

HARMONIZATION OF HTA-BASED REIMBURSEMENT AND REGULATORY APPROVAL ACTIVITIES: A QUALITATIVE STUDY

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ABSTRACT

Background

Regulatory approval and reimbursement are necessary to bring health technologies to market. As both are distinct processes, the lack of interaction between regulators and payers has been criticized for resulting in health system inefficiencies.

Objectives

This study describes the experiences of health system stakeholders on the development and implementation of initiatives to better harmonize HTA-reimbursement and regulatory activities, as well as Canadian perceptions on such initiatives.

Methods

Thematic analysis of semi-structured interviews was conducted. Participants represented those whom have published or worked actively in this area or who held positions in HTA and/or reimbursement agencies that gave them insight into the Canadian healthcare system. Interviews were recorded, transcribed and analyzed to identify emerging themes and relationships.

Results

Fourteen individuals from twelve organizations participated, including representatives from Canada, US, UK and Netherlands. Harmonization was identified as either a means to: (i) develop economies of scale in the generation of clinical data; and/or (ii) align the lifecycle of a health technology. For such initiatives to be successfully implemented, the following key issues emerged: (i) fostering healthy relationships; (ii) promoting well-intentions; (iii) defining governance and leadership clearly; and (iv) securing organizational infrastructure.

Conclusions

Attempts to harmonize reimbursement and regulatory activities is in its infancy; although, much can be learned from current Canadian and international experiences. Within Canada there is much interest, although concerns have been raised on the extent to which harmonization is possible. Successful policy implementation would require inter-agency collaborations, with particular attention towards capacity building and strong leadership.

Key Words: *Health technology assessment; product approval; healthcare industry; health policy*

To obtain market access, a health technology (for the purposes of this paper, defined as pharmaceuticals, biologics or medical devices) must navigate through a complex web of interactions influenced by health policies, regulations and funding mechanisms. Numerous contact points exist involving various stakeholders (e.g. regulators, payers, physicians, patients) that

each represents a decision-making step in the approval, adoption, diffusion or utilization of a health technology. In particular, two well-recognized hurdles to this process are regulatory approval and reimbursement.

Regulators represent the first line of contact towards market access, evolving as a policy response to past concerns on public health, safety and commercial interest on health products.¹ Health Canada is the federal regulatory agency responsible for the scientific evaluation of the safety, efficacy and manufacturing quality of drugs and medical devices under the authority of the Food and Drugs Act.² Before being available for sale, all products must receive market authorization to signify their compliance to federal regulations (with the exception of Class I medical devices).^{3,4} This licensing is provided upon satisfactory regulatory review and represents a ‘proof of concept’ approval.^{5,6}

Market access is further dependent on the financing mechanisms within the healthcare system. Often, payers’ decisions on whether to reimburse a product are informed by health technology assessments (HTA) whose objective is to ascertain the relative value (e.g. safety, effectiveness, cost-effectiveness) of a health technology under normal clinical settings compared to current standard(s) of care.^{5,6} HTAs may further consider the feasibility of access given the potential economic, societal, organizational, legal and ethical implications.⁷ Despite Canada’s publicly-funded national healthcare system, the provision and financing of healthcare is decentralized to each individual province. The existing HTA activities reflect this with roots at the provincial level (i.e. Alberta: Alberta Health Services, Alberta Health and Wellness; Ontario: Health Quality Ontario and Québec: Institut National d’Excellence en Santé et en Services Sociaux (INESSS)). A national, independent HTA body, the Canadian Agency for Drugs and Technology in Health (CADTH), exists to streamline a pan-Canadian HTA process.⁸ All agencies share similar objectives in providing impartial, evidence-based information to the payers of provincial insurance plans. While the pathway to market access is similar between drugs

and medical devices, slight, but important, differences do exist according to the category of the health technology (*see Table 1*).

