Roundtable on Real World Evidence

System Readiness – Are we ready to use routinely collected data to improve health system performance?

Summary Report – September 2014

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Preface

Public sector decision-makers have increasingly relied on the use of evidence to inform policy in the last 20 years. Health care systems now routinely use clinical trial evidence to support clinical practice, regulatory and payer decisions regarding which new technologies and approaches should be adopted. Provinces are increasingly recognizing that spending more on health has an opportunity cost – increasing expenditure means less resources available for other government priorities (Box 1). This means the role of evidence to support decisions has become more important than ever. This recognition has led to an increased use of data routinely collected for the purpose of reimbursing provider services, monitoring hospital activities, or for management of individual patient care. These data can provide decision-makers with real-world evidence (RWE) to inform or revisit health system decisions.

Box 1. Opportunity costs around evidence use

"There are always finite resources to work with but I think the price of not paying attention to the evidence in the way that we need and organizing ourselves to do that… has put health care as a whole in a position where it is an opportunity cost decision for government [*against other government priorities*] that really is the dilemma."

-Workshop participant

Bringing together a wide spectrum of stakeholders in evidence development health system use, this roundtable sought to bridge the knowledge and understanding gaps that can often hamper the use of RWE in health care. In particular, the roundtable aimed to provide a shared and improved understanding of the role of RWE– and how it can be used alongside other types of evidence to inform health care decision-making.

The main objectives for the roundtable were:

- **Discuss the current and potential state** of the use of routinely collected data within health systems to improve health outcomes.
- Identify **opportunities and barriers** to incenting and organizing policy makers, health system administrators, care providers, industry, and researchers to use and apply appropriate methods.
- **Articulate some directions and goals** for more appropriate and widespread use of routinely collected data to improve health outcomes within Canadian health systems.

The structure of the roundtable was as follows:

Opening and Opening Remarks

- *Moderator*: Chris Henshall, Health Economics Research Group, Brunel University
- Neil Maresky, VP Scientific Affairs, AstraZeneca Canada Inc.
- Honourable Minister Fred Horne, Ministry of Health, Alberta

PART I: The value of using real world evidence

Real World Evidence in Canada – Backgrounder.
- What is the state of observational data and collection in Canada?
- What initiatives have been successful/what does the future hold?

Eddy Nason, Director Health and Innovation, Institute on Governance, Toronto

International Perspectives – Successful use of real world evidence to monitor and improve technology performance

• What methodological and system barriers exist? • What strategies and initiatives have been used to overcome them?	Jaclyn Bosco, Associate Director, Epidemiology, Real-World & Late Phase Research, Quintiles
National Perspective – How we can use real world evidence today? • What are we able to measure and analyze using current data? What can't we analyze? • What initiatives hold to improve use of real world evidence?	Tara Gomes, Assistant Professor, Leslie Dan Faculty of Pharmacy, University of Toronto
Questions and Answers from Audience	
PART II: Moderated Panel Discussion **Real World Evidence in Canada - What is Needed?**	**Moderator**: Chris Henshall
What questions can routinely collected data allow us to address that we can't address satisfactorily through other methods (either alone or at all)?	**Panel Members**:
What types of data are of most value to health systems, producers, providers and patients?	Cy Frank, CEO, Alberta Innovates – Health Solutions
What challenges and barriers exist to generating and using health system data, for example: • Defining/standardizing the data to be collected? Developing systems to collect, record and share data reliably? Ethical and legal issues?	Greg Rossi, Vice President, Payer and Real World Evidence, AstraZeneca
What can be done to overcome these barriers, for example through: • Dialogue and partnership with clinicians, patients and the public? Providing resources and/or creating incentives for collecting and sharing data? Technical developments in data collection, storage, processing and coordination/sharing? What challenges exist in the analysis and interpretation of observational data, and what are the priorities for methods development? What could we do with the data and methods we have already?	Adrian R. Levy, Professor and Head, Community Health and Epidemiology, Dalhousie Anne MacFarlane, Vice President, Western Canada and Development Initiatives Vasanthi Srinivasan, Executive Director of Ontario SPOR support unit
An Action Plan for Canada - Moving forward • What do we need to do to make better use of the data and methods we currently have? How can we reach agreement on priorities for defining, collecting and sharing data to supplement what we have already? What action is required to address the ethical, legal and "social contract" issues? What action is needed in Canada to contribute to and benefit from the international effort to improve methods for the analysis and interpretation of observational data, and to reach consensus on the validity of these data and methods to support key decisions?	
Summary of Discussion	Chris Henshall
Closing Remarks – Next Steps	Don Husereau, Institute of Health Economics

The roundtable hosted by the Institute of Health Economics was supported by, developed and delivered in partnership with AstraZeneca Canada. It was held in association with the Canadian Agency for Drugs and Technologies in Health 2014 Symposium.

Executive Summary

In April 2014, we held a roundtable discussion current and future role of real world evidence (RWE) in Canada, bringing together multiple stakeholders from across Canada and internationally. The workshop aimed to highlight existing challenges, facilitators and potential ways forward for the use of RWE to improve patient health and the health system in Canada. The roundtable discussed some of the background on existing approaches to RWE from Canada and from other countries, before moving into discussions engaging senior decision makers, researchers, health professionals and industry representatives.

What is real world evidence?

Primarily, RWE can be considered to be "*data collected in actual practice for many purposes and applied to prove or disprove a hypothesis that may have nothing to do with its original remit*".[1] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) identifies RWE as "*data used for decision making that are not collected in conventional randomized controlled trials (RCTs)"*.[2]

Real-world evidence is a broader concept than just observational studies to aid clinical decisions, it is evidence from a wide variety of different data types that can be used to additionally support needs assessment, administrative, and pricing and coverage decisions.[3,4] The data used to provide RWE can be organized by type of outcome (clinical, economic, patient-reported), research study design (pragmatic trials, observational studies), and data source (supplementary data collection alongside RCTs, large simple trials, patient registries, administrative claims database, surveys, and medical records).[5]

Why is it becoming of increased importance:

- **To public payers and evidence assessment agencies:** Payers must balance the need to provide improved health outcomes and access to new technologies with budgetary considerations. Clinical trials developed for regulatory purposes may be insufficient to resolve payer uncertainty.

- **To researchers:** Techniques and tools to analyze data for RWE have become increasingly widespread and accessible to researchers. Researchers are now able to answer an increasing number of important health services and policy questions without the considerable expense, length of time, and complication of conducting high-cost experimental studies.

- **To industry:** Industry views RWE as an additional opportunity to demonstrate the value of medicines, for both the patient and the health system. It may also provide new opportunities for industry to work with payers to advance novel approaches to pricing and reimbursement.

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[1] IMS Consulting Group (2011).. New York, NY: IMS Consulting Group.
[2] Garrison *et al*. (2007).. *Value in Health*, 10(5): 326-335.
[3] Sproule and Nason (2011). Edmonton, AB: Institute of Health Economics.
[4] Morgan *et al.* (2013).. *Healthcare Policy*, 8(4): 45-55.
[5] Ibid.

Real World Evidence Issues identified at Roundtable:

- **Fit-for-purpose real-world evidence:** The roundtable noted that a major issue for Canada is a lack of a clear policy framework that suggests when and where RWE is useful, and also what approach is best suited to specific questions or issues. Building a conventional fit-for-purpose approach with input from all stakeholders could encourage more systematic use of real-world to inform health system decisions.

- **Linking real world evidence with innovation and research**: There is a need to build a culture that does not make artificial distinctions between health service delivery and research and recognizes the value and role RWE can play in fostering health care system innovation.

- **Aligning real world evidence with public and patient outcomes, and policy priorities:** Patients, providers and the public may be too far removed from decisions to use RWE to appreciate its potential to improve the quality and efficiency of care. A greater understanding of the value of RWE is required. Some current RWE initiatives lack meaningful participation by all stakeholders.

- **Data linkage for real world evidence:** There is still a need to use common healthcare information technology (IT) data structures and vocabularies to allow better linkage and analysis so that RWE can become a more useful tool to support decisions in the health system.

- **Address the challenge of federal and provincial roles in real-world evidence:** It is clear that the federal government can facilitate standardization, but provinces are often the ones who can implement and use RWE practically. Clarifying these roles in the future is paramount, possibly through creating pan-Canadian guidelines for its use, that still allow provinces to implement to their own priorities within those guidelines.

Next steps for Canada on real world evidence

- **Determining where real world evidence is most suitable and what evidence to use:**

    - The roundtable concluded that the initial focus of RWE in Canada should be to support appropriateness of care initiatives, such as those being undertaken by the Health Care Working Group (HCWG) of the Council of the Federation. The HCWG could also play a real role in adopting common IT data structures.

