum)	Not reported	0/140	31/140
	Examining whether different factors influence the effectiveness of educational outreach visits (27)	<p>Educational outreach visits allow trained persons to visit clinicians where they practice and offer them information on how to change their practices to improve how they care for their patients. The information offered might include feedback about their performance, or could be based on how to overcome obstacles in changing behaviours.</p> <p>Multifaceted interventions that included educational outreach and distribution of educational materials and/or other intervention compared to a control group, compared to audit and feedback and compared to educational materials, were all found to be generally effective for improving appropriate care.</p>	2007	8/11 (AMSTAR rating from www.rxforchange.ca)	1/69	0/69	17/69

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
		<p>Educational-outreach interventions used alone compared to a control group and compared to educational materials were found to be generally effective.</p> <p>There was insufficient evidence for comparisons of multifaceted versus educational meetings, educational outreach visits versus continuity of care, and multifaceted versus reminders.</p> <p>The authors concluded that educational-outreach visits alone or when combined with other interventions have relatively consistent and small effects on prescribing that are potentially important. The effects on other professional behaviours, however, appeared to be more variable. Additionally, the authors point out that while educational-outreach visits may be costly, the savings may outweigh the costs if the intervention is targeted at inappropriate prescribing and its effects are enduring.</p>					
	Examining effects of on-screen, point-of-care computer reminders on processes and outcomes of care (29)	For supporting better coordination of providers' use of genetic testing and related services, computer reminders in B.C. led to a 4.2% median improvement in process adherence for all outcomes, 3.3% for medication ordering, 3.8% for vaccinations and 3.8% for test ordering. Generally, point-of-care computer reminders achieve small improvements in physician behaviour.	2008	9/11 (AMSTAR rating from McMaster Health Forum)	1/28	0/28	21/28
	Examining patient-mediated interventions to improve professional practice (35)	<p>A review of 25 studies examined patient-mediated interventions to improve professional healthcare practice. Included studies evaluated four types of patient-mediated interventions: patient-reported health-information interventions; patient-information interventions; patient-education interventions; and patient decision aids.</p> <p>While it was found that patient-reported health-information interventions and patient-education interventions probably improve healthcare professionals' adherence to recommended practice, patient-information interventions and patient decision-aid interventions demonstrated little to no effect. For the interventions with positive outcomes, the effect size was considered small or moderate.</p> <p>Strategies involved patient-reported health information saw patients give information about their own health, concerns, or needs to the doctor. This was typically done through a questionnaire filled out by patients</p>	2018	10/11 (AMSTAR rating from McMaster Health Forum)	1/25	0/25	10/25

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
		<p>prior to a consultation, which was given to the doctor at the consultation. Patient-education strategies involved patient participation in programs on topics such as self-management, which aimed to increase their knowledge about their condition.</p>					
	<p>Examining the effect of feedback provision on medication adherence for people with chronic diseases (25)</p>	<p>A review of nine studies examined the effect of feedback provision on medication adherence for people with chronic diseases.</p> <p>Overall, it was found that the provision of physicians with feedback may lead to little or no difference in medication adherence, patient outcomes, or health-resource usage. Doing so may, however, improve processes of care, such as catalyzing more medication changes and more dialogue with patients. None of the studies reported any adverse events due to the feedback intervention.</p> <p>Authors noted that the findings should be interpreted with caution as the certainty of evidence was low for all outcomes. This was mainly due to their high risk of bias, high heterogeneity across studies, and indirectness of evidence.</p>	<p>2016</p>	<p>10/10 (AMSTAR rating from McMaster Health Forum)</p>	<p>1/9</p>	<p>0/9</p>	<p>9/9</p>
	<p>Examining the effects of printed educational materials on professional practice and healthcare outcomes (36)</p>	<p>Printed educational materials are utilized to improve healthcare professionals' knowledge, attitudes, skills and awareness to improve practice and patient outcomes. Common means of presentation include paper formats (e.g., monographs), publications in peer-reviewed journals, and clinical guidelines. The review focused on passive dissemination of printed educational materials, which involves the distribution of published or printed recommendations for clinical care (including monographs, publications in peer-reviewed journals, and clinical practice guidelines) being delivered personally or through mass mailing. Most of the printed educational materials utilized in the studies were endorsed, did not specify an educational component, were printed in black and white with a few tables and figures, and were longer than two pages.</p> <p>The systematic review included 45 studies (31 of which were interrupted time series analyses and 14 were randomized controlled trials), and nearly all included studies (44/45) aimed to compare the effectiveness of printed educational materials to no intervention. When used alone and compared to no intervention, the review found that printed educational materials have a small beneficial effect on professional-practice outcomes. However, the review indicated that there is insufficient</p>	<p>2011</p>	<p>8/11 (AMSTAR rating from www.rxfchange.ca)</p>	<p>12/50</p>	<p>0/50</p>	<p>0/50</p>

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
		<p>information to reliably estimate the effect of printed educational materials on patient outcomes.</p> <p>The authors also aimed to identify the influence of various characteristics of printed educational materials in determining the effectiveness of the intervention. It was noted that effectiveness may vary more according to: 1) source of information; 2) tailoring; 3) purpose; 4) level of evidence; and 5) format. Effectiveness may not vary much based on the frequency, mode or duration of delivery.</p>					
	Examining tailored interventions to address determinants of practice (37)	<p>Tailored interventions to change professional practice are interventions planned following an investigation into the factors that explain current professional practice and any reasons for resisting new practice. These factors are referred to as barriers to change.</p> <p>It was found that the selection of interventions tailored to prospectively identified barriers is more likely to improve professional practice than no intervention or than dissemination of guidelines or educational materials alone. The overall effectiveness of such interventions, as indicated by the meta-regression, is modest. However, there is wide variation in effectiveness between studies and between the targeted behaviours within single studies, from lack of effect to relatively large effect.</p> <p>There is currently insufficient evidence on the most effective approaches to tailoring, including how barriers should be identified and how interventions should be selected to address the barriers. There is also no evidence about the cost-effectiveness of tailored interventions compared to other interventions to change professional practice. As such, authors recommend that it is reasonable to employ low-cost tailored interventions in practice, but that evidence on the cost-effectiveness of the alternative methods of tailoring is needed to justify the use of more costly tailored approaches.</p> <p>In 13 studies, more than one method was used to identify barriers. These methods include interviews with health professionals and occasionally patients (n= 11), focus group interviews (n=10), questionnaire surveys (n=6), review of the literature (n=4), review of performance data (n=2), a meeting or workshop (n=2), and other methods including observation and consultation with an expert group (n=4). Some studies employed a</p>	2014	8/10 (AMSTAR rating from McMaster Health Forum)	0/32	0/32	0/32