The distinct mandates of regulatory and reimbursement agencies have led them to have separate activities and information requirements, reflecting their decision-making needs.⁵ However, interest in harmonization has emerged due to criticism that the existing status quo has been ill-suited in stimulating innovation^{9,10}, gathering evolving clinical evidence¹¹, enabling timely patient access^{9,11} thereby, resulting in lost opportunities to realize population health gains. Broadly, harmonization involves the streamlining of regulatory and reimbursement processes and/or aligning of evidentiary requirements.¹² An increasingly popular view is that such initiatives may carry positive implications across, and within, the healthcare system in terms of patient care, innovation and system sustainability.^{6,11-13}

However, such strategies may carry inherent risks. Separate regulatory and reimbursement functions permit health technologies to be produced through quality assurance mechanisms while remaining sold on a free market. Harmonization may lead to over-regulation that hinders the abilities for markets to function and, consequently, to market failures. It may also result in a loss of local decision-making control and the application of data methods and standards not acceptable for that jurisdiction.¹⁴

While existing attempts at harmonization of regulatory and reimbursement activities have been described¹², few studies seek to identify the elements necessary to minimize the risks and maximize the benefits. By identifying the barriers and facilitators of current experiences in harmonization, this may better inform other jurisdictions interested in implementing their own policies towards greater alignment. In the present study, we explore the experiences of those involved in developing and implementing projects that foster greater harmonization between regulators and reimbursement decision-makers for drugs and medical devices, both within and outside Canada, and further investigate the perceptions held by Canadian stakeholders on this topic.

TABLE 1 Differences in Regulatory Approval and HTA-Reimbursement between Pharmaceutical and Medical Devices in Canada

		Pharmaceuticals	Medical Devices
Regulatory Approval	Regulatory body	Therapeutics Product Directorate (TPD) within Health Canada ³	Medical Devices Bureau (MDB) within Health Canada ⁴
	Regulation	Food and Drug Regulations ³	Medical Devices Regulations ⁴
	Regulatory oversight	Procedures and evidentiary requirements apply equally to most brand-name products. Evidentiary needs are less for generic drugs. ⁵	Procedures and evidentiary requirement is dependent on a product's risk class (four classes exist). Product license is not required for medical devices in the lowest risk class (class I). ⁴
	Assessment Focus	Efficacy Safety Manufacturing practices	Efficacy and Performance Safety Manufacturing/Design principles
	Strength of clinical evidence	Clinical trials, preferably randomized controlled trial with either placebo or active comparator	Dependent on product class: Class I & II: pre-clinical studies Class III & IV: clinical trials, randomized controlled trial or observational studies are accepted
	License renewal:	Not required	Yearly renewal, submitted by manufacturer
HTA-Reimbursement	Payer	Each province has a publicly-financed drug formulary with some third-party private payers	Dependent on the technology although funding comes from a mix of provincial, hospital-based programs, healthcare providers and third-party payers
	HTA Agencies	National independent HTA body (CADTH) except in province of Quebec (INESSS)	A mix of national activities by CADTH, provincial activities (e.g. INESSS, HQO) and local hospital-based agencies
	Route to obtain coverage recommendation	Formal HTA (under the Common Drug Review or similar structure)	Both formal HTA and informal advocates exist
	Data collection	Pre-market	<i>If by HTA assessment:</i> Pre-market <i>If by advocates:</i> Mix of pre- and post-market
	Assessment Focus	Effectiveness Safety Economics, budgetary impact Social, ethical, legal, organizational	<i>If by HTA assessment:</i> Effectiveness Safety Economics, budgetary impact Social, ethical, legal, organizational <i>If by advocates:</i> Unknown as process is not transparent
	Strength of evidence	Pragmatic RCT, observational studies, decision-analytic techniques	<i>If by HTA assessment:</i> Pragmatic RCT, observational studies, decision-analytic techniques <i>If by advocates:</i> Unknown as process is not transparent

METHODS

This study received ethics approval (certificate: 13-562) from McMaster University Hamilton Integrated Research Ethic Board Committee;

with informed consent obtained from all participants. The Consolidated criteria for reporting qualitative research (COREQ) guidelines were adhered to in the reporting of this study.¹⁵

Participant Selection

Participants can be broadly defined as individuals whom have published on harmonization, whom have acted as spokespersons to harmonization initiatives or whom have held positions that provided them with insight into the Canadian healthcare system. These groups were selected because the former two could provide an in-depth understanding to how harmonization initiatives work while the latter could address the Canadian perspectives. Authors who have published or been actively involved on harmonization were identified from a previous systematic review.¹² A list of individuals who were employed or who had a working relationship with four Canadian HTA organizations was further generated (i.e. CADTH, HQO, INESSS, Alberta Health and Wellness). Participants were further encouraged to provide the contact information of others whom satisfy the inclusion criteria with sampling continued until theme saturation was reached.