    - Another important focus is priority setting of future research with real-world evidence. There was a feeling that current use of RWE is limited to questions that can be answered with existing data, rather than asking important questions and then building evidence to answer that question. Creating national data inventories and setting priorities for future research could help researchers and policymakers understand what new data is required.

- **Make use of existing data and infrastructure in Canada:**

    - There was consensus that Canada already holds a significant amount of data for RWE analysis, but that accessing the data and linking it can be a challenge. Encouraging patients and health professionals to engage in RWE by helping them understand its economic value should improve access to data and address privacy issues.

- **Build capacity for real world evidence in Canada:** This includes building research, data and infrastructure, and receptor capacity for RWE:

    - Improving the research culture in the health system through enhanced data collection and analysis by health professionals could be accomplished through initiatives such as CIHR's Strategy for Patient Oriented Research (SPOR) that are currently providing patient-centred approaches to research

- **Create a 'safe space' for all stakeholders to continue to discuss and develop real world evidence:**

    - The health service and policy research community should continue to hold roundtables such as this one that provide an opportunity for all stakeholders to come together and discuss how to use RWE so it is fit for purpose, and also to compare and understand examples of RWE implementation from across Canada and internationally.

    - There was unanimous support for continuing the rich conversations that this roundtable brought to the RWE field. In particular, the opportunity to move from the initial discussions of this roundtable, to a more focused conversation on next steps and how to implement them in Canada.

It was clear from participants that this roundtable provided a valuable space to discuss the RWE issue in a way that it had not yet been done in Canada. Taking the lessons from this meeting and placing them into practice (and policy) remain the challenge, but the stakeholders present at the roundtable clearly see this as the first step along that road.

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Roundtable on Real World Evidence
System Readiness – Are we ready to use routinely collected data to improve health system performance?

In Canada, real world evidence (RWE) is becoming an increasingly important part of the health care decision making discussion. From its use in health technology assessment and investment decisions, all the way through to its use in analyzing safety and effectiveness for new health care approaches, RWE is providing opportunities for consideration of new and timely evidence in the health care sector.

Real world evidence is a broader concept than just observational studies to aid clinical decisions, it is evidence from a wide variety of different data types that can be used to additionally support needs assessment, administrative, and pricing and coverage decisions. RWE data can be primary data collected for the purpose of evaluation, or secondary data routinely collected in administrative databases. It can be also be collected prospectively through other means such as surveys, patient registries, or electronic medical records. The data used to provide RWE can be organized by type of outcome (clinical, economic, patient-reported), research study design (pragmatic clinical trial or observational study), and data source (supplementary data collection alongside RCTs, large simple trials, patient registries, administrative claims database, surveys, and medical records). While RWE itself might rely on simple data, its analysis can be complex and this creates challenges for its use in decision-making.

As major international HTA organizations, increasingly acknowledge RWE and how to incorporate it[6], RWE is becoming more prevalent and more important in Canada and elsewhere (for example even in their work). This suggests that now is the time for stakeholders across the health care system (from decision makers, researchers and health professionals to those in the private sector developing health technologies and insuring individuals) to come together and create a shared understanding of how RWE can best support an evidence-informed health care system.

[6] See, for example, the Chapter on selecting observational studies for comparing medical interventions in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://www.ncbi.nlm.nih.gov/books/NBK47093/) as well as Sir Michael Rawlins, former chairman of the National Institute for Health and Care Excellence, call for removing randomized controlled trials from their "uncomfortable pedestal" (Lancet 372;9656: 2152–61).

The current use of real world evidence

(Presenters: Eddy Nason, Jaclyn Bosco, Tara Gomes)

Using RWE is not a new phenomenon. In Canada, RWE is currently being used for a number of reasons, ranging from pricing decisions through to appropriateness of care (see Box 2 for examples of the current use of RWE in Canada). Just how it is used varies significantly from province to province as can be seen in specific examples, such as analysis of geographic variation in opioid prescribing by province, survival rates related to hysterectomies in Ontario and self-monitoring of blood glucose (and its main tools for home use). What is clear for Canada, and was pointed out by one speaker, was that there is a significant amount of data to use for RWE in the country.

- Evidence generation to support policy and practice
- Economic decision making
- Safety
- Effectiveness
- Clinical treatment guideline development
- Access issues for patients
- Context dependent real world effectiveness
- Quality monitoring

Box 2. Current use of RWE in Canada

These examples, as well as more detailed examples identified in Appendix A, show that there is some patchwork use of RWE across the country, it is clear that there is no standard approach to the use of RWE – nor even a standard definition of RWE that can allow simple comparison of different approaches across Canada.

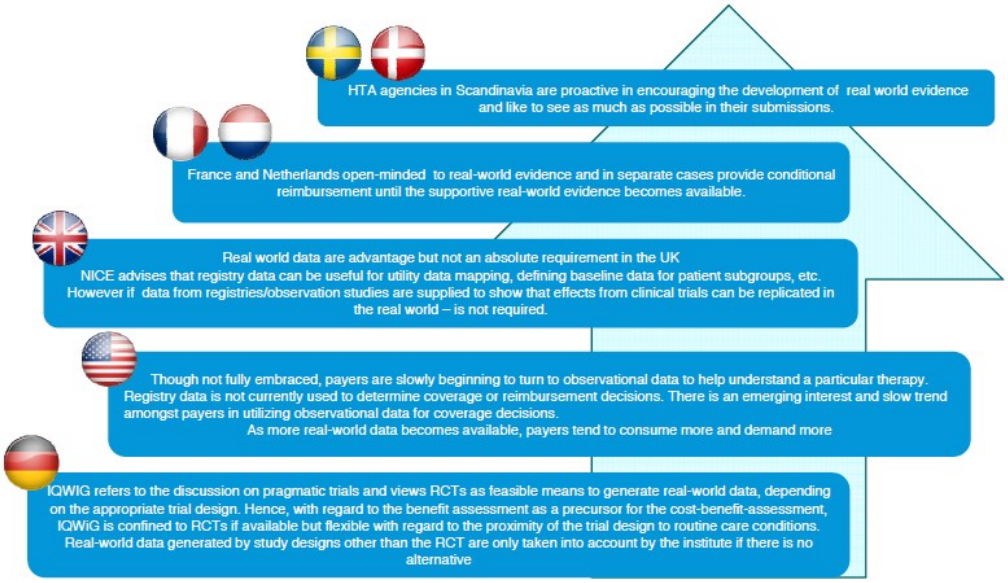
What does seem clear is that there are some common challenges in the current use of RWE from different Canadian examples. These challenges include:

- Getting a clearer definition of RWE that can allow stakeholder from different organizations and groups to have a shared understanding of RWE.
- Understanding in greater detail the issues of internal validity and generalizability of results from RWE analyses (for example understanding confounding variables and their role in RWE analyses).
- Knowing that sometimes using different or more complex approaches to analyzing RWE will not lead to a better understanding of outcomes – since the data itself can't be fixed by analysis. For example where databases are not deep or broad enough to answer questions effectively; where the quality of coding of data at collection is questionable; or where data linkage is unsatisfactory to answer questions with confidence.

While Canada is wrestling with some of these challenges, there were also additional key questions raised during the meeting. One participant asked why the demand to use and interpret RWE varies so much across provinces. This also led to additional questions, such as when it would be best to use RWE rather than other approaches in Canada. This second question led to significant discussion around why to use RWE, who might want what type of evidence, and what capacity different stakeholders have to produce, analyze, understand and use RWE. However, there was no consensus from either panelists or participants on how to answer either of these questions for Canada.