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
		<p>variety of methods. The depth of investigation of barriers was categorized as low in six studies, moderate in 13, and high in seven.</p> <p>Studies reported barriers in the following EPOC domains: administrative concerns (n=13), clinical uncertainty (n=9), patient expectations (n=5), information management (n=3), sense of competence (n=2), financial disincentives (n=2), and other (n=15). Barriers in the 'other' category included negative staff attitudes, anxiety about changing practice, a perception that the clinical issue was not a priority, and advocacy of certain drugs by pharmaceutical companies.</p> <p>In terms of the influence of prospective identification of barriers on intervention design, six studies reported drawing on behavioural theory to guide the choice of strategies in response to the identified barriers. The other 20 studies made no reference to any theoretical foundation when developing interventions.</p>					
	Examining the effects of computer-generated reminders on professional healthcare practice and outcomes (30)	<p>A review of 35 studies examined the effects of computer-generated reminders on professional healthcare practice and outcomes.</p> <p>Reminders in half the studies sought to enhance compliance with preventive guidelines while the other half targeted compliance with disease-management guidelines for acute and chronic conditions. In general, reminder systems can help clinicians overcome barriers in knowledge transfer, provide reminders to perform tests or physical exams, or prompt them to prescribe appropriate medications.</p> <p>It was found that computer-generated reminders, when delivered on paper to healthcare professionals, probably improved quality of care slightly compared to usual care (median improvement 11.0%). When reminders were coupled with another co-intervention, care was improved by 4.0% when compared to the co-intervention alone without reminder. These findings were based on moderate-certainty evidence.</p> <p>Due to the uncertainty of the evidence, the authors could not determine whether reminders, alone or coupled with co-interventions, could improve patient outcomes. The heterogeneity of reminder interventions included in this review also suggests that different reminders may serve to improve quality of care in different ways under different conditions.</p>	2016	10/11 (AMSTAR rating from McMaster Health Forum)	3/35	0/35	5/35

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
	Examining interventions to improve the appropriate use of polypharmacy for older people (53)	<p>A review of 32 studies examined interventions to improve the appropriate use of polypharmacy for older adults.</p> <p>Of the included interventions, one consisted of a computerized decision support (CDS) while the other 31 were complex, multifaceted pharmaceutical-care-based approaches. Pharmaceutical care involves promoting the correct use of medicines by identifying, preventing, and resolving medication-related problems. Interventions were carried out by healthcare professionals such as general practitioners, pharmacists and geriatricians in a variety of settings.</p> <p>From the pooled evidence, study authors deemed it uncertain whether pharmaceutical care improves medication appropriateness. It was also uncertain whether pharmaceutical care reduces the number of potentially inappropriate medications and proportion of patients with one or more potentially inappropriate medications. Pharmaceutical care was found to potentially reduce the number of potential prescribing omissions, although this was based on weak evidence. Finally, pharmaceutical care was found to contribute little or no difference in hospital admissions and quality of life.</p> <p>Overall, it remains unclear whether interventions to improve appropriate polypharmacy can result in clinically significant improvements.</p>	2018	10/11 (AMSTAR rating from McMaster Health Forum)	Not reported.	0/32	32/32
	Examining professional, structural, and organizational interventions in primary care for reducing medication errors (38)	<p>A review of 30 studies examined various types of professional, structural, and organizational interventions in primary care for reducing medication errors. Four of the included studies addressed professional interventions while 26 described organizational interventions.</p> <p>Professional interventions involved the use of health information technology to identify individuals at risk of medication problems, computer-generated care as suggested and approved by a physician, electronic notification systems regarding dose changes, drug interventions and follow-up, and educational interventions seeking to help physicians improve drug prescriptions. Organization interventions, on the other hand, involved medication reviews by pharmacists, nurses or physicians, as well as clinician-led clinics and home visits.</p> <p>Reviewers found that professional interventions probably make little or no difference to the number of hospital admissions and mortality in the</p>	2016	10/11 (AMSTAR rating from McMaster Health Forum)	Not reported	0/30	30/30

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
		<p>study population. They also make little or no difference to the number of emergency-department visits.</p> <p>In terms of organizational interventions, it is uncertain whether they reduce the number of hospital admissions, emergency-department visits, or mortality.</p> <p>Overall, the authors determined that interventions in primary care for reducing preventable medication errors probably make little or no difference to the number of people admitted to hospital or the number of hospitalizations, emergency-department visits, or mortality. The results should be interpreted with caution, however, due to the significant variation in heterogeneity of the pooled estimates.</p>					
	Examining the effect of computerized drug-dosage advice on prescribing practice (31)	<p>A review of 23 articles examined the effect of computerized drug-dosage advice on prescribing practice. Interventions usually targeted doctors, although some involved pharmacists and nurses as well. Most of the interventions worked by providing advice about appropriate drug dosages to healthcare professionals who then decided whether to follow them.</p> <p>Overall, computerized advice for drug dosage provided significant benefits in five key areas: 1) increasing the initial dose of medications; 2) increasing serum concentrations; 3) reducing the time to therapeutic stabilization; 4) reducing the risk of toxic drug level; and 5) reducing the length of hospital stay.</p> <p>It must be noted, however, that the computer systems did not increase or decrease how often serious side effects, such as strokes or death, occurred.</p> <p>Findings from this review should be interpreted within the context of its limitations. Notably, the quality of the evidence in the study was generally low, with significant heterogeneity across individual comparisons.</p>	2007	8/10 (AMSTAR rating from McMaster Health Forum)	1/23	0/23	23/23
	Examining interventions designed to optimize prescribing for	<p>A review of 12 articles examined interventions designed to optimize prescribing for older people in care homes.</p> <p>Of the 12 included studies, 10 involved medication review with a pharmacist or doctor, four involved multidisciplinary case-conferencing,</p>	2015	10/10 (AMSTAR rating from McMaster	0/12	0/12	12/12

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	older people in care homes (45)	<p>five involved an educational element for healthcare professionals, and one involved the use of clinical decision-support technology.</p> <p>Overall, it was found that interventions to optimize prescribing may lead to fewer days in hospital (one study out of eight), a slower decline in health-related quality of life (one study out of two), improved medication appropriateness (five studies out of five), and the identification and resolution of medication-related problems (seven studies). The authors were uncertain about whether the intervention reduces medicine costs, the number of adverse drug events, or mortality.</p> <p>The overall quality of the evidence was deemed to be low or very low; results should be interpreted in the context of these limitations.</p>		Health Forum)			
	Examining interventions to improve antibiotic prescribing practices in ambulatory care (26)	<p>A review of 39 studies examined the effect of various interventions seeking to improve antibiotic prescribing practices in ambulatory care. These interventions included printed educational materials for physicians, audit and feedback, educational outreach visits, educational meetings, financial and healthcare system changes, patient-based interventions, physician reminders, and multifaceted interventions.</p> <p>It was found that the use of printed education materials or audit and feedback alone resulted in little to no change in prescribing practices. Interactive educational meetings were found to be more effective than didactic lectures, while educational outreach visits and physician reminders had mixed results.</p> <p>Patient-based interventions involving the delay of prescriptions for infections not immediately indicative for antibiotics reduced antibiotic use by patients and did not result in excess morbidity.</p> <p>Overall, multifaceted interventions involving combinations of physician, patient, and public education were the most successful in reducing antibiotic prescribing for inappropriate indications.</p> <p>The authors note that the effectiveness of an intervention on antibiotic prescribing is strongly dependent on the particular prescribing behaviours and characteristics of a particular community. As such, no single intervention can be recommended for all behaviours in any setting.</p>	2002	6/10 (AMSTAR rating from McMaster Health Forum)	6/39	0/39	39/39