Potential interviewees were purposefully selected to ensure inclusion of a broad range of professional groups and jurisdictions. Some informants had previous interactions with our research team but not pertaining to this research topic. To recruit, all were approached by e-mail that introduced the investigators' objectives and study interests. Non-responders were sent a reminder e-mail two weeks after the first invitation.

Interviews

All, except one, of the interviews were conducted by telephone. Participants selected their preferred interview location and time, with most conducted at the participant's work office. Each informant participated in a single interview, conducted according to a semi-structured interview guide that was developed iteratively with feedback incorporated from members of the research team to ensure content validity. This permitted collection of pertinent information relating to our study's objectives but with additional flexibility for the interviewers (primary interviewer: R.G.; observers: B.T.

and/or L.M.) to probe deeper and pursue new leads. The questions varied depending on the interviewee's role. Academics who have proposed theoretical frameworks of harmonization were asked to discuss their frameworks in finer detail, including a discussion of any empirical cases. Individuals representing HTA, payer or regulatory perspectives were asked to discuss their perceptions and/or experiences with harmonization, including the objectives, processes and outcomes of any prior or existing attempts. Interviews ranged from 25 to 45 minutes, with typical interviews lasting 30 minutes.

Data Analysis

Following conventions of qualitative research, data collection and analysis occurred iteratively. Given the lack of published studies on this topic, data analysis was conducted inductively using thematic analysis. Rather than applying a predetermined conceptual framework to guide the analysis, recurrent and significant themes emerged from the raw data.^{16,17} The interview transcripts were studied and familiarized by one researcher (B.T.) to develop a coding frame based on the major themes and subthemes. The major themes related to our two research objectives, namely expectation and experience, and included:

- Opinions about the objectives and opportunities of harmonization, which are classified under the theme "Expectations";
- Perceived barriers and facilitators to past, current or potential initiatives to harmonization, which are classified under the theme of "Experiences".

The coding frame referred to common words, phrases or sentences that were specific to each theme or subtheme. Segments (i.e. paragraphs and sentences) were then coded and labelled manually according to this coding frame (B.T.), which facilitated the analysis, comparison and review of the interview segments by themes and the documentation of the inter-relationships between subthemes.

Individual transcripts were not returned to participants for additional comments;

although, the final analysis of the aggregate transcripts was sent to participants to solicit feedback on the results.

RESULTS

Interviewee Description

Of the 17 individuals approached in this study, 14 responded to our invitation and completed the interview. The informants represented twelve organizations from four countries: Canada (65%), United States (14%), United Kingdom (14%), and Netherlands (7%) and had diverse roles, including regulatory (7%), HTA producers and users (57%), academia (21%) and non-profit agencies (14%). Unless otherwise stated, the results below relate to harmonization of both pharmaceutical and non-pharmaceutical health technologies.

Expectations: Opportunities and Objectives to Harmonization

Different views existed on whether harmonization is indeed an issue and whether it is desirable to work towards. Many respondents noted that payers have previously struggled to align even amongst themselves given its heterogeneous perspectives and the contextual nature of HTA assessments. Even within Canada, difficulties have risen in arriving at a consensus on an appropriate standard of care for use in HTA assessment as this may vary across provinces and territories. This issue is further complicated when considering the international scope of most clinical trials which are designed to satisfy the needs of numerous regulatory and reimbursement agencies. Harmonization inherently extends beyond jurisdictions although: *“(Payer’s) job is to get value for money from this health system. I frankly don’t care what they are doing in Germany or France or Canada. I am actually paid not to care”* (Interviewee 2, Consultant from UK).

Despite scepticism on the feasibility to harmonize regulators and HTA-payers, many still felt that it could present an opportunity to: (i) develop economies of scale in the evidentiary requirements; and/or (ii) align a product’s lifecycle.

(i) *Develop economies of scale in the evidentiary requirement*

The distinct data needs between regulators and payers have led to frustrations on the sustainability of existing processes.