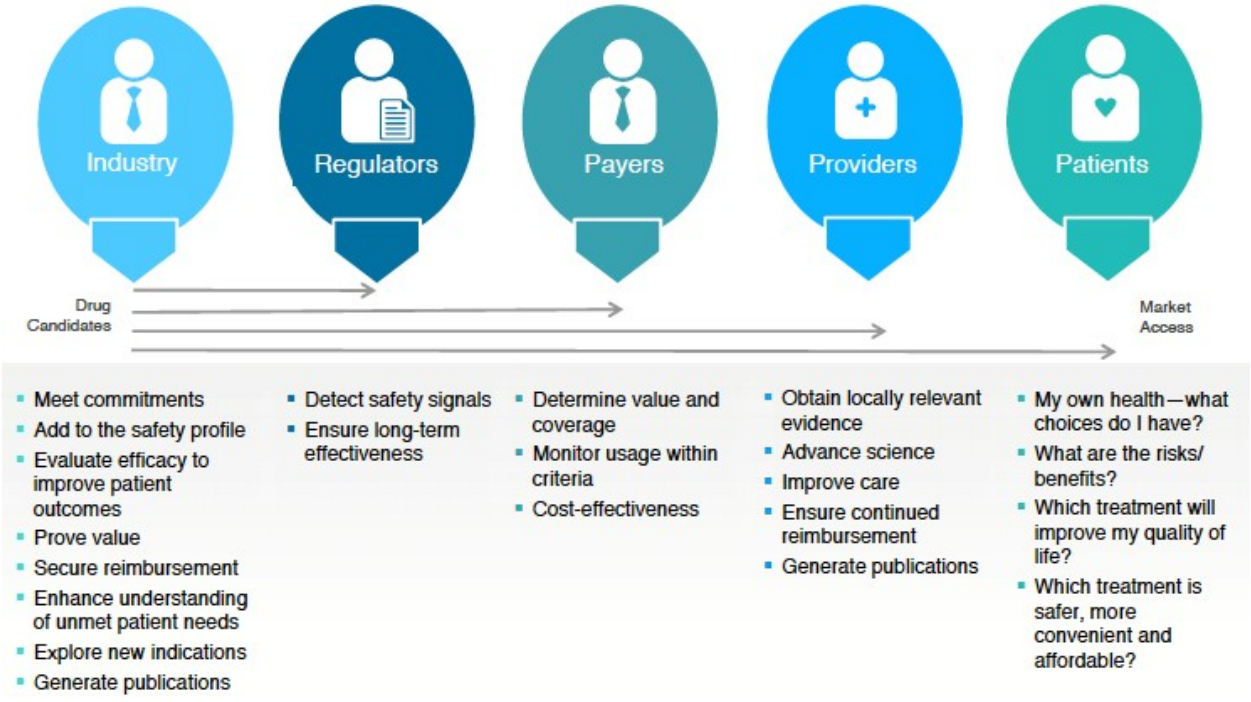
Outside of Canada, there has also been significant interest in RWE as a means of collecting evidence to support health system decision-making. While most countries have some examples of RWE use, it is clear that Scandinavian and Northern European countries are leading the way. Further details on initiatives in different countries can be found in Appendix A.

Figure 1. International use of real world evidence (taken from Bosco presentation)



Internationally, the need to understand different stakeholder needs in using RWE is becoming increasingly acknowledged. Figure 2 illustrates the substantial variation in the needs of different groups engaged in either the development or use of RWE.

Figure 2. Stakeholder needs for real world evidence use (adapted from Eichler et al, 2010[7]).



[7] Eichler, Hans-Georg, et al. *Nature Reviews. Drug Discovery* 9 (4): 277–91.

Three successful international examples of RWE use were presented, as a means of reflecting on differing stakeholder needs:

- The National Registry for Myocardial Infarction (NRMI),
- The National Oncological PET Registry (NOPR), and
- The British Society for Rheumatology Biologics Register (BSRBR).

The NRMI represents a commitment to post-market surveillance for thrombolytic therapy in the US, and illustrates how a registry can provide continuous feedback to hospitals on therapeutic outcomes that lead to real-time practice changes and improved outcomes such as timing of administration of thrombolytics and specific dosage needs for different patient populations.

In contrast, the NOPR represented the first use of coverage with evidence development for imaging technology. The interaction of medical professional bodies and government was seen as the key to achieving positive outcomes for patients (such as reduced biopsies and more appropriate oncology treatments).

The BSRBR was intended to examine long-term safety and effectiveness of biologics and has been used to develop NICE anti-TNF therapy guidelines. The success of the BSRBR was attributed to the interaction of patients and medical professionals with academia and industry, which facilitated and encouraged data collection and analysis.

What do we need to accelerate real world evidence use in Canada?

Panel: Greg Rossi, Cy Frank, Adrian Levy, Anne MacFarlane, Vasanthi Srinivasan.

It was clear from the early presentations and Q&A session that there is significant interest, potential and need for the use of RWE in Canada. The panel of experts expanded on this issue, with a particular focus on what would be needed for Canada to accelerate the use of RWE. Each panelist was provided a short period to outline their specific thoughts on the issues around RWE.

The diverse perspectives of the panel, which included domestic and international experts from both the public and private sector and roles in academia, health care, policy and industry, led to a number of different observations. These included:

- Needing to better understand the interface of RWE with innovation and the understanding of diseases. Panellists highlighted the importance of collecting appropriate information that can inform the use of innovation for appropriate disease management.

- The question of 'Why to use RWE' and noting that it should be put in place for the benefit of the public and patients including the transparency around RWE use required when it is a public good. There should additionally be a common understanding of the value of improving access to technologies (and procedures) underpinning the use of RWE.

- Aligning RWE with public sphere improvements such as the use of patient-reported outcome measures and health care patient experiences to examine value for money, for example. This requires engaging patients and the public in RWE discussions, data collection and even analysis of RWE data.

- Providing meaningful engagement with all potential stakeholders in RWE, with a special focus on understanding the risk-benefit trade-offs that stakeholders must make in their use of RWE.

- Identifying potential examples of RWE-like approaches from outside health care. One example given was the approach taken in Alberta around environmental decision-making where evidence is not always complete.

- Noting that there are opportunity costs around the development and use of RWEs and that these should be considered in decisions on when and how to use RWE.

- Identifying the importance of data centres and repositories for use in RWE development and analysis.

- Noting that we currently often address questions that we are able to easily answer with currently available evidence rather than tailoring evidence collection and development to answer the most needed questions. This includes not using some existing data to its full potential, such as cancer staging data for better cancer treatment safety and effectiveness, or using electronic medical record data that has been coded adequately.

- The challenge of linking data for more comprehensive evidence and analysis, for example due to ethics, privacy concerns, parochialism over ownership of data, etc. One example identified was the ability to link health and social care data for mental health issues in Ontario.

- Identifying the need to link RWE work to existing priorities: for example, provincial and federal policy priorities in health care such as the Health Canada Innovation Working Group, existing innovation and research priorities such as the CIHR Strategy for Patient Oriented Research, and ongoing collaborations between the public and private sectors such as the Value Demonstration Initiative in Ontario.

In the discussion that these comments engendered, there was a rich analysis of some particularly key issues for accelerating RWE in Canada.

1. What is real world evidence in Canada?

There is considerable confusion and debate over what constitutes RWE (see page 10 for more details), and the roundtable discussed the concept of what RWE really is for Canada. In short, the consensus at the roundtable was that RWE could be considered to be interchangeable with evidence from 'routinely collected data'. Examples given of what RWE might be derived from included: data on social outcomes, pragmatic trials data, appropriateness of care data, electronic medical record data, patient reported outcome measures, etc. RWE for Canada can be considered to be evidence that comes from sources other than RCTs and that can help to inform decision-making.

2. What should we use real world evidence for in Canada?

While much of the discussion in the literature around RWE has been around its role in pricing and reimbursement decisions for new technologies, such as its use in product listing agreements, there was more interest in the roundtable in the part that RWE could play elsewhere in the health system. For example, the success of RWE was noted in existing approaches to safety and effectiveness such

as the Canadian Network for Observational Drug Effect Studies across Canada (see page 13 for more details). Indeed, different speakers regularly identified the potential for the **use of RWE for appropriateness of care** – with one even going as far as to suggest that provinces themselves could develop accepted levels of appropriate use of new health technologies that could be determined using RWE.

The overarching feeling from participants at the roundtable was that the role of RWE was predominantly in delivering **evidence for health system performance**, rather than focusing on the value of new drugs or technologies where it was felt that randomized clinical trial evidence collected for regulatory purposes was likely to still provide the best evidence. While it was acknowledged that RWE could play a role in pricing and reimbursement decisions in the future, it was generally considered that at this time, a focus on analyzing health system performance was more likely to have impact.

Using RWE evidence for policy was also identified as a key point through the roundtable. With a number of senior policy makers and influencers present at the roundtable, it was noted that there should be a role for RWE in informing decisions. This means not only producing high quality RWE, but also ensuring that the capacity exists in decision making to both analyze and use RWE as part of the decision making process.

3. What are the major barriers, facilitators and incentives for the use of RWE in Canada?

Canada is a complex country in terms of health care, with the delivery of health care generally falling under provincial or territorial jurisdiction. The challenge of **pan-Canadian versus provincial approaches** to any aspect of health care is also true for approaches involving RWE. In particular for RWE, there are challenges geographically around policies on data collection and privacy, as well as around appropriate use of RWE for decision-making. One roundtable observer noted that while national strategies can be attractive for their standardization and large data sets, provinces are the ones in a position to actually integrate RWE data and infrastructure, as well as their ability to use the data for decision-making changes.

An additional barrier identified during the roundtable was the **lack of a 'safe space'** for different stakeholders to come together and have open conversations about RWE that focuses on the issues around RWE use, rather than representing interests of particular groups in conversations. This roundtable was noted as a first opportunity to begin such 'safe' dialogues, and it was hoped that this would lead to further progress in finding the most appropriate use for RWE in Canada.