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
	Examining interventions aimed at improving antibiotic prescribing practices for hospital inpatients (26)	<p>A review of 221 studies examined interventions aimed at improving antibiotic prescribing practices for hospital inpatients.</p> <p>Authors found that the included interventions could be categorized broadly into two categories: restrictive techniques (which apply rules to help physicians prescribe properly); and enablement techniques (which provide advice or feedback to help physicians prescribe properly).</p> <p>When interventions were used, the number of hospital inpatients treated according to antibiotic prescribing policy increased from 43% to 58%, and the duration of antibiotic treatment decreased by 1.95 days from 11.0 days. The risk of death was similar between control and intervention groups, suggesting that antibiotic use can likely be reduced without adversely affecting mortality.</p> <p>Overall, it was determined that the assessed interventions lead to prescribing practices that are more in line with antibiotic prescribing policies. Both restriction and enabling techniques were successful in achieving their intended goals.</p>	2015	9/10 (AMSTAR rating from McMaster Health Forum)	Not available	Not available	221/221
	Examining interventions for reducing medication errors in children in hospital (33)	<p>A review of seven studies examined interventions for reducing medication errors in children in hospital.</p> <p>Of the seven included studies, two involved clinical pharmacists, two involved computerized prescribing systems, one involved a barcode medication administration system, one involved the use of a structured prescribing form, and one involved a checklist and feedback system.</p> <p>It was found that the introduction of a clinical pharmacist resulted in a significant decrease in serious medication errors in intensive-care settings, but such results were not replicated on the medical and surgical ward. The use of a computerized prescribing system and check and control checklist similarly did not have conclusive results. The barcode medication administration system and preprinted order sheet resulted in a significant reduction in medication errors, but their effects of harm reduction remain unclear.</p> <p>Overall, the review yielded inconsistent results and none of the studies resulted in a significant reduction in patient harm.</p>	2014	9/10 (AMSTAR rating from McMaster Health Forum)	2/7	0/7	7/7

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from medicines
	Examining interventions to reduce the prescription of inappropriate medicines in older patients (34)	<p>This overview of 24 systematic reviews examined interventions to reduce the prescription of inappropriate medicines in older patients.</p> <p>The interventions were analyzed in five thematic categories: medication review services, pharmaceutical interventions, computerized systems, educational interventions, and others.</p> <p>Medication review included many interventions that could be performed by prescribers or other health professionals. These interventions typically worked by providing prescribers with recommendations to improve the quality of prescription and increase prescription safety. Promising results were found in interventions involving pharmacists, although no positive effect was found for reducing hospital admissions or mortality.</p> <p>Pharmaceutical interventions involved the clinical practice of pharmacists and other members of the healthcare team to solve or prevent problems that interfere or could interfere in their patients' pharmacotherapy. It was found that pharmaceutical interventions seemed to improve prescriptions to older patients taking multiple different medications, although this effect could be even more pronounced if pharmacists are given a more active role in the prescribing process.</p> <p>Computerized systems allow electronic prescription and records about the medications taken by every patient and can provide risk alerts when potential drug interactions are detected. These systems can work at both the physician and pharmacist levels – when prescribing and dispensing drugs. Although positive results were found for this intervention in reducing potentially inappropriate drug prescriptions, computer systems may not capture the full picture of a patient's medication use if they purchase drugs from non-participating pharmacies or take over-the-counter medications.</p> <p>Educational interventions may include educational sessions for health professionals aiming to reduce drug use, educational materials, programs for prescribers or consumers, and patient education interventions. It was found that education interventions may reduce inappropriate drug prescribing and the duration of hospitalization when used alone or combined with other interventions.</p>	2017	(No rating tool available for this type of document)	Not reported	Not reported	24/24

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		<p>Overall, the interventions analyzed showed positive results and most of them helped reduce the number of prescriptions of potentially inappropriate medication to older patients.</p>					
Patient targeted strategies	Examining interventions targeting healthcare providers to improve medication adherence (40)	<p>A review of 218 documents examined interventions targeting healthcare providers to improve medication adherence.</p> <p>In general, authors found that interventions had a greater effect when they were composed of multiple strategies. Even so, the meta-analysis revealed that interventions targeted at healthcare providers generally significantly improved patient medication adherence.</p> <p>The most common diseases among patients in included studies were diabetes, cardiac diseases, hypertension, hyperlipidemia, HIV, renal disease, asthma, lung disease, stroke, and gastrointestinal diseases.</p> <p>Many of the interventions studied were targeted at healthcare providers. For example, a common intervention format involved research staff who trained providers to increase skills to enhance patient adherence. These skills included methods to uncover patients' barriers to adherence, methods to find solutions to barriers, methods to teach patients about adherence, and the availability of standardized adherence treatment checklists.</p> <p>Other interventions sought to integrate care across providers in efforts to improve adherence. Such interventions generally focused on improving practitioners' communication skills for inter-team and practitioner-patient communication.</p> <p>Patient adherence information to providers was used in another subset of studies. These interventions involved medication monitoring systems or practitioners who monitored patients' adherence behaviour.</p>	2015	6/11 (AMSTAR rating from McMaster Health Forum)	Not reported	Not reported	218/218
Patient targeted strategies	Examining interventions for enhancing	<p>A review of 182 studies examined patient-centred interventions for enhancing medication adherence.</p> <p>Overall, there was significant heterogeneity in this review in terms of patients, treatments, intervention types, adherence measurement methodologies, and clinical outcomes. Interventions in the majority of</p>	2013	8/10 (AMSTAR rating from McMaster)	Not reported	Not reported	182/182

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	medication adherence (54)	<p>studies targeted more than one medication. In the 17 studies with lowest risk of bias, interventions were generally complex and multifaceted, and included patient support from family, peers or allied health professionals. Only five of these studies improved both medication adherence and clinical outcomes; no common characteristics could be delineated for their success.</p> <p>Among included studies, even the most effective interventions did not result in large improvements.</p>		Health Forum)			
	Examining reminder packaging for improving adherence to self-administered long-term medications (48)	<p>A review of 12 studies examined reminder packaging for improving adherence to self-administered long-term medications.</p> <p>As an intervention, packaging of medications with reminder systems for the day or time of week is an attempt to help people better adhere to their long-term medication regimens.</p> <p>It was found that reminder packaging increased the pills taken by 11% compared to normal packaging. Similarly, reminder packaging significantly decreased diastolic blood pressure and glycated haemoglobin levels, though no effect was seen in systolic blood pressure. One study showed that the use of a reminder packaging aid was preferred by patients with low literacy levels.</p> <p>Further research is necessary to improve the design and targeting of these devices.</p>	2011	9/11 (AMSTAR rating from McMaster Health Forum)	0/12	1/12	12/12
	Examining medication-adherence interventions (49)	<p>A review of 63 articles examined various pathways to improve medication adherence across clinical conditions. Included interventions ranged from relatively low-cost, low-intensity telephone and mail interventions to relatively intense interventions like care coordination, case management, and collaborative care.</p> <p>Of the reviewed evidence, the most consistent result was that various types of interventions improved medication-adherence outcomes for hypertension, heart failure, depression, and asthma through reductions in systolic and diastolic blood pressure, reductions in emergency-department visits, improved symptoms, better quality of life, improved pulmonary function, and improved healthcare utilization. These interventions generally involved case management, face-to-face</p>	2011	7/10 (AMSTAR rating from McMaster Health Forum)	Not reported	Not reported	63/63