“The fragmentation of data requirements is absolutely staggering and it doesn’t make sense” (Interviewee 6, Academic from the U.S.)

Almost all respondents addressed harmonization as a means to develop economies of scale in the evidentiary data to better support both regulators’ and payers’ decision-making. The focus so far has been on designing trials or developing methods that can robustly collect and analyze data to address both assessors’ questions; or in setting common definitions and/or data requirements (e.g. endpoints) such that both assessments can be supported – for the most part – by the same body of evidence. This may reduce duplication of work and lead to a common understanding on the meaning of the evidence.

(ii) *Aligning a product’s lifecycle*

Presently, regulatory approval and reimbursement are sequential processes. Nearly all participants discussed harmonization in terms of better aligning the stages of assessment:

“Everyone has different ideas in mind, from doing different things around aligning time-scales, to doing things around joint decision-making and, at the extreme spectrum of the scale, comes creation of a single process and decision-making body” (Interviewee 2, Consultant from U.K.)

In this context, harmonization is process-oriented; focused on reducing the time between regulatory and reimbursement decisions. For example, CADTH was noted to have introduced a process whereby HTA assessment of a drug can be submitted before regulatory licensing. Early pilots found the time between assessment decisions was reduced compared with the conventional processes.

Drugs vs. Medical Devices

Differences exist in the current regulatory/reimbursement pathways of drugs and medical devices (*see Table 1*). Technology-

specific issues that were raised were found to not be unique to harmonization but rather exacerbated by efforts to harmonize. Data collection by drug versus device manufacturers presently occurs at different time points: in the case of drugs, it is predominantly focused at the pre-market phase, whereas in the case of devices, it is focused on post-market surveillance. Devices may not necessarily have robust evidence to support HTA assessment especially considering that their regulatory evidentiary requirements differ according to its risk class. As a result, greater progress has been noted with achieving consensus on drug review methodology between agencies whereas, it remains less resolved with medical devices.

“When you’re dealing with many classes of devices, evidence of clinical efficacy is just not part of the regulatory landscape. Then, it’s a very different issue from talking of pharmaceuticals where you have both groups who actually agree where they start which is reasonable quality evidence on clinical utility” (Interviewee 2, Consultant from U.K.)

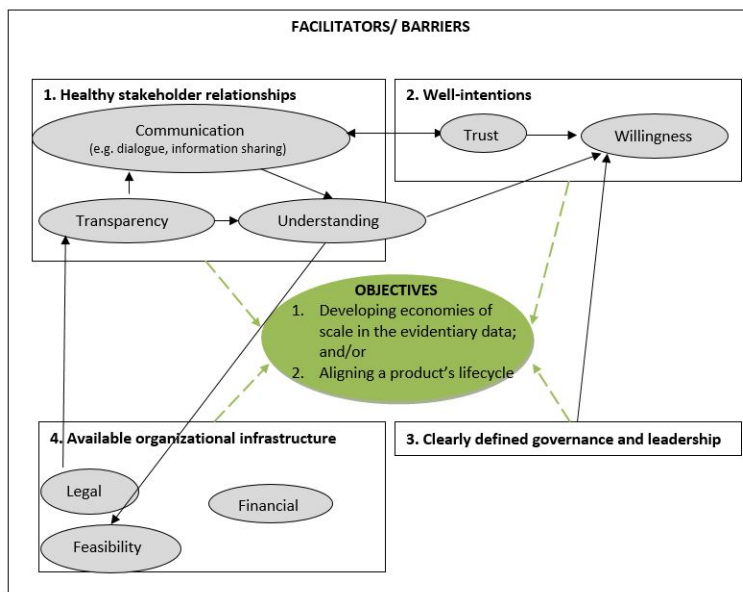
Furthermore, the effectiveness of devices is often dependent on the organizational infrastructure of the healthcare system, which is less evident in the case of pharmaceuticals. Payers must therefore factor in this contextual piece when assessing the effectiveness of a medical device; whereas regulators, whom are concerned with efficacy, may not necessarily consider the organizational systems impact.

Such differences between drugs and medical devices must be carefully considered as it may impact the overall success of a harmonization initiative.

Experiences: Barriers and Facilitators to Harmonization Initiatives

The key elements to support harmonization emerged under four themes: (i) fostering healthy stakeholder relationships; (ii) promoting well-intentions; (iii) defining governance and leadership clearly; and (iv) securing organizational infrastructure (see Figure 1).