A further issue that was noted as both a barrier and as a facilitator was the presence of **existing RWE data in Canada**. It was identified by a number of participants that there are isolated pockets of excellent RWE data across the country but that trying to bring data together, either from different regions or from different subject areas, was a major challenge in Canada (i.e., linking of data). In addition to data linkage issues, there are also broader policy concerns around the use of data for RWE gathering – due to complex issues such as privacy concerns, ethics panels and parochialism over the control of data.

Another issue identified by a number of participants, was the concept of **capacity building for RWE**. Capacity for RWE was mentioned in light of a number of types of capacity, including capacity for researchers to develop RWE, capacity for analysts to understand RWE, capacity for knowledge users

to be able to incorporate and interpret RWE, capacity for research on subjects outside clinical subject areas (such as sociology, complex-adaptive systems, etc.), as well as data capacity.

In terms of the capacity of researchers to develop RWE, it was noted that this could include provide training in issues such as HTA and health economics that could support RWE development. For analyst capacity, it was noted that due to the complexities of analysis and interpretation for RWE, having analysts able to provide understanding for RWE users would significantly increase the chances of RWE being used appropriately. For decision makers and proposed RWE users, it was noted that receptor capacity to be able to interpret and put RWE into practice would be an essential capacity component for successful use of RWE. In addition, the capacity of researchers from outside of the usual clinical and health economics groups was identified as being important for capacity to build and use RWE – especially with a desire to link disparate data sets including social data. In addition to people capacity, data capacity was noted as a major issue – particularly in light of the ability capture and share data, and even to capture complex linked data.

What next steps can we take for real world evidence today in Canada?

Moderator: Chris Henshall; Panel: Greg Rossi, Cy Frank, Adrian Levy, Anne MacFarlane, Vasanthi Srinivasan.

Based on the issues identified through the discussion, the participants were united in their view that RWE was an issue worth pursuing in Canada. However, it was also clear from presenters and participants alike that there was no easy or clear path to take in order for Canada to succeed in its use of RWE.

The first issue that needed to be addressed for Canada was where to start in further developing RWE in Canada – what are the clear next steps that could be taken in order for the country to become a leader in the use of RWE? In reality this can almost be split into two sections – the things that we should do (i.e., what would be best for Canada), and the things that we could do (i.e., what we can reasonably achieve in Canada).

What we should do

The challenge in Canada of a National (or pan-Canadian) versus a provincial approach to RWE is a complex one that requires the input of many stakeholders. However, one suggestion from the roundtable was to use **to set national ground rules for data** for RWE. For example, by developing a national policy on data collection and re-use, provinces could still collect data that is appropriate for their specific questions and needs, but would do so in a way that data could be linked across Canada (and be allowed to be used across Canada). One example of this approach mentioned that already exists in Canada was the presence of biomarker databases across Canada.

One of the major issues identified that should be addressed early in Canada was to consider the **incentives in the current health system** that do not support the use of RWE – or indeed provide much incentive for the use of evidence in making health care decisions (one example suggested was payment approaches for health professionals). This is a complex issue to address, and one that would undoubtedly take time, but incentivizing actions has been shown to be effective in the health system (e.g., payment for results approaches in the UK) and as such an incentives approach could prove very useful for improving RWE collection and use in Canada.

As noted above, there are also clear parallels from other countries that can shed light on the approaches to RWE that can work for Canada. This use of **international comparisons for RWE** is an approach that participants at the roundtable clearly considered a useful step in informing the growth of appropriate RWE for Canada. One issue bought up by a participant was the work of the European Healthcare Innovation Leadership Network on post-launch value assessment (PVA) for new health technologies. The PVA recommendations of the Network showcase the importance of RWE to clarify the value of new technologies, and to ensure their effectiveness is maximized. The work of multinational pharmaceutical companies was also noted in the area of RWE, since they have the capacity to investigate RWE use across jurisdictions where they may have to conform to payer demands for RWE. One example noted was that of AstraZeneca's pan-European work on comparative effectiveness research for diabetes.

What we could do

One actionable approach to improving RWE in Canada was the suggestion to **split RWE into different domains** based on the evidence gathering or analytical approach that it entails, and then to focus on the best ways to implement more appropriate use of that RWE approach where it is best suited. For example, this could be to focus on the use of observational data on safety to support health professionals in improving the safety of particular practices by supporting evidence gathering from health professionals and patients. This approach is heavily aligned with the concept of 'fit-for-purpose' evidence analysis in the health system.

Another action that could be taken immediately in Canada that was suggested, was to identify where we would want to **answer questions with new data**, and where we would want to **ask questions of existing data**. By clearly articulating which approach is best suited to a particular issue being addressed, Canada could clarify the role and the domain of RWE that would provide the most appropriate evidence to support decisions or change related to the health issue.

A common theme of the roundtable was the **role of the research and innovation system** in the appropriate use and uptake of RWE. By putting clear guidance on research into the health system, and clear guidance on RWE into the research system, it would be possible for both stakeholder groups to be more closely aligned to producing appropriate RWE for use in decision-making. One example of this approach identified was to expand the academic health science(s) systems approach that couples universities with care providers to embed a research culture into the health system. This approach could improve both data collection and analysis by health professionals. A more research-oriented approach could also be taken, similar to CIHR's Strategy for Patient Oriented Research (SPOR) that intends to increase patient-centered approaches to research and could easily be focused on RWE if appropriate. By aligning research initiatives with RWE, there is a clear benefit for the research initiative in building data to show real world impacts related to research investments, as well as health care investments.

Already noted earlier, the issue of **data privacy** was something that the roundtable returned to on a number of occasions. In terms of ways to improve RWE based on privacy and access to data issues, it was noted that currently patients in Canada assume their data are shared between health professionals and that extending this to using anonymized data for RWE purposes would not be unrealistic. In order for this to occur, there would need to be a more flexible and open approach to

data ownership than is currently seen across Canada, aligned with a clear approach to engaging patients in the benefits of health data informing RWE.

Finally, the presence of the roundtable itself was considered the first step in a journey to bring stakeholders together on issues around RWE in Canada. Apart from the opportunity to have honest conversations in a 'safe space' for all stakeholders, the roundtable also offered a starting point for the **sharing of RWE practices** from across stakeholders and across the country. This sharing of practices is likely to be vital in growing appropriate use of RWE in Canada – since it allows people to discover what has worked and when. This can then feed many of the other actions noted above (knowing what is fit for purpose in RWE, linking research and innovation to RWE in the health system, and addressing data privacy issues). It would also help to build capacity across the country and amongst different stakeholder groups by continually informing people of approaches and methods in place for RWE.

Next steps

While this was the first time that stakeholders in Canada have come together to discuss RWE, it will clearly not be the last. There was overwhelming consensus amongst participants that this meeting could be the springboard for further discussion – in particular to start shifting the focus from the initial conversations held at this roundtable, to more focus on the actions that stakeholder groups and regions can take either individually or together in order to drive the agenda forward on RWE use in Canada.

Appendix A: Background document for the roundtable

Real World Evidence: Backgrounder on the use of real world evidence to improve health system performance

Abstract: This paper provides an overview of the definition, use and development of real world evidence in health care decision-making. It assesses the situation in Canada as well as identifying approaches from other jurisdictions. The paper provides an overview of the barriers and facilitators identified for the further development and use of real world evidence in Canada (and beyond) and concludes with proposed approaches to taking the topic forward in Canada. The paper is designed to inform a national roundtable of Canadian stakeholders discussing real world evidence development and use. The paper provides a basis for discussions during the roundtable.

Introduction

Canadian decision makers are increasingly utilizing health technology assessment processes that include formal methods of economic evaluation (i.e. analyses of value for money or return on investment) to inform investment and dis-investment decisions in the health care system.[8,9] While such analyses can be conducted alongside clinical trials conducted to meet regulatory requirements, they are not ideal due to inherent limitations in the external validity of the results (i.e. efficacy vs. effectiveness).[10] More commonly, evaluations, including cost-effectiveness analysis are based on models that incorporate disparate sources of data. The primary limitation with these approaches are that the results are dependent on selection and availability of data sources as well as analytic and structural assumptions that are not always evident to those interpreting the findings.

Conducting evaluations using real-world data is a potential remedy to address the limitations associated with current approaches. These data could be primary data collected for the purpose of evaluation, or secondary data routinely collected in administrative databases (or prospectively through other means such as surveys, patient registries, or electronic medical records). These approaches are become more common in the health sector, with international and Canadian examples being put in place.

What constitutes real world evidence?