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		<p>education with pharmacists, and pharmacist-led multicomponent interventions.</p> <p>Despite the promise exhibited by many of these approaches, only a subset were found to be effective in increasing adherence and better health outcomes. Relatively little evidence linked improved adherence to improvements in other outcomes like biomarkers, mortality, morbidity, quality of life, patient satisfaction, healthcare utilization, and costs.</p>					
	<p>Quantifying the risk of non-adherence to prescribed medicines in publicly insured populations exposed to co-payments (60)</p>	<p>The aim of this review was to quantify the risk of non-adherence to prescribed medicines in publicly insured populations exposed to co-payments.</p> <p>This review included seven studies. Of the included studies, four studies were cohort designs and three studies were controlled before and after studies. Four of the included studies focused on Medicare insurance plans and three of the studies focussed on co-payment increases in Veteran Affairs.</p> <p>Six studies were included in a meta-analysis to assess the effect of people exposed to co-payments compared to people not exposed to co-payments. The results of the analysis found that there were increased odds of non-adherence when people were required to co-pay for their medications.</p> <p>This review is limited by the heterogeneity in the research methodologies used within the included studies and the variations in follow-up times. Moreover, it was suggested that the presence of publication bias within the review may also limit the findings of the review.</p> <p>Overall, this review found increased odds of non-adherence to medications among people exposed to co-payments.</p>	<p>2012</p>	<p>9/11 (AMSTAR rating from McMaster Health Forum)</p>	<p>Not reported</p>	<p>7/7</p>	<p>7/7</p>
	<p>Examining the impact of calendar blister packaging and pill organizers for long-term</p>	<p>Patient forgetfulness is a common factor associated with medication non-adherence. The aim of this review was to examine the impact of calendar blister packaging and pill organizers for long-term medication use.</p> <p>This review included 10 studies which examined the benefits and harms of calendar blister packaging and calendar pill organizers for self-administrated, long-term medication use. Three of the included studies</p>	<p>2010</p>	<p>8/10 (AMSTAR rating from McMaster Health Forum)</p>	<p>Not reported</p>	<p>0/10</p>	<p>10/10</p>

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	medication use (41)	<p>examined calendar blister packaging and seven of the included studies examined calendar pill organizers. The studies included patients who were taking medications for hypertension, Type 2 diabetes, epilepsy or serious mental illness.</p> <p>Eight of the studies used pill counts and prescription refill rates to measure adherence. The remaining two studies assessed medication adherence by measuring blood concentrations of the medications in patients supposed to be taking them. Two of the included studies did not have sufficient adherence-outcome data. Thus, out of the eight evaluable studies, it was found that six studies reported an increase in medication adherence.</p> <p>Nine of the studies assessed clinical outcomes. Of these nine studies, only one reported an improvement in a clinically important treatment outcome that was associated with an improvement in medication adherence.</p> <p>This review is limited by the low methodological quality of the available evidence, and the high risk of bias that was present in the included studies. Moreover, the adherence outcomes present within the included studies were heterogeneous.</p> <p>Overall, this review demonstrated that calendar blister packaging and pill organizers may provide improvements in medication adherence. Future research should be directed towards conducting trials of higher methodological quality to confirm the effectiveness of the interventions.</p>					
	Assessing the effects of eHealth interventions on medication adherence (43)	<p>Non-adherence to medications poses a significant health risk, and electronic health interventions may offer a solution to this problem. The aim of this review was to assess the effects of such interventions on medication adherence.</p> <p>This review included 13 studies, which included web-based monitoring systems, customized educational and monitoring websites, web-based disease specific management programs, telemedicine, internet-based self-management programs and online discussion groups.</p> <p>This review highlighted that significant variations exist within the available electronic health interventions. Despite the differences, this</p>	Not reported	6/10 (AMSTAR rating from McMaster Health Forum)	0/13	0/13	13/13

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		<p>review found that five studies had a significant effect on adherence. A moderate effect on adherence was found in six studies and no significant results on medication adherence were found in the remaining two studies.</p> <p>The included studies used self-reporting measurements, pill counts and prescription refills to measure adherence. Seven studies measured long-term adherence, using an interval of six months or longer. There was no evidence found to suggest that the duration of the intervention was related to the effectiveness of the intervention.</p> <p>This review demonstrates that electronic health interventions can be effective in improving medication adherence. However, the results of this review should be used cautiously due to the self-reported scales used to measure adherence.</p>					
	Examining the effect of drug reminder packaging on medication adherence (42)	<p>Non-adherence to medications impairs clinical and economic outcomes for patients and the healthcare system. This review aimed to examine the effect of drug reminder packaging on medication adherence.</p> <p>This review included 30 studies, including 10 randomized controlled trials, 19 controlled clinical trials and one cohort study. The medical conditions treated in the studies were hypertension, diabetes mellitus Type 2, geriatric conditions, helicobacter pylori infection, HIV, vitamin supplementation, chronic mental illness, hypercholesterolemia, epilepsy, pain relief, anticoagulation and chlamydia infection.</p> <p>Within the included studies, there was considerable variation between the definitions and measures of adherence. The most common method of measuring adherence was pill count and self-report. Other measures of adherence included refill data, therapeutic drug monitoring, appointment keeping and clinical measures.</p> <p>Twelve studies found that there were significant improvements in medication adherence in patients who received drug reminder packaging as part of a multifaceted adherence strategy. Improvements were also found when drug reminder packaging was a single intervention, but the improvements were less significant.</p>	2013	6/10 (AMSTAR rating from McMaster Health Forum)	0/30	2/30	30/30

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		<p>This review was limited by language restriction in the search process, which may have led to the exclusion of relevant articles. This review is also limited by the low methodological quality of the included studies.</p> <p>Overall, this review found a positive effect of drug reminder packaging on medication adherence. However, future research should include studies of higher methodology quality to further support the findings.</p>					
	Examining patient-centred medication-management interventions (39)	<p>Patient-centred approaches may be an effective way to improve medication adherence. The aim of this review was to examine patient-centred medication-management approaches.</p> <p>This review included 60 studies which included interventions to improve medication management through four patient-centred domains: shared decision-making, methods to enhance effective prescribing, systems for eliciting and acting on patient feedback about medication use and treatment goals.</p> <p>Twenty-six studies included educational interventions delivered with or without additional behavioural or social support, which included counselling, health coaching, motivational interviewing, patient self-monitoring or e-health. Eleven studies included augmented pharmacy services. Eight studies included decision aids or shared decision-making. Seven studies included case management. Five studies included feedback of adherence or clinical values to health professionals monitoring medication behaviours.</p> <p>Educational interventions were commonly delivered by multidisciplinary teams, were repetitive and occurred over varied periods of time which made making comparisons across studies difficult. Sixteen of the studies examined the effect of the intervention on medication adherence and typically, patients receiving the intervention had higher adherence rates than patients receiving usual care.</p> <p>Augmented pharmacy-service interventions were found to be used in settings with medically complex patients with multiple comorbid conditions. The effectiveness of these interventions was found to be mixed; however positive changes were observed more often than negative or non-significant changes.</p>	2013	5/10 (AMSTAR rating from the Program in Policy Decision-making)	2/60	Not reported	60/60