FIG. 1



(i) Fostering Healthy Stakeholder Relationships

The need to build healthy relationships, both internally and externally with stakeholders, was mentioned by all respondents. Harmonization is a

multi-stakeholder initiative and most agreed that harmonization should involve, at minimum, the regulators and payers with an invitation to other stakeholders.

“You’d also want to be able to have the (healthcare) provider community involved... if you exclude industry from the conversation, you are likely going to introduce mechanisms and processes ... that are going to be blind to some of their concerns and issues around this, so why not bring them to the table or at least provide them an opportunity to provide input into where the challenges are for them... I don’t think we can exclude patients from that conversation” (Interviewee 5, HTA from Canada)

Three subthemes emerged that were prerequisites in forming relationships: communication; mutual understanding; and transparency. Continuous and open dialogue should be kept, with equal opportunities to communicate. Poor knowledge of each other’s functions, roles and remits can propagate misunderstandings and lead to unintended policy consequences that can create misalignment as suggested from numerous cautionary tales including the one below:

“Notice of compliance with conditions was a softer-type of policy we [regulators] had introduced because of the pressure on approvals for HIV/AIDs and largely oncology drugs ... we were letting these drugs out earlier than we normally would, after phase 2 clinical trials, and then tried to get data once they were on market. That was confusing to reimbursement decision-makers and there was very little uptake of those drugs in the system” (Interviewee 4, Regulator from Canada)

Understanding can be achieved through dialogue and communication. Through greater awareness of each other’s evidentiary needs and processes, one can then identify similar decision points and evidentiary requirements that can be better harmonized. Dialogue also serves an equally important role in highlighting inter-agency differences in order to gain a realistic understanding on the extent to which harmonization is feasible.

Transparency, another facilitator to achieve mutual understanding, was predominantly an issue in Canada. Existing information-sharing practices were suggested to be severely limited:

“The most important thing that we would like is transparency from the regulator ... That is the

biggest challenge, the biggest barrier and that is the biggest challenge we hear from the drug plans” (Interviewee 1, HTA from Canada)

“It would seem untenable that a publicly-funded healthcare system couldn’t get the information that supported a licensing recommendation for a product being held in confidence in one arm of government when another part is asking for it” (Interviewee 5, HTA from Canada)

The lack of transparency in the Canadian system may stem from the existing regulatory framework of proprietary and confidentiality agreements. Information – such as whether a product submission has been received, a product’s expected price, its indication, the assessment methodology, the reason and potentially, the outcome, of the regulatory decision – may all be considered confidential. Many stated the need for mechanisms that, while protecting data confidentiality, would also ensure better transparency across agencies and to the wider public. Discussion relating to transparency is long overdue and will need to consider what and when information can be shared between agencies.

(ii) Promoting well-intentions

Increased support towards fostering interactions between regulators and HTA-reimbursement bodies has been observed. Indeed, it was remarked that:

“Five or seven years ago, the regulators would have never come to the table and chatted with us (payers). They had the opinion that what we say is ‘gospel’ ” (Interviewee 1, HTA from Canada)

To gauge stakeholders’ willingness to harmonize, many initiatives begin as voluntary pilots. In many cases, confidence was required that existing roles would remain despite harmonization to prevent “protecting turf” mentality. Building trust through open dialogue, keeping an open-mind and setting a proper tone can further foster an environment conducive of greater interaction.

Some have observed that there is a natural reluctance towards harmonization given that this brings about change. Each agency may want to guard what it does and how it is done, leading to an unwillingness to participate amongst stakeholders.

“Inevitably, when you harmonize you compromise... When you harmonize, you don’t necessarily get what you want, but overall you get a better world” (Interviewee 2, Consultant UK)

Harmonization extends beyond regulators and payers. Many respondents noted the need for manufacturers’ support. Resistance from industry may limit the extent to which information can be shared and the outcomes of harmonization.