To be able to speak about RWE and its development and use, it is vital for us to be able to define it, and identify its constituent parts. Primarily, RWE can be considered to be "data collected in actual practice for many purposes and applied to prove or disprove a hypothesis that may have nothing to

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[8] Tarride, McCarron, Lim *et al.* (2008). Economic evaluations conducted by Canadian health technology assessment agencies: Where do we stand? *Int J Technol Assess Health Care*, **24**: 437–44.

[9] Battista, Côté, Hodge and Husereau (2009). Health technology assessment in Canada. *Int J Technol Assess Health Care*, **25**: 53–60.

[10] Avorn J (2007). In defense of pharmacoepidemiology--embracing the yin and yang of drug research. *N Engl J Med*, **357**: 2219–21.

do with its original remit".[11] Real world evidence is a broader concept than just observational studies to aid clinical decisions, it is evidence from a wide variety of different data types that can be used to additionally support needs assessment, administrative, and pricing and coverage decisions.[12,13] The data used to provide RWE can be organized by type of outcome (clinical, economic, patient-reported), research study design (pragmatic trial or observational study), and data source (supplementary data collection alongside RCTs, large simple trials, patient registries, administrative claims database, surveys, and medical records).[14]

The main components of RWE are existing health care databases. Traditionally that has meant health care administrative databases such as those designed to monitor hospital activities, but that is now expanding to include electronic health records, prescribing databases and patient registries. In addition to the administrative data, there is also evidence being developed specifically to address the real-world effectiveness and safety of new and existing therapeutics in Canada. This includes pricing strategies such as coverage with evidence development or conditional reimbursement,[15] and networked research approaches to bring together RWE from smaller scale evaluations of real world effectiveness and safety (e.g. CNODES – see page 13). Additionally, principles defining how conditional reimbursement and coverage with evidence development should work have also been developed in Canada, and these help to define how one aspect of RWE is collected.[16]

Supporting this definition and the components, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) created a Task Force on Real-World Data that set out their definition of RWE using a 'negative definition' (i.e. what RWE is, is defined against what it is not). It identified RWE as "data used for decision making that are not collected in conventional randomized controlled trials (RCTs)".[17] The characterization of the data that forms RWE for ISPOR included organizing by type of outcome (clinical, economic, patient reported), by hierarchies of evidence (by strength of research design) and by data source (supplementary data collection alongside RCTs, large simple trials, patient registries, administrative claims database, surveys, and medical records).[18]

One major challenge in the defining of RWE is that the data itself is simple to define, but the analysis of that data to provide evidence for decision-making is much more complex to define. Indeed, it is noteworthy that all definitions around RWE focus on the data itself, rather than the evidence that informs decision-making (the analysis and interpretation of that data).

Approaches in Canada

With Canadian most decision makers on health care distributed by province / territory, and data bodies spread across pan-Canadian, regional or provincial actors, trying to address how RWE is being

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[11] IMS Consulting Group (2011). *Real-world evidence: transforming the industry into the 'prove it works' era*. New York, NY: IMS Consulting Group.
[12] Sproule and Nason (2011). Edmonton, AB: Institute of Health Economics.
[13] Morgan *et al.* (2013).. *Healthcare Policy*, 8(4): 45-55.
[14] Ibid.
[15] Ibid.
[16] Menon, McCabe, Stafinski and Edlin (2010). Principles of design of access with evidence development approaches: a consensus statement from the Banff Summit. *Pharmacoeconomics*, **28**: 109–11.
[17] Garrison *et al*. (2007). Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value in Health*, **10**(5): 326-335.
[18] Ibid.

used and developed in Canada is a complex issue. Considering provinces/regions and then pan-Canadian initiatives gives us an approach to categorizing who is doing what – but the challenge still remains that RWE is something that does not sit simply within the current decision making 'geography' of Canada.

In addition, there is also evidence from the literature, that Canada has put in place a number of approaches to the use of RWE and the infrastructure to support it. For example, it has been noted that Canada has evolving primary care electronic health records and significant insurance claims datasets. However, the lack of accurate prescribing and compliance data make the use of good data in other areas more difficult to calibrate for decision-making.[19]

In addition to the data, there are also signs of progress in Canada on institutional frameworks around the use of evidence. For example, CADTH's role in reviewing medicines allows for the use of RWE in addition to (or replacing) randomized control trial (RCT) data. However, there is little evidence that CADTH reviews are yet using such data in the place of RCT data (or where RCT data does not exist).[20]

Recent research has identified four national approaches using RWE in Canada that were designed to help provincial payers avoid paying for non-responders.[21] One good example of this was the agreement that Merck-Frost entered into with provincial governments to cover the full costs of surgery for patients that did not respond to one year of treatment with their drug, finasteride.[22] Other examples from Canada of RWE use include: the use of data on hospitalization rates and in-hospital mortality to inform treatment guidelines for a cardiovascular disease drug (spironolactone); prospective observational studies on safety and effectiveness for procedures that affect launch and ongoing access for patients (e.g., limiting access to high risk surgical patients or those with particular conditions); and, economic simulation data linked to the application of new programs for diabetes (i.e. prospective cost-effectiveness studies using RWE).[23]

Ontario

In Canada, the province of Ontario has promoted the use of conditional funding with evidence development using primary or secondary data sources.[24] Some of the examples of RWE approaches in Ontario include the transfer from metal to drug-eluting stents for coronary artery disease patients based on the development of RWE on the effectiveness and safety of drug eluting stents against bare-metal stents.[25]

Another example from Ontario is the Ontario Biologics Research Initiative (OBRI). This is an approach that brings together multiple stakeholders from academia, industry, healthcare and the public sector in order to develop RWE on drug surveillance for rheumatoid arthritis biologics.[26] This

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[19] Hughes and Kessler (2013). *RWE Market Impact on Medicines: A lens for pharma*. London, UK: IMS Health.
[20] Ibid.
[21] Ibid.
[22] Hughes and Kessler (2013); Klemp, Frønsdal and Facey (2011). *Managed Entry Agreements: What Principles Should Govern the Use of Managed Entry Agreements?* Manuscript for IJTAHC (Policies).
[23] Hughes and Kessler (2013).
[24] Levin, Goeree, Levine *et al.* (2011). Coverage with evidence development: the Ontario experience. *Int J Technol Assess Health Care*, **27**: 159–68.
[25] Tu and Bowen *et al*. (2007). Effectiveness and Safety of Drug-Eluting Stents in Ontario. *N Engl J Med*, **357**:1393-1402
[26] Bombardier (2010). *The Ontario Biologics Research Initiative (OBRI): An Innovative Platform for Real-World Drug Surveillance and Evidence-Based Practice Indicators*. Poster Presentation, Toronto, ON: ICES. (Available at: http://tinyurl.com/prtkyca)

approach has proved so successful in generating information and engagement across stakeholders in fact, that OBRI has expanded and rebranded to become the "Ontario Best-practices Research Initiative" (still OBRI) – with a more general focus on RWE of rheumatoid arthritis interventions than simply biologics.[27]

Alberta

Alberta Health has set up guidelines around the development of evidence to support pricing decisions in the province.[28] These guidelines provide for the inclusion of evidence development as part of the explicit approach to pricing decision-making for the province. In addition, the Alberta Ministry of Health (Alberta Health) is increasingly looking at how to use broad evidence bases for an understanding of value for their health interventions and services (interviews and personal communication). Alberta Health also has other examples of RWE use from a non-pharmaceutical context. For example, the Alberta Health Technologies Decision Process (AHTDP) is working on the use of coverage with evidence development for technologies and services. It is also engaged in the use of RWE to support disinvestment and policy impact reviews.[29]

Quebec

Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) have been analyzing new therapeutics for the province since 2011, and have been developing ways to integrate RWE into their work in a way that goes beyond simple budget impact analysis to try and use RWE to support decision-making on effectiveness and safety.[30] One example of this approach from INESSS is in the use of bevacizumab (Avastin™) for off-label prescribing. In this case INESSS used RWE to support their analysis of the off-label use of Avastin™ in terms of better understanding of its safety and efficacy for its off-label use.[31]

Pan-Canadian initiatives

While public drug listing decisions are traditionally made at the provincial level – even taking into account the development of the Pan-Canadian Pricing Alliance (PCPA) – there are a number of pan-Canadian approaches to the understanding and development of RWE to support decision-making.

Canadian Network for Observational Drug Effect Studies (CNODES)
Developed by the Drug Safety and Effectiveness Network (DSEN) in 2011 with significant funds from CIHR ($17.5m), CNODES is a collaboration of over 60 researchers from across Canada who are working together to produce and analyze population-level datasets on drug safety and effectiveness. The ultimate aim for CNODES is to produce large datasets that can be rapidly accessed across the country in order to understand the risks associated with different medications.