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		<p>Decision aids and shared decision-making interventions were initiated at the time of medication prescribing. These interventions were not found to result in improvements in adherence or other outcomes.</p> <p>Case-management interventions were commonly delivered by nurses and care teams. All of the case-management intervention studies that measured adherence found significant improvements in adherence to medications.</p> <p>The feedback interventions aimed to promote changes in patients' medication regimes. These interventions were provided through the use of health information technology, direct patient report or medical record review. One of the five studies that used feedback interventions showed improved medication adherence.</p> <p>This review is limited by the heterogeneity in the included populations, clinical settings, study methodology and measurement tools. This heterogeneity prohibited the use of a meta-analysis.</p> <p>Due to the limited and heterogeneous available evidence on patient-centred medication-management interventions, it is not clear what effect that patient-centred medication-management interventions have over traditional medication-adherence interventions. Thus, additional research is needed to further investigate patient-centred medication-management interventions.</p>					
	Assessing the effectiveness of text messaging on medication adherence (44)	<p>Mobile telephone text messaging may provide a solution to medication non-adherence. The review aimed to assess the effectiveness of text messaging on medication adherence.</p> <p>This review included eight randomized controlled trials that tested the effectiveness of text messaging on medication adherence. The eight trials were divided into two groups: trials that used one-way text messaging versus no text messaging, and trials that used two-way text messaging versus no text messaging.</p> <p>Five of the studies included patients with human immunodeficiency infection, two studies involved patients receiving blood pressure or lipid-lowering treatment, and one study included individuals receiving malaria prophylaxis. Adherence was measured using the 'Medication Event</p>	Not reported	5/10 (AMSTAR rating from the Program in Policy Decision-making)	Not reported	5/10	10/10

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		<p>Monitoring System' in two of the one-way text messaging studies, self-reporting in two studies and pill counts in one study. Self-reporting was used in all of the two-way text-messaging trials.</p> <p>The results of the meta-analysis found that one-way text messaging had little to no effect on medication adherence. However, the results found that two-way text messaging has a significant effect on medication adherence.</p> <p>Adherence was measured by self-reporting in a majority of the trials, which relies on recall of doses by the individuals and is prone to error. This error in reporting may limit the findings of the included studies, and the overall accuracy of the review.</p> <p>Overall, two-way text messaging may be a useful method for improving adherence to medications and one-way text messaging has little to no effect on improving adherence to medications.</p>					
	<p>Examining the use of financial reinforcers for enhancing adherence to medications (50)</p>	<p>Financial-reinforcement interventions are being used more frequently in healthcare settings to improve medication adherence. The aim of this review is to examine the use of financial reinforcers for enhancing adherence to medications.</p> <p>This review included 21 studies of which 15 were randomized controlled trials and six were non-randomized studies. Eight studies involved individuals with tuberculosis, five studies involved individuals with drug abuse, three studies included individuals with HIV, two studies included individuals with hepatitis, two studies included individuals with psychosis and one study included individuals at risk for incurring a stroke.</p> <p>The financial-reinforcement interventions were found to significantly improve adherence relative to control conditions in both the randomized and non-randomized studies. Moreover, it was found that interventions that were longer in duration and reinforced patients at least once a week resulted in more significant improvements in adherence.</p> <p>A limitation to this study is that the outcomes were not consistently defined among the included studies, which introduces heterogeneity into the analysis and the outcomes of this review.</p>	<p>2011</p>	<p>5/11 (AMSTAR rating from McMaster Health Forum)</p>	<p>Not reported</p>	<p>16/21</p>	<p>21/21</p>

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		Overall, this review demonstrates that the provision of financial reinforcers has the potential to improve adherence to medications.					
Other health-system arrangements that can help providers and patients with appropriate use	Assessing the effects of planning the discharge of patients moving from the hospital to home (52)	<p>Discharge planning is a common healthcare practice used to try to reduce the length of first-time hospitalizations, readmissions, and to improve the co-ordination of healthcare services after hospital discharge. The aim of this review was to assess the effectiveness of planning the discharge of individual patients moving from the hospital to home.</p> <p>This review included 30 randomized controlled trials. Twenty-one of the studies included older patients with a medical condition, five studies included patients with both medical and surgical conditions, one study included psychiatric patients, one study included both general medicine and psychiatric patients, and two studies included patients who had experienced a fall.</p> <p>Three of the included studies evaluated the effectiveness of a discharge plan on medication use. One study reported data on adherence to medications, knowledge about medications and patterns of hoarding of medications. One study reported data on medication errors and found that the intervention resulted in a reduction of medication errors. One study assessed clinically important medication errors and found no difference between the intervention and control groups. Due to the heterogeneity in reported outcomes and small number of studies, the results could not be pooled in a meta-analysis.</p> <p>Overall, further research is needed to assess the effect of planning the discharge of patients from the hospital to home on medication use and subsequent outcomes.</p>	2015	10/11 (AMSTAR rating from McMaster Health Forum)	3/30	0/30	30/30
	Examining the effect of medication review on health outcomes of hospitalized patients (46)	<p>Medication review is a strategy that has been implemented to improve prescribing and to prevent adverse drug events. This review examined whether the delivery of medication review by a physician, pharmacist or other healthcare professional leads to improvement in health outcomes of hospitalized patients.</p> <p>This review included 10 randomized controlled trials. The medication review was conducted by a pharmacist in four of the studies, by a team of pharmacists and pharmacy technicians in one study, a physician in two studies, by a clinical pharmacologist in one study, and by a team of both pharmacists and physicians specialized in clinical pharmacology in two</p>	2015	11/11 (AMSTAR rating from McMaster Health Forum)	0/10	0/10	10/10