“It is much easier for them [regulators and payers] to do things knowing that industry isn’t going to complain or that they can go with industry backing to their ministry” (Interviewee 2, Consultant from UK)

Perceived industry’s views have been mixed, with protectionism and risk aversion posing a particular challenge. Some manufacturers may prefer to defend its existing position with little desire to take on the additional risks associated with a harmonized regulatory/reimbursement pathway. Such unwillingness may be partly due to a poor understanding of the objectives of harmonization and a biased emphasis on its risks. Respondents observed that manufacturers’ trepidations often arose from the belief that payers might be able to influence market authorization decisions and vice versa.

Canadian interviewees further noted that industries are mobilized around the issue of transparency and data confidentiality with a strong desire to preserve the existing status quo. Manufacturers’ concerns may be attributable to the fact that each assessment agency handles proprietary information differently in Canada. While regulators are governed by strict confidentiality codes, the payers’ framework is focused on ensuring transparent decision-making.

(iii) Defining governance and leadership clearly

Leadership and clearly-defined roles and responsibilities are necessary to minimize a culture of blame if the intended outcomes of harmonization are not attained. As described by one respondent:

“Unless one takes responsibility for it and provides the leadership ..., it will always be an unfulfilled

conversation” (Interviewee 4, Regulator from Canada)

Strong leadership can positively impact the outcomes of a harmonization project. Indeed, several respondents mentioned that the success of their initiatives were attributable to a group’s or an individual’s passions and beliefs. Upper-level political guidance, providing top-down support, may also facilitate success, as greater accountability may incentivize buy-in from all stakeholders. However, allocation of responsibilities is a sensitive topic. For instance, where healthcare provision is devolved such as the case in Canada, existing responsibilities may be fiercely defended.

“You have to respect the autonomy of the provinces to run their own health systems and make decisions about the impact of the outtake of non-drug technologies on their own and whether they wish to pay for that or not” (Interviewee 9, HTA from Canada)

(iv) Securing organizational infrastructure

Harmonization will bring along changes to the present regulatory and reimbursement pathways that would otherwise not be possible unless the infrastructure can support it. The majority of respondents mentioned the need for legislative change since regulators’ and in some cases payers’ remits are defined by their governments. Specifically, Canadian respondents stated that present-day regulations were well overdue for modernization as these were written when no formal reimbursement structure existed. As previously mentioned, current laws limit the extent to which information can be disclosed between agencies. New regulations are thus needed that consider the present-day healthcare system and promote open dialogue and greater transparency.

The concept of feasibility was frequently mentioned. For instance, in terms of aligning evidentiary needs, many respondents mentioned the impracticality of creating a perfect clinical trial that includes all possible comparators of interest. Rather, one must design a trial that realistically attempts to meet the needs of each decision-maker as best as possible. Similarly, when conducting early tri-partite dialogue, a

respondent noted that the number of stakeholders present should be limited, in order to achieve a balance between the depth and the breadth of the discussions. Processes should be designed to be as undemanding as possible to existing workloads and should complement the available infrastructure when possible. Approaches to harmonization should also remain flexible and adaptable. Pilot exercises were perceived positively by many as an evaluation of feasibility to identify barriers and explore potential solutions before being expanded and formalized.

Respondents involved in harmonization activities all spoke to the fact that it requires a tremendous amount of support, including intellectual power and time. Several initiatives required securing financial resources (e.g. user fees) or an alternative revenue stream to ensure the sustainability and self-sufficiency of these activities.

In incorporating the lessons learned so far, we find that a fine balance exists in harmonizing regulatory and reimbursement processes. Indeed, as summarized by one respondent:

“There is one thing to have alignment and another that you can create misalignment and actual confusion in the system, depending on how you do things” (Interviewee 4, Regulatory from Canada)

DISCUSSION

Many organizations do realize the potential benefits of harmonization as it is considered a vehicle towards improving efficiency in the decision-making process; bridging the disconnect between assessment agencies and their stakeholders; encouraging more timely patient access to the necessary therapeutics and stimulating innovation. Similar to the existing literature, our interviews found that the focus of harmonization was either on the evidentiary content and/or processes.¹² Many approaches exist or have been proposed, including: early dialogue, alignment of evidentiary needs, parallel submission, and adaptive licensing.¹²

Most respondents believed there is a limit to harmonization, especially since regulators and payers fundamentally ask different sets of

questions. HTA-guided reimbursement involves a value assessment where outcomes are linked to price and, therefore, requires contextualization of the evidence to its respective jurisdiction. This is beyond the regulatory responsibilities.