Currently, CNODES has over 40 million people's health and prescription records available for analysis by its researcher members as the starting point in pharmacosurveillance research. In addition to

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[27] See: http://www.obri.ca/about-obri/
[28] Rawson (2014). Real World Data in Canada: Use, challenges and future directions. *Provincial Reimbursement Advisor*, **17**: 39-43.
[29] See: http://www.health.alberta.ca/initiatives/AHTDP.html
[30] Hughes and Kessler (2013).
[31] Bouchard et al. (2012). *Anti-angiogenic Drugs in the Treatment for Age-related Macular Degeneration: Issues Associated with Their Use in Québec*. Montreal, QC: INESSS. (Available at: http://www.inesss.qc.ca/en/publications/publications/publication/les-medicaments-antiangiogeniques-dans-le-traitement-de-la-degenerescence-maculaire-liee-a-l.html)

providing data and information to its researcher members, CNODES is also developing approaches to making information on medicine safety and effectiveness available to decision makers, clinicians and even patients.

CNODES has broken down their work into four main areas, each with a team of researchers assigned to it: Database, Methods, Training, and Knowledge Translation. In addition to these teams, CNODES has a central coordinating centre. This structure allows CNODES to develop expertise in specific aspects of the RWE use in decision-making. Thus far, some examples of CNODES work include: high-dose statins and the risk of acute kidney injury; proton pump inhibitors and the risk of hospitalization for community-acquired pneumonia; atypical antipsychotics and diabetic ketoacidosis (risk factors and incidence); and, statins and risk of diabetes.

Strategy for Patient Oriented Research (SPOR)
CIHR have recently (2013) instigated the Strategy for Patient Oriented Research (SPOR) as a new approach to improve the ability of the health system to provide the right patient with the right treatment at the right time. Within SPOR, one aspect is about developing provincial or regional Support Units, whose role will be to provide expertise and support to local researchers and groups working on patient-oriented research. Two major aspects of the work of Support Units will be to develop and maintain data platforms and services, and to support the work of real world clinical trials. Due to the new nature of SPOR Support Units (in that they are only now in 2014 starting to develop themselves) it isn't clear exactly how these aspects of SPOR will help in the collection and analysis of RWE to support decision-making. It is clear, however, that they will play a large role in the development and management of RWE at a regional or provincial level, and in the knowledge translation of that evidence to those in decision-making positions in the health system.

The Canadian Platform To Increase Usage of Real-World Evidence (CAPTURE)
Developed by the Canadian Partnership Against Cancer (CPAC) in 2011, CAPTURE is a web platform to support cancer-control and health-system planners in using evidence to inform decisions on the effectiveness of cancer therapies for individuals or groups of patients in particular contexts. CAPTURE will also in the future enable chronic disease prevention practitioners and program managers to assess and report on the results of their work and to learn from one another's experience. Since the launch of CAPTURE in 2011, 248 interventions have been logged and are available to help practitioners better evaluate the effectiveness of their programs and policies.[32] CAPTURE is an interesting story in the development of RWE in Canada since it currently focuses on interventions widely, and not specifically on new therapeutics. As such, it provides a different approach to capturing evidence for the health care system to consider in wider intervention development and application.

Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database
The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database is a multi-disease surveillance system based on primary care electronic medical record (EMR) data.[33] It uses data from multiple practice-based research networks that include physicians, and incorporates a number of different EMR systems (since these vary across provinces). With data that has been cleaned, coded and de-identified, it provides information on individuals with chronic conditions (diabetes,

[32] See: http://www.partnershipagainstcancer.ca/priorities/2007-2012-initiatives/primary-prevention-2007-2012-strategic-initiatives/the-canadian-platform-to-increase-usage-of-real-world-evidence-capture/ (Accessed March 10th 2014).
[33] http://cpcssn.ca/research-resources/cpcssn-data-for-research/

hypertension, osteoarthritis, depression, chronic obstructive lung disease, dementia, Parkinson's disease and epilepsy). The CPCSSN database provides the opportunity for significant studies into a number of areas including ongoing drug surveillance, infectious and chronic disease surveillance, and decision-making on patient safety.[34]

International lessons Other health jurisdictions outside of Canada are increasingly utilizing integrated information systems to provide real-world evidence in real time to make better informed resource allocation decisions to
improve patient outcomes while also promoting system sustainability.[35]

USA

As our nearest neighbour, and by far the largest single pharmaceutical market in the world, the US is often the first port of call in any international assessment of issues relating to the Canadian health care system. In the case of RWE, there have been a number of interesting developments in the US in recent years. One of the most important of those changes was the introduction of Comparative Effectiveness Research (CER), particularly with a boost in funding in 2009.[36] CER has been built around the need for better evidence on the effectiveness of new therapeutics in clinical practice (against existing practices), rather than a simple effectiveness RCTs. In 2010, the Patient Centred Outcomes Research Institute (PCORI) developed the guidelines for CER – in order to support the delivery of RWE for decision making in a patient-centered fashion.[37]

Building on this work around CER, the US Institute of Medicine (IOM) commissioned a workshop to address the issue of observational studies in the health system.[38] This workshop brought together multiple stakeholders to address the issues surrounding observations studies and how their data might provide value to the health care system. Their conclusions were around how observational studies can support a learning healthcare system, and how analysis and linkage to other data can create robust evidence for health care decision-making. The workshop identified several themes around methods for observational studies (to improve rigour, analysis etc.), policy related to observational studies (transparency of study approaches to improve policy uptake, setting funder requirements for observational studies), and stakeholder engagement (linking studies to stakeholder needs, stakeholder levels of understanding for complex analysis of observational data).[39]

At the level of individual health care institutions (and payers for pharmaceuticals), Kaiser Permanente is often mentioned in Canadian circles as an innovator in evidence-based health care. In terms of RWE, this is also true for Kaiser's approach to developing evidence of effectiveness for their interventions. For example, recent work funded at Kaiser is to compare "the long-term and real-

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[34] Keshavjee, Martin, Williamson and Birtwhistle (no date). Using CPCSSN Data in Primary Care Research: The Art of the Possible. Poster presentation. (Available at: http://cpcssn.ca/wp-content/uploads/2013/07/CPCSSN-Art-of-the-Possible-Poster-Jun-2013.pdf)

[35] Bornstein S (2012). An integrated EHR at Northern California Kaiser Permanente: Pitfalls, challenges, and benefits experienced in transitioning. *Appl Clin Informatics*, **3**: 318–25.

[36] Hughes and Kessel (2013).

[37] Manchikanti , Falco , Benyamin *et al.* (2011) The impact of comparative effectiveness research on interventional pain management: evolution from Medicare Modernization Act to Patient Protection and Affordable Care Act and the Patient-Centered Outcomes Research Institute. *Pain Physician*, **14**(3):E249-82.

[38] Institute of Medicine (2013). *Observational Studies in a Learning Health System: Workshop Summary*. Washington, DC: The National Academies Press.

[39] Ibid.

world effectiveness of initial management strategies for DCIS". The study uses data from a major cancer study on ductal carcinoma in situ (DCIS) and generates RWE on risks of recurrence and treatments for those diagnosed and treated for DCIS (including assessing specific surgery approaches, risk assessments for individuals, and safety and effectiveness measures).[40] The report of this study is yet to be made public, but it reflects a continued trend at Kaiser to use observational studies data to support their decision-making, particularly in oncology.[41]

While Kaiser Permanente is well known in Canada, major payers for pharmaceuticals such as WellPoint have not commanded as high a profile. However, WellPoint provides an interesting case in the use of RWE in the US.[42] As a major private insurer and payer for drugs, WellPoint has developed an 'outcomes based formulary' that links their purchasing choices to outcomes evidence. The guidelines underpinning the use of evidence for the WellPoint formulary emphasize the importance of randomized, active comparator, naturalistic trials in supporting the clinical and cost-effectiveness case for a drug product, and the need to monitor and validate claims made for the product over its life cycle.[43]

From the point of view of independent consultancies also getting involved in RWE in the US, IMS has been particularly active. The main work of IMS in this field in the US has been to develop 'Pharmetrics Plus' – a comprehensive database of over 150m individual health plan claims data harvested from across the country and with de-identified but detailed records allowing linkage to other datasets.[44] This dataset provides the basis for a wide variety of RWE studies to support decision making, including: cost of care; adherence and persistence to treatment; prevalence and safety; market access initiatives and HTA readiness; and commercial activities such as adherence and compliance programs and patient flow mapping.