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		<p>studies. The medication review was completed using the validated 'Screening Tool of Older Persons Potentially Inappropriate Prescriptions' in two studies, by a computer decision-support system in one study, and manually by the healthcare professionals in the remaining seven studies.</p> <p>No evidence was found to suggest that medication review reduces mortality or hospital admissions. However, evidence was found to suggest that medication review may reduce the number of emergency-department visits. The specific type of medication review was not found to influence the findings.</p> <p>Limitations to this review include the low methodological quality of the included studies.</p> <p>Overall, it was found that medication review may reduce the number of emergency-department visits, but further research of higher quality is needed to support the findings.</p>					
	<p>Assessing the effect of medication reconciliation on improving transitions of care (47)</p>	<p>Medication discrepancies that occur during transitions of care have been linked with several adverse events. This review assessed the effect of medication reconciliation on medication discrepancies, patient-related outcomes and healthcare utilization during care transitions.</p> <p>This review included 25 randomized controlled trials. Twenty-three studies were pharmacist-mediated, one study involved an electronic reconciliation tool and one study involved medical record changes.</p> <p>Twenty studies were pooled in a meta-analysis to assess the effect of medication reconciliation on the presence of at least one medication discrepancy or the absence of medication discrepancies. It was found that medication reconciliation reduced the presence of medication discrepancies, however there was a high degree of heterogeneity within the medication reconciliation interventions. As a result of the heterogeneity, this result should be interpreted with caution. Furthermore, there were no significant differences found with healthcare utilization, medication adherence, unplanned readmission rates and adverse effects of medications.</p>	2018	11/11 (AMSTAR rating from McMaster Health Forum)	4/25	0/25	25/25

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		Overall, the quality of the included randomized controlled trials was poor, and the results should be interpreted cautiously. Further research should be conducted with improved study design and rigour.					
	Examining the effect of outpatient pharmacists' non-dispensing roles on patient and health professional outcomes (28)	<p>The role of pharmacists has changed over time and has moved away from solely dispensing medications, to collaborating with other healthcare professionals and the community. This review examined the effect of outpatient pharmacists' non-dispensing roles on patient and health professional outcomes.</p> <p>This review included 43 studies, of which 36 were pharmacist interventions targeting patients and seven were pharmacist interventions targeting health professionals.</p> <p>Five studies targeted patients' reported process-of-care outcomes, and these studies quantified the effect of pharmacist interventions on prescribing. Within these studies, one study showed improvement in eliminating therapeutic duplication, three studies found that there was a decrease in the total amount of medications prescribed, and one study showed an improvement in testing and prescribing for patients with hyperlipidemia. Moreover, 29 studies reported clinical and patient outcomes. Improvement was found in nearly all of the clinical outcomes, however these improvements were not all statistically significant.</p> <p>Seven studies targeted health professionals and measured the change in prescribing of specific medications for specific disease states. Educational outreach visits by a pharmacist to promote guideline-based prescribing was found to improve prescribing for four disease states. One study showed that pharmacist-provided academic detailing increased the number of lipid-treatment prescriptions in females who required cholesterol treatment.</p> <p>This review was limited by the heterogeneity in the comparison groups, clinical conditions, outcome variables and type of intervention which prohibited a meta-analysis.</p> <p>Overall, pharmacist interventions were found to be beneficial in improving both patient and health professional outcomes.</p>	2007	11/11 (AMSTAR rating from McMaster Health Forum)	2/43	0/43	43/43
	Assessing the effects of non-	In order to address and manage the demand on healthcare services, non-medical prescribing by nurses, pharmacists, allied health professionals,	2016	11/11 (AMSTAR	6/46	4/46	46/46

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	<p>medicinal prescribing for managing acute and chronic health conditions in primary- and secondary-care settings (51)</p>	<p>and physician assistants may be an approach to improve access to medicines.</p> <p>This review included forty-six studies which examined non-medical prescribing. Within the included studies, prescribing was conducted by nurses in 26 studies and by pharmacists in 20 studies. No studies were found with non-medical prescribing among other health professionals.</p> <p>Four of the included studies were undertaken in low- and middle-income countries and the remainder of the studies were undertaken in high-income countries. Forty-two studies were conducted in ambulatory-care settings, two studies were conducted in secondary-care settings, one study was conducted in the workplace and one study was conducted in an aged-care setting.</p> <p>The findings of this review suggest that non-medical prescribing can deliver comparable outcomes to standard medical prescribing. However, these results should be interpreted with caution as there were a limited number of well-designed randomized controlled trials included in the meta-analyses of the results. Clinical outcomes were found to have equivalent or beneficial results compared to standard care. There was no significant difference in adherence outcomes between non-medical prescribing and standard medical prescribing. Most of the studies reported more prescribed drugs, and a greater variety of prescribed drugs among non-medical prescribers.</p> <p>It is possible that differing terminologies for non-medical prescribing may have limited the number of studies found for this review. Moreover, heterogeneity in the included studies prohibited a quantitative synthesis of all of the outcomes.</p>		<p>rating from McMaster Health Forum)</p>			
Equity section	<p>Examining the medication adherence rates of Indigenous Australians (68)</p>	<p>There is a significant difference in life expectancy between Indigenous and non-Indigenous Australians. It has been suggested that this is as a result of the low medication adherence rates of Indigenous Americans. However, there has been no comprehensive investigations undertaken to support this theory.</p> <p>This review included 47 studies which examined the adherence rates of Indigenous Australians. These studies reported on adherence rates,</p>	2015	<p>9/10 (AMSTAR rating from McMaster Health Forum)</p>	0/47	47/47	47/47

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		<p>outcomes of adherence, barriers and enablers to adherence, and suggested strategies to improve adherence.</p> <p>Six articles quantified the adherence rates of Indigenous Australians and found that two thirds of Indigenous Australians took their medications at least some of the time. Self-reported data within these included studies found that Indigenous Australians were less-adherent than non-Indigenous Australians. Three studies examined associations between adherence and clinical outcomes and suggested that poor clinical outcomes were a result of inadequate medication adherence.</p> <p>Barriers of medication adherence that were reported by both patients and health professionals included having other socio-cultural obligations, having to travel far from their community, cost, stopping medications when feeling better, experiencing medication issues when at home, and cultural and religious beliefs. Enablers of medication adherence that were reported by both patients and health professionals included dose administration aids, establishing good patient-provider relationships, patient and community education sessions, and family support.</p> <p>Health professionals suggested that culturally appropriate resources that were designed to enhance patient education about health and medications would improve adherence. Health professionals also emphasized the need to address the social determinants of health that have an impact on the Indigenous population. Patients suggested that support groups would help improve adherence.</p>					
	<p>Assessing the effects of strategies to improve adherence to medications for the prevention of cardiovascular diseases in disadvantaged groups (69)</p>	<p>Medication non-adherence is a growing problem in socio-economically disadvantaged groups, and this issue makes it increasingly difficult to reduce the global burden of cardiovascular diseases. This review aimed to determine the effects of strategies to improve medication adherence to cardiovascular disease-related medications in socio-economically disadvantaged groups.</p> <p>This review identified 14 randomized controlled trials which tested strategies to increase cardiovascular disease medication adherence in patients who may experience health inequity. In this review, inequity was defined by place of residence, occupation, education or socio-economic position. Five studies included patient-directed strategies, two studies</p>	<p>2012</p>	<p>7/10 (AMSTAR rating from McMaster Health Forum)</p>	<p>0/14</p>	<p>14/14</p>	<p>14/14</p>