Despite some scepticism by Canadian stakeholders on the feasibility of harmonization, existing opportunities have shown the potential of such initiatives if certain key elements are also present. Harmonization may have a degree of complexity that requires careful implementation. Respondents with experience offered advice that applies universally irrespective of the approach to harmonization. Poor inter-/intra-agency relationships, wrong intentions, a lack of organizational infrastructure and ambiguous leadership may hinder the success of any initiatives. Experience of other harmonization initiatives has shown that lengthy periods of collaboration and exchange of ideas are necessary to bring participants to the point of accepting common approaches. Some of these challenges align with a previous literature review that found three key challenges: i) development of trust and openness in order to foster mutual understanding; ii) a means to handle confidential information; and iii) an infrastructure with available resources.¹² These three challenges fall, within this study, under the themes of fostering healthy relationships and available organization infrastructure. The interviews further identified two additional barriers: the need for well-intentions from both agencies and clear governance and leadership to spearhead such initiatives.

Approach-specific barriers and facilitators were not identified given the focus of our interviews. However, some studies have begun to emerge that address specific approaches to harmonization. The outcomes of a recent Health Technology Assessment international (HTAi) policy forum that focused on identifying issues regarding adaptive licensing were recently published.¹⁸ Of the six key issues identified, three matched our study findings: ‘to clarify the roles and responsibilities of stakeholders’, ‘to determine costs of such approaches and how they will be met’ and ‘to understand the implications of adaptive approaches on current legal and ethical

standards'. These issues, referred to in this paper as 'defining the governance and leadership clearly' and 'securing organization infrastructure' broadly apply to any approaches to harmonization. The remainder of the issues identified in the policy forum may be more specific to features of adaptive licensing. These include the need to define goals and set priorities; to develop an acceptable manner for evidence collection; and to understand the differences between drugs and devices.¹⁸

While it may be difficult to measure the degree to which existing harmonization projects have overcome these barriers, infrastructure changes can be easily observed. Some innovative solutions to address the above challenges include pilot-testing schemes for proprietary information sharing (e.g. Federal Drug Administration (FDA) and Centers for Medicare & Medicaid Services (CMS)' memorandum of understanding for parallel review¹⁹; Health Canada and CADTH's information-sharing agreements²⁰). Similarly, some agencies are creating business lines such as introducing user fees to support the operating costs of their harmonization activities (e.g. National Institute for Health and Care Excellence (NICE)'s scientific advice program²¹ or the MaRS Excellence in Clinical Innovation Technology Evaluation (EXCITE) program).²²

This study was exploratory in nature. It draws on evidence from a small number of key informants, mostly from Canada, which may limit the transferability of our findings to other jurisdictions. However, we believe these limitations are offset by the selection of key informants who are part of an extensive international network as their opinion may be helpful in identifying broader patterns across the international community as a whole. The existing study has further been focused on the views of regulatory and HTA agencies along with key academics in this field. A clear limitation is the lack of industry perspective as they represent a key stakeholder to this process. Future work should focus on understanding their perspectives on this topic. Our study has found that both regulators and reimbursement bodies understand the importance of industry support although the degree and nature of manufacturers' involvement

will vary across jurisdictions and initiatives. The policy forum report suggested that industry overall welcomed adaptive licensing approaches, although concerns still remain that uncoordinated harmonization by regulators and payers may lead to greater consistency within jurisdictions but widening variations between them.¹⁸

Significant resistance is expected if regulatory and reimbursement processes are merged into a single process that is managed by a single agency. Rather, it is important to recognize that harmonization, albeit possible, will likely focus on better aligning certain aspects and elements in both pathways while respecting the differences in the objectives of regulators and HTA/payers. This study has highlighted that, successful implementation of harmonization will require inter-agency collaborations, with particular attention paid towards capacity building and strong leadership. To further advance our knowledge on the barriers and facilitators of these initiatives, strong monitoring and evaluation of harmonization projects is required. By reporting the outcomes and sharing the successes and challenges that have been encountered, this will contribute towards expanding our knowledge on what works and what does not work, in which context and why, such that others embarking on harmonization activities could draw upon and learn.

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