UK

The UK is often held up as a positive example of the way that RWE can inform decision making in the health care system.[45] One major reason for this position is the presence in the UK of the National Institute for Health and Care Excellence (NICE – formerly the National Institute for Clinical Excellence). NICE has been active in the application of RWE for its decision making on new therapeutics – putting in place systematic review processes that engage RWE as well as clinical trial data (e.g. the use of comparators, reference populations, and value metrics such as QALYs).[46]

The ability of NICE to request such approaches is based heavily on the ability of the UK to capture real world data through its NHS IT systems; it's pay-for-performance data on physicians; and national observational datasets such as the CPRD (Clinical Practice Research Datalink). CPRD is considered by

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[40] See: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=711

[41] The Advisory Board Company (2013). The Daily Briefing: How Kaiser Permanente uses effectiveness data to cut costs. Available at: http://www.advisory.com/daily-briefing/2013/06/11/how-kaiser-permanente-uses-effectiveness-data-to-cut-costs

[42] Hughes and Kessel (2013).

[43] Sweet *et al.* (2005). The WellPoint Outcomes Based FormularySM: enhancing the health technology assessment process. *Journal of Medical Economics*, **8**(1-4): 13-25.

[44] IMS Health (2012). *IMS LifeLink PharMetrics Plus™ – U.S.: Real World Evidence-Real World Impact*. Alexandria, VA: IMS Health.

[45] For example, the UK was ranked #1 in IMS Health's recent analysis of international approaches to RWE use (Hughes and Kessler: 2013).

[46] Hughes and Kessler (2013).

many in the UK as equivalent to producing clinical trials data (meeting the so called 'Gold Standard) and its usage by researchers has resulted in nearly 900 clinical reviews and papers.[47] Interestingly, despite the development of such strong datasets in the UK, there are still significant challenges faced in terms of data linkages (partly due to the devolved nature of the health care system in the countries in the UK).[48]

In terms of the link of RWE in the UK to decision making on new therapeutics, there is good evidence that the UK approach is leading to a wide variety of different styles of RWE implementation in decision-making. This includes coverage with evidence development approaches and ongoing access decisions. In addition, NICE also produces guidelines for drugs across their lifecycle that builds on RWE. In an IMS analysis of international RWE use, they noted 16 case examples of RWE in therapeutics decision making.[49]

Australia

While Australia is not a leader in the use of RWE, there are some examples of where specific Australian studies have provided significant data to use in RWE-based decision-making. One such example is a study on the HPV vaccine (Gardisil). In this study, covering patients from across Queensland, significant amounts of data were developed on the effectiveness and safety of human papillomavirus (HPV) vaccination in young Australian women.[50] The study showed clearly the differences in effectiveness of the vaccine based on the dosage levels provided to patients. However, since this is new research, the decision making in the health system that could be linked to this study is currently absent.

Nationally, Australia is increasingly interested in RWE, with the 2009 government review of the HTA capacity in Australia citing a need for increased post-market surveillance and its associated use of RWE.[51] These recommendations around post-market surveillance include the recommendation to improve selective use of national patient registries such as the National Joint Replacement Registry (NJRR). This recommendation comes with the explicit acknowledgement that for RWE from national registries to be successful there will need to be buy-in from GPs and physicians who manage medical records. The HTA review in Australia also identified the need for better data linkage, and strategies and standards for the use of RWE in investment decisions for new technologies.

Sweden

Sweden is notable in the international RWE landscape as somewhere with high quality, linked datasets on RWE. These datasets cover primary and secondary care with nearly 100% coverage.[52] Not only is there excellent population coverage, but the use of national ID numbers in Sweden has also allowed data to be linked across databases while remaining de-identified. The use of RWE in Sweden is also strong, with national organizations such as the TLV (The Dental and Pharmaceutical Benefits Agency) and SBU (the Swedish Council on Health Technology Assessment) both outlining

[47] http://www.cprd.com/intro.asp
[48] Hughes and Kessler (2013).
[49] Ibid.
[50] Crowe *et al.* (2014). Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia *BMJ*, **348**:g1458.
[51] Department of Health and Aging (2009). *Review of Health Technology Assessment in Australia*. Canberra, Australia: Government of Australia.
[52] Hughes and Kessler (2013).

how to use RWE in making health care purchasing and coverage decisions.[53] There have also been examples of RWE developed by pharmaceutical firms informing coverage decisions in Sweden, such as the presence of Atacand™ on Swedish formularies.[54]

Netherlands

The Netherlands has a long history of RWE use in decision-making, and as such it has developed specific programs and organizations to support data collection for RWE use. These include PHARMO and IPCI.[55] PHARMO is an independent organization that maintains a large database network on real life patient data that it uses to perform its own studies on epidemiology, drug utilization, drug safety, health outcomes, and utilization of healthcare resources, as well as providing evidence to support risk management, outcomes research, market access and health economics decision making.[56] IPCI is the Integrated Primary Care Information database housed at Erasmus University in Rotterdam. It provides GP maintained electronic patient records for use in academic studies and post-market surveillance of new drugs by pharmaceutical companies.[57]

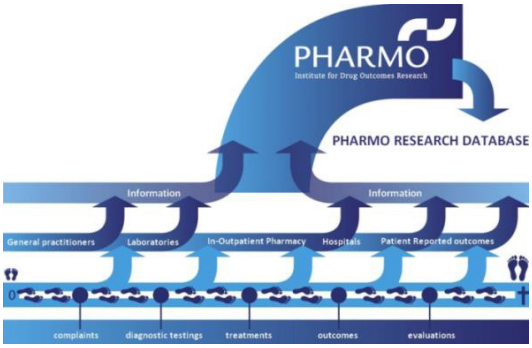

Figure 3. PHARMO database and its underpinning data

In addition to the data available for RWE use, the Netherlands also has policies and guidance on the use of RWE in decision making, through organizations such as CVZ (the Dutch Health Care Insurance Board) with their guidance on which databases to use for RWE, and ZonMW (the Netherlands Organization for Health Research and Development) with their subsidy programs for measurement of adherence, efficiency and outcomes.[58] Indeed, at a national level, the Netherlands uses a four-year RWE planning approach to determine whether high cost drugs should be used in hospitals.[59]

Trans-national approaches

While it is not common for any decision making group to work across national borders, pharmaceutical companies and, increasingly, consultants often work trans-nationally.

Pharmaceutical companies are developing their own capabilities to address the collection and analysis of RWE (ostensibly since many of the major markets are now requiring such capacity). One excellent example of this is the move by AstraZeneca to increase their own development and analysis of RWE, including partnering with other relevance organizations to support RWE collection.[60] Internationally, AstraZeneca already has RWE partnerships with the Health Authority of Abu Dhabi in Saudi Arabia, and the Murcian Health Authority in Spain. These partnerships offer joint expertise

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[53] Ibid.
[54] Eklind-Cervenka, Benson, Dahlström *et al*. (2011). Association of candesartan vs losartan with all-cause mortality in patients with heart failure. *JAMA*, **305**:175-182.
[55] Hughes and Kessler (2013).
[56] See: http://www.pharmo.nl/about-us/who-we-are
[57] See: http://www.erasmusmc.nl/med_informatica/research/555688/?lang=en
[58] Hughes and Kessler (2013).
[59] Ibid.
[60] Keohane (2011). The reality of 'Real World Evidence': An industry point of view. Presentation to ISPOR. Available at: http://tinyurl.com/nzb4cj5 (Accessed March 14th 2014).

and learning to support understanding of cardiovascular and chronic obstructive pulmonary disease (COPD).[61]

Perhaps more interestingly is the role that consultants are now playing in transnational approaches to RWE. These roles range from providing expertise and consulting on the development and delivery of RWE systems for organizations (including data analytics approaches that could make a large difference to the ability to use RWE in decision making in different jurisdictions),[62] to the housing of large amounts of evidence and literature on RWE activities around the world.[63] Despite growing capacity within the private sector, there remains a great opportunity for standardization and learning across international borders.

Barriers and facilitators to using real world evidence

Leveraging existing secondary data sources to support health technology assessment are appealing to decision makers in Canada but actual implementation is uncommon. Understanding some of the main barriers to RWE use and the facilitators for its uptake are key in developing conversations between stakeholders in RWE in Canada.

Barriers

A number of structural barriers have been identified in the literature around RWEs in Canada.[64] These identified barriers were reconfirmed and added to by the small number of interviewees involved in this project – suggesting that there are some significant hurdles for RWE to overcome if it is to be implemented more widely in Canada.

Alignment of processes and incentives

One commonly cited barrier is around aligning processes and incentives between analysts and policymakers.[65] Within this concern is the issue of ensuring that all parties are able to clearly see the rigor and veracity of the analysis of the RWE, and be able to agree on its implications for decision-making. This is a challenge where the incentives for those in industry differ from those in government around pricing decisions for example. This was highlighted in interviews where individuals suggested that the conflict between the needs of industry and those of decision makers and analysts makes the practical implementation of RWE particularly challenging in Canada.