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		<p>included physician-directed strategies, and seven studies included both patient- and physician-directed strategies.</p> <p>The strategies directed towards patients included education sessions, persuasion through goal-setting, the use of behavioural contracts, blood pressure monitoring reports, and behaviour modelling through a computer interface. The strategies directed towards the providers included training sessions, accreditation, point-of-care testing and regulated quality-assurance programs. The strategies directed towards patient and physicians included multidisciplinary disease-management services, patient education alongside treatment algorithm, continuing medical education and telephone follow-up.</p> <p>Effect estimates were calculated in 10 of the included studies and in five of these studies there was significantly improved medication adherence. Four of the studies involved patient- and physician-directed strategies, and one of the studies involved patient-directed strategies. These studies resulted in significant improvements in relative adherence from by 16%, to 169%.</p> <p>This review is limited by the English language restriction that was incorporated into the review’s search strategy, the potential for outcome-reporting bias, and the inability to obtain data from four of the included studies.</p>					

Appendix 2: Systematic reviews and economic evaluations relevant to Element 2 – Make sure the right medicines are accessible

Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from investments in medicine
Make sure the right medicines are accessible	Exploring the resultant effects of implementing cap and co-payment policies on the rational use of medicines, healthcare utilization, health outcomes, and costs (58)	<p>This is an update to a review first published in 2008. It is comprised of 32 articles that aim to assess the effects of implementing cap and co-payment policies. Only studies that focused on at least one of the following outcomes were included in the review: medicine use; healthcare utilization; health outcomes; and costs.</p> <p>Of the 32 included articles, five examined the effects of enforcing a cap policy. Across the studies, it was found that the addition of restrictive caps may limit both medicine usage and insurers' expenditure, but the outcome on health service utilization remained inconclusive.</p> <p>Six articles focused on the intervention of a combination of cap, co-insurance, and ceiling policies. The findings of these studies suggested the possibility of an increase in medicine use, while lowering the cost for both insurers and patients.</p> <p>Six articles evaluated the consequences of a fixed co-payment policy. It was reported that this intervention may decrease both the use of medications and its costs for insurers.</p> <p>The two articles that dealt with implementing tiered fixed co-payments both had limited evidence to accurately conclude on any effects of medicine use and cost.</p> <p>Ten articles assessed the effects of a ceiling with fixed co-payment. These studies reinforced the idea that implementing this policy would have an insignificant impact on patients' medicine use and a very minor impact on health-service utilization.</p> <p>Ten articles investigated the effects of adding both a ceiling and co-insurance. It was revealed that this could marginally decrease patients' medicine use and short-term expenditure for insurers, while continuing to increase health-service utilization.</p>	2013	9/9 (AMSTAR rating from McMaster Health Forum)	9/32	0/32	32/32

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from investments in medicine
		The authors recognized limitations with their evidence base. Primarily, the lack of studies and insignificant role that low- and middle-income countries played in contributing towards the data set.					
	Assessing the impacts of pharmaceutical pricing and purchasing policies on health outcomes, healthcare utilization, drug expenditures, and drug use (61)	<p>This is an update to a previously published review. It includes 18 studies that investigate the effects of implementing pharmaceutical pricing and purchasing policies on key determinants, such as health outcomes, healthcare utilization, drug expenditures and drug use.</p> <p>Of the 18 included studies, the vast majority examined reference pricing. Two of the studies noted a relative decrease of 18% and four studies reported a decrease of 10% in cumulative drug expenditures for insurers on both reference and cost-share drugs one year beyond the transition period. In contrast, reports of a median relative change of 15% were found in the prescriptions of reference drugs across another four studies.</p> <p>The results of one study examining index pricing showed an increase of 55% in the use of generic drugs, while during the same time period there was a 43% decrease in the use of brand-named drugs.</p> <p>Although the quality of the evidence base was reportedly low, the authors found that after implementing reference pricing for up to two years, it may: increase the prescriptions of ‘reference medicine’; decrease the prescriptions of cost-share drugs; and decrease the overall spending of insurers. Similarly, the authors’ findings on index pricing suggest that this policy can lead to the more widespread use of lower-cost generic drugs as it would help to move away from brand-named drugs.</p> <p>As a result of the variation between the policies, there was significant heterogeneity in the overall savings from these implementations.</p> <p>Despite the conclusions that emerged, the authors do recognize the importance of finding studies in grey literature for future updates on this topic.</p>	2005	9/10 (AMSTAR rating from McMaster Health Forum)	8/18	0/18	18/18
	Investigating the impact of implementing policies that use financial incentives on drug use,	This is an update to the original review that was first published in 2007. It seeks to determine the impact of implementing financial policies that affect prescribers’ practices on drug use, healthcare utilization, health outcomes and costs.	2015	8/10 (AMSTAR rating from McMaster)	0/18	0/18	18/18

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from investments in medicine
	healthcare utilization, health outcomes and costs (59)	<p>This review consisted of 18 studies from six high-income countries, with significant heterogeneity between the types of policies and interventions being implemented in the various locations.</p> <p>The review discussed key interventions, including: pharmaceutical budget caps or targets; pay-for-performance policies; and reimbursement-rate policies.</p> <p>The authors of this review suggest that applying budget caps or targets can lead to an adequate decrease in each patients' overall drug use, while the effects of the latter two interventions remain inconclusive due to the evidence base being very low.</p> <p>Overall, the findings would imply that implementing financial incentive policies may lead towards a decrease in both medication costs and prescriptions, with poorer health outcomes being the only major consequence as a result of these new policies.</p> <p>A few limitations in the data set were reported, such as a lack of studies originating from lower-income countries, and the absence of government reports. Thus, more advanced considerations should be taken for future updates.</p>		Health Forum)			
	Analyzing the effects of policies that restrict the reimbursement of targeted medications on health outcomes, healthcare utilization, costs and drug use (56)	<p>This review examined 29 studies in order to assess the effects of implementing a policy that would restrict the reimbursements of 11 selected drug classes.</p> <p>Of the 11 that were targeted, studies pertaining to the anti-inflammatory and gastrointestinal classes were the most frequently analyzed. There was significant heterogeneity in the effects of these policies among the different drug classes.</p> <p>Among the six studies that investigated the addition of this policy on gastric-acid suppressant and non-steroidal anti-inflammatory drugs, two prominent trends were observed: a reduction in drug use; and increased savings for up to two years.</p>	2009	10/11 (AMSTAR rating from McMaster Health Forum)	11/29	0/29	29/29

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		<p>The implementation of this policy on second-generation anti-psychotic drugs resulted in an increase in both treatment discontinuity and the usage of other health services. Moreover, removing the restriction on reimbursements for anti-hypertensives and statins are reported to lower overall drug costs while increasing the rational use of these drugs.</p> <p>The findings of this review would suggest the implementation of this policy when low-cost alternative medications are available.</p>					
	<p>Exploring the relationship between drug cost-sharing and healthcare-services utilization, healthcare costs, and health outcomes (57)</p>	<p>The review examined a total of 18 articles in order to investigate the relationship between drug cost-sharing and healthcare-services utilization, healthcare costs, and health outcomes. Specifically, it aimed to assess the impact of varying the amount spent on pharmaceuticals on one's health and use of healthcare services.</p> <p>Eleven studies analyzed drug cost-sharing and healthcare utilization, while 10 studies evaluated drug co-payments and healthcare costs, and another seven pertained to drug cost-sharing and health outcomes.</p> <p>Based on the findings from the review, three key takeaways can be noted. The first is the impact of out-of-pocket payments on healthcare utilization. Among the 11 articles studied, nine had statistically significant reports, whereby changing cost-sharing policies (increasing OOPs) had considerable effects on increasing demand for outpatient and inpatient services, hospitalization and emergency-room visits. The second takeaway is the inverse relationship between OOP payments and healthcare costs, with seven of the existing 10 studies providing statistically significant data. The final takeaway is a result of five statistically significant studies which demonstrated that a decrease in OOPs may enhance the health status of patients – with subjective health, cardiovascular events and mortality being the most selected for health outcomes.</p> <p>Overall, the reviewers acknowledge that while they had several findings, a few limitations in the review should be considered, including the large number of retrospective studies included, and the lack of studies included from grey literature.</p>	2016	7/10 (AMSTAR rating from McMaster Health Forum)	2/18	0/18	18/18