Collection and analysis

Additionally, there are barriers related to the way RWE is collected and analyzed.[66] Literature cites challenges around the adequacy of study design, timeframe available for conducting studies, and the challenges in measuring and valuing policy-relevant outcomes.[67] In addition, interviews noted the challenge of agreement on the most appropriate analysis approach for RWE, since the data itself can be analyzed in a number of ways that can all potentially support different decisions. This is similar to

[61] Ibid.
[62] http://www.hcltech.com/lifescience-healthcare/rwe-data-analytics
[63] http://www.imsheorbibliography.com/
[64] For examples, see: Berger, Mamdani, Atkins and Johnson (2009). Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report--Part I. Value. *Heal J Int Soc Pharmacoeconomics Outcomes Res*, 12: 1044–52.
[65] Berger, Mamdani, Atkins and Johnson (2009); Keohane (2011).
[66] Garrison *et al*. (2007).
[67] Berger, Mamdani, Atkins and Johnson (2009).

another barrier identified with acceptability of decision-making based on non-randomized studies, and concerns about validity attached to those decisions.

Data access
Access to data is also cited as a barrier in furthering RWE. From the private sector's point of view this challenge comes from the ability to access provincial health system data on the outcomes related to their products (either through not being allowed to access the data at all, or through complex ethics and policy approval processes making access difficult).[68] This issue is compounded by the fact that data is managed by physicians, rather than by provincial systems – meaning that individual physicians can play a large role in determining the quantity and quality of data available for RWE. From the public sector point of view data access relates to the data that is currently being collected by pharmaceutical companies, where the need for proprietary data makes access to full datasets impossible for those working in the public sector. This challenge is exacerbated by the relationship between the private and public sectors, where there is little trust in the analyses performed within each sector and the relevance of those analysis findings (see the above barrier on analysis challenges).

Willingness to use RWE
Another challenge noted in Canada has been around the willingness of decision makers to actually use RWE instead of requiring RCT data. The interviews suggested that while there are guidelines in place for decision makers on the use of RWE, there is still a mindset that without RCT data, the evidence to support decision-making is not strong enough and RWE is therefore not considered appropriate.

Inter-provincial RWE
One barrier identified at the decision-maker level was the acceptability of using RWE for provincial decisions that originated outside of their own jurisdiction. Interviewees suggested that it is a considerable challenge to get inter-provincial RWE to be considered for decision-making as provincial decision makers are concerned about how RWE would apply to their own provincial context.

Harvestable offsets
The final barrier identified is specifically around how RWE might impact the decision making process. While issues of 'harvestable offsets' are wider than the issue of RWE and its involvement in decision making, it is clear that the ability to use evidence to inform decisions that has effects beyond the drug budget for a province is still a challenge to take forward in government.[69] The reason for this is the inability to harvest in the drug budget any savings made in hospital or care budgets that come as a result of improved evidence on drug effectiveness or safety. Without this incentive to use RWE in order to realize these savings, the incentive to improve RWE use in decision-making for drug-related decisions will remain a challenge.

Facilitators

The facilitators for the use of RWE in Canada are widespread and reflect a desire across stakeholders to use RWE if it is deemed appropriate.

[68] Rawson (2014).
[69] Ibid.

Desire to use RWE
The first of these facilitators is the desire shown by those in both the private and public sectors to engage in the use of RWEs. This is clear from the development of things such as PLA guidelines for provincial drug pricing, the guidelines for the use of RWE in national analysis groups such as CADTH, and the movement of pharmaceutical firms to deliver products in a way that includes the development of RWE to support more nuanced decision making.

Data collection
In addition to this shared desire, there is also a wealth of data being collected and monitored across Canada. This can be seen in the increasing volume of electronic health data being maintained across the country.[70] It can also be noted in the development of increasing numbers of data storage and analysis groups from the pan-Canadian level (Statistics Canada, CIHI) through to the provincial level (e.g. Manitoba Centre for Health Policy, Institute for Clinical Evaluative Sciences). With increasing data availability, the prospect of using RWE in decision making becomes one of analysis and linkage, rather than one of collection. There are also increasing numbers of pan-Canadian initiatives involved in developing and analyzing RWE in Canada (see page 13).

Analysis and linkage of data
Analysis and linkage are also a reason for encouragement in Canada. For example, in Ontario, the Institute for Clinical Evaluative Sciences (ICES) are engaged in linking multiple datasets on health and social care outcomes in order to better understand real world outcomes (personal communication). There is also evidence from the interviews to suggest that datasets in the public domain are also becoming more closely linked to those in the private sector. One example of this is the work on validating Canadian primary care electronic medical records that has brought together academics, those working on provincial data, consultants and the pharmaceutical industry.[71]

International experiences
Finally, the ability to learn from international experiences in RWE is a reason for optimism in Canada. There are numerous forums in place across the country that are actively looking to engage with knowledge developed internationally. This includes forums such as the one developed by the Institute for Health Economics that this background paper is designed to support. It is clear from the literature that engagement across stakeholders will be important in moving this issue forward,[72] and the ability for forums to engage groups and provide lessons from multiple jurisdictions will be important in developing RWE in Canada.

Potential ways forward for Canada

While there are barriers and facilitators in Canada, there are also a number of potential approaches to move RWE forward that have either been identified in the literature or through the interviews for this process.

Publicly funded infrastructure for data collection and analysis

As noted above, there is a significant challenge and an opportunity around the use and analysis of real world data. One of the major challenges associated with this is the accessibility of data. It was

[70] Hughes and Kessler (2013); Rawson (2014).
[71] Dziarmaga, Frise, Tarride and Corner (2014). *Validation of a Canadian Primary Care Electronic Medical Record Database*. Poster Presentation.
[72] Garrison *et al*. (2007).

suggested in an interview that one approach to addressing the data access issue would be to develop some form of publicly funded infrastructure for real world data collection and analysis. Currently, Canada is moving towards publicly funded data infrastructure for electronic medical records, and it is not a significant leap to consider also developing infrastructure to collect data on patient outcomes related to interventions. However, the challenge in managing this data is around aggregation (the need for similar datasets across provinces) and analysis (the ability to analyze very large and complex patient datasets). Developing pan-Canadian public infrastructure for this could address those two issues, as well as dealing with issues such as free-rider problems, privacy issues (since aggregated data is easier to de-identify) and structural issues in data consistency.

Clear guidelines on use and analysis of real world evidence

One clear potential way forward for Canada (or indeed any jurisdiction) is to develop some clear guidelines on the use and analysis of RWE.[73] By developing some standards around approaches to data collection and analysis, as well as on interpretation and use in decision-making, it will be possible to frame RWE in a way that allows all stakeholders to understand their role in moving from developing evidence to its use in decision making. This can reduce duplication of effort and ensure that data and analyses that are developed are appropriate and trusted by all parties.

Focus on data for patient care, rather than data for pricing

With the need for RCT data in the analysis of new drugs and therapeutics, it seems pertinent to mine the increasingly rich seam of data on effectiveness and safety that is being developed across Canada. In addition, the infrastructure to capture data on patients and the practice of medicine is one that is already in existence and much less complex than the multi-sectorial infrastructure that needs to be developed to provide RWE for pricing decisions (i.e. to build infrastructure that can deal with private sector data and public sector data and their respective privacy issues). Focus on the practice level of medicine can build understanding and standardization for RWE, and also help to develop true understandings of patient pathways through health care that can inform provincial decision on care approaches.

Further collaboration and engagement across stakeholders

Both the document review and the interviews are clear in their assessment of the need for greater collaboration between different stakeholders in the development, analysis and use of RWE for decision-making.[74] This requires an ability to bring together all groups involved in the capture, storage and analysis of data, as well as those who are likely to use RWE to be able to support decision-making. Developing some form of ongoing forum in which the stakeholders in RWE can engage will allow the concept of RWE to develop further in Canada. Any such forum will need to explicitly link to decisions and action to implement RWE where appropriate, as well as being able to partition responsibilities amongst players to ensure that RWE can be furthered by the right people in the right place. The IHE roundtable on RWE is the starting point for just such a forum.

[73] Garrison *et al*. (2007).
[74] Rawson (2014); Garrison *et al*. (2007); Keohane (2011).

Appendix B: Stakeholder groups interviewed

Below we identify the stakeholder groups represented in the interview process for this work.

Stakeholder Group
Academics
Data holders
HTA organizations
Consultant Groups

Appendix C: Interview protocol

- What constitutes RWE to you?
- What approaches do you know of in Canada/internationally that are examples of good or novel practices?
- What do you see as barriers and facilitators in using RWE?
- What do you see as potential ways forward for Canada in the use of RWE?
- Is there anything that we haven't talked about in this interview that we should have?