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Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from investments in medicine
	Evaluating measures that European countries can implement to help decrease the prices for generic drugs (62)	<p>The focus of this review revolved around two main themes: the first aimed to target measures that can be implemented by European countries in order to decrease reimbursed prices for generic drugs; the second was determining ways to maximize savings when dealing with problems that may arise with generics.</p> <p>There is strong evidence to suggest that the implementation of pricing policies on generics in European countries have reduced the costs for omeprazole and simvastatin. Moreover, the findings of this review note that some countries, including France, Sweden, and the United Kingdom, have reported savings with the widespread distribution of these cost-effective drugs. Thus, the authors propose the endorsement of various initiatives that seek to increase the availability of generics in the future.</p>	10	2/9 (AMSTAR rating from McMaster Health Forum)	0/29	0/29	29/29
	Determining the correlation between prescription drug coverage and health outcomes (55)	<p>This systematic review included 23 studies with the aim of finding a relationship between prescription drug coverage and health outcomes. In the 23 studies, three prominent relationships were analyzed: the health status of patients with and without drug insurance; expanding drug coverage on health outcomes; and the adverse effects of implementing insurance restrictions on patients' health outcomes.</p> <p>The findings of this review suggest that expanding prescription drug insurance can play a crucial role in decreasing the use of other healthcare services, while still contributing positively to patients' health outcomes. The authors of the review suggest adopting the Affordable Care Act expansions in order to improve the health status for those low-income families using state-based health insurance.</p>	2014	6/10 (AMSTAR rating from McMaster Health Forum)	0/23	0/23	23/23
	Determining the effectiveness of strategies that can provide vulnerable populations access to health insurance coverage (70)	<p>This review identified two studies that primarily focused on assessing the effectiveness of strategies that broaden coverage on health insurance for children living in the U.S. Specifically, these strategies were narrowed down to increasing the enrolment of vulnerable populations in these programs, with 'vulnerable populations' referring to individuals, including but not limited to, the elderly, low-income individuals, immigrants and children.</p> <p>The first study consisted of a case manager providing assistance and information on health insurance to minority groups. The second study was</p>	2012	Not reported	0/2	0/2	2/2

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		<p>concerned with distributing health insurance application forms in hospitals.</p> <p>The findings from both the studies suggest that those who received information, applications forms and support are more likely to register their children for health insurance programs. Moreover, the results from the first study further indicate that those who received insurance information and support may also be more content with the application process, receive insurance approval in a timelier manner, and be more likely to ensure their children remain insured.</p> <p>Despite the few conclusions that did arise, the authors acknowledge the uncertainty of translating this data to different settings and population groups.</p>					

Appendix 3: Systematic reviews and economic evaluations relevant to Element 3 – Adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics

Element	Focus of systematic review or economic evaluation	Key findings	Year of last search	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada	Proportion of studies that deal explicitly with one of the prioritized groups	Proportion of studies that focused on achieving greater impacts from investments in medicines
Adopt a rapid-learning orientation focused on connecting existing assets and filling gaps across the seven characteristics	Examining attempts to adopt the Learning Health System paradigm, with an emphasis on implementations and evaluating the impact on current medical practices (66)	<p>The review examined a total of 32 documents (a range of reports, scientific publications and other related grey literature), which included 13 studies, in order to examine the attempts to adopt the Learning Health System paradigm.</p> <p>A learning healthcare system is driven to generate and apply the best evidence for collaborative healthcare, while focusing on innovation, quality, safety and value. Patients are a major factor in this model of health provision, given the emphasis on collaboration and collective decision-making. This review examines the attempts to implement this model of medicine.</p> <p>The results of this review indicate that there has been very little action in terms of implementing learning health systems, despite a great deal of interest. It is possible that there is great trust placed in the learning health system without proper assessment of impact. This may have contributed to the low number of studies qualifying for inclusion in the review. A major focus should be placed on assessment and reporting, considering that many attempts to adopt this system of health have been attempted and not reported. Existing frameworks for assessing medicine applications can be used to assess the efficacy of learning health systems. Further, reporting of the evaluation of these systems must be comprehensive. Lack of consistency across studies diminishes quality and effectiveness, and makes it difficult to assess outcomes.</p> <p>Taken together, the Learning Health System paradigm must be of central focus to researchers moving forward. While the central tenets of this approach are supported by researchers, there is a lack of assessment. The impact of such a system must be evaluated in order to boost adoption.</p>	2015	3/10 (AMSTAR rating from McMaster Health Forum)	0/13	Not reported in detail	0/13
	Examining the spectrum of ethical issues that is raised for stakeholders in a	The review examined 65 studies in order to determine the spectrum of ethical issues raised for stakeholders in a “Learning Health Care System”.	2015	1/9 (AMSTAR rating from McMaster	Not reported in detail	Not reported in detail	65/65

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	Learning Health System (67)	<p>A Learning Health Care System embodies an approach for integrating clinical research and clinical practice, in order to address problems of effectiveness and efficiency in the healthcare system. In such a system, knowledge generation should be embedded so that health systems can learn and grow. However, this blend of research and practice raises ethical dilemmas such as confidentiality and consent. This review aimed to summarize pertinent ethical issues in order to guide decision-making among healthcare professionals and policymakers.</p> <p>The ethical issues arising in Learning Health Care Systems can be broken down into different phases. In the phase of designing activities, ethical issues include the risk of negative outcomes that may result from activities that are not academically rigorous. As well, it is possible that stakeholders will not engage with this stage, which can affect trust and support in a learning activity. In the ethical oversight of activities, confusion surrounding ethical obligations and regulations can hinder progress. In conducting activities, the involvement of participants can lead to ethical difficulties with consent and data management. In implementing learning, main difficulties arise in changing practice efficiently, maintaining transparency, and reducing unintended negative consequences.</p> <p>The distinction between “research” and “practice” often creates ethical confusion, as many learning healthcare activities do not fit this dichotomy. Strategies to cope with these ethical problems include implementing policies and procedures, providing training and guidance for ethical committee members, and streamlining ethical-review processes. The rights of individuals must be protected as healthcare quality improves.</p> <p>Future research should focus on clarifying these ethical dilemmas and contribute to improving the quality of healthcare.</p>		Health Forum)			



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