Canada's Drug and
Health Technology Agency

CADTH Methods and Guidelines

Guidance for Reporting Real-World Evidence: Response to Stakeholder Feedback

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

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Executive Summary

This initiative forms the foundation for transparent reporting of real-world evidence (RWE) studies in Canada and facilitates appraisal of RWE for the purpose of supporting decision-making.

Guidance for Reporting Real-World Evidence was developed by a working group (WG) that included representatives of Health Technology Assessment (HTA) organizations, regulators, methods experts, and pan-Canadian data holders.

Guidance for Reporting Real-World Evidence aligns with international principles for decision-grade RWE, and is consistent with documents previously issued by CADTH, the Institut national d'excellence en santé et en services sociaux (INESSS), and Health Canada. As such, the guidance is neither more restrictive nor more demanding than current global standards.

Importantly, not all recommendations may be applicable and differing components of the guidance should be applied as appropriate, depending on the study design.

The principles in this guidance document will be adopted by Health Canada, CADTH, and INESSS. Each of the partnering organizations intends to use the guidance as appropriate to their individual organization's needs, while remaining anchored by the principles outlined in the document.

CADTH will subsequently develop implementation procedures for how RWE will be appraised, and how deliberative committees will use RWE in decision-making, with appropriate submission templates and other tools. This implementation work will include collaboration with patients, industry, and committees.

Guidance for Reporting Real-World Evidence will be most relevant to those developing evidence for submissions to regulatory and HTA bodies, as well as those who review and appraise evidence for health technologies in Canada.

Presentations were organized for key regulatory personnel and HTA advisory and deliberation committees. Additionally, stakeholder engagement was sought through a series of meetings, public information sessions, and a 6-week public consultation and stakeholder feedback period.

This Response to Stakeholder Feedback report summarizes feedback received during the consultation period on the draft version of the guidance document.

Fifty-four written submissions were received during a public consultation period, with two-thirds of the comments coming from the pharmaceutical industry, the patient community, and RWE service providers.

Feedback was organized into 9 major themes:

- Health System
- Data Considerations (Canada, International)
- Standards (Principles) and Methods
- Implementation Considerations

- Patient Engagement
- International Alignment and Harmonization
- Clarity, Readability, and Accessibility
- Consent, Privacy, and Confidentiality
- Research Ethics Approval

Major themes were responded to by the Guidance for Reporting Real-World Evidence WG, with additional responses from Health Canada from the regulatory perspective and from CADTH and INESSS from the HTA perspective.

Fifty-one RWE reporting–specific issues were identified from the feedback and included in a survey, with 8 issues discussed due to a lack of consensus (less than 70% agreement) by the Expert Methods Panel. Of the 51 issues, all but 6 resulted in modifications to the guidance document.

Future work will include more in-depth engagement with the patient community to better understand patient perspectives on the integration of RWE into decision-making.

Introduction

CADTH, Health Canada, and INESSS collaboratively embarked on a goal to create a foundation document to promote transparent reporting of RWE studies being submitted to regulators and HTA agencies. Transparent reporting will enable respective health system stakeholders to appraise the quality of the work submitted.

External stakeholder engagement and feedback were sought on the draft guidance document through a series of workshops and meetings, and through public consultation. Presentations were organized for key regulatory personnel and HTA advisory and deliberation committees. Stakeholders at the various input meetings and workshops included patients and patient organizations, health care professionals, data holders, research networks, academics, national and international regulators and HTA bodies, pharmaceutical and research organizations, commercial RWE service providers, professional societies, and others.

After a series of public information sessions, a consultation period for the guidance document was launched on November 10, 2022, and continued through to January 6, 2023. The number and types of stakeholders who provided formal feedback during this consultation period are listed in Table 1. The majority of the feedback received came from the pharmaceutical industry, the patient community, and commercial RWE service providers.

Table 1: Stakeholder Feedback by Category

Stakeholder category	Number of stakeholders, n (%)
Pharmaceutical industry	19 (35)
Patients and patient organizations	13 (24)
Commercial real-world evidence service providers	7 (13)
Researchers and academics	4 (7)
General public	3 (6)
Governments	3 (6)
Health system partners	2 (3)
Data holders and registries	1 (2)
Private drug plans	1 (2)
Professional societies	1 (2)
Total	54 (100)

Stakeholder Feedback

This Response to Stakeholder Feedback report summarizes the feedback received by theme and describes the process used to revise the guidance document. All feedback received was reviewed by the Methods Authorship Team and the Leadership Review Team. Specifically, members of the Methods Authorship Team and Leadership Review Team independently reviewed the feedback and grouped comments into themes that could either be applied throughout the document (e.g., consistency of language) or represented RWE reporting–specific feedback. The final list of major themes was determined by consensus between the Methods Authorship Team and Leadership Review Team. In addition, the Methods Authorship Team identified specific methodological issues that were used to inform the development of a survey of the Expert Methods Panel.

Themes included both methodological issues and health system issues related to HTA and regulatory approval.

Major themes were responded to on behalf of the Guidance for Reporting Real-World Evidence WG as a whole, which included the Expert Methods Panel, the Methods Authorship Team, and the Leadership Review Team. Where relevant, additional responses were added by Health Canada from the regulatory perspective and by CADTH and INESSS from the HTA perspective. Stakeholder feedback about nonmethodological topics were addressed in this response document or were recommended for further exploration in future work, or for consideration as part of other initiatives.

Fifty-one specific methodological issues were identified among the major themes. These issues were addressed through a survey and discussion with the Expert Methods Panel. Major revisions to the document to address RWE reporting–specific feedback were presented to the Expert Methods Panel for final approval

and were included or excluded based on whether there was 70% or greater consensus from the Panel. Items not reaching 70% consensus or flagged by a panel member were discussed in an Expert Methods Panel meeting and revised or excluded.

The recommendations in the *Guidance for Reporting Real-World Evidence* document were then revised by the Methods Authorship Team. All members of the Expert Methods Panel and the Leadership Review Team were given an opportunity for a final review of the revised Guidance for Reporting Real-World Evidence document.

This Response to Stakeholder Feedback document is divided into 2 sections:

- Major Themes
- RWE Reporting–Specific and Technical or Methodological Feedback

Major themes included:

- Health System – Considerations for Regulators (Health Canada), HTAs (CADTH, INESSS), and Payers (Federal, Provincial, and Territorial; Private)
- Data Considerations (Canada, International)
- Standards (Principles) and Methods
- Implementation Considerations (Procedures, Processes)
- Patient Engagement
- International Alignment or Harmonization
- Clarity, Readability, Accessibility, and Other Factors to Facilitate Adoption
- Consent, Privacy, and Confidentiality
- Research Ethics Approval

In section 1, for each major theme and its specific items, a response is presented from the Methods Authorship Team on behalf of the entire Guidance for Reporting Real-World Evidence WG, with additional responses presented from the HTA or regulatory perspective (Tables 2 to 10).

In section 2, the 51 RWE reporting–specific and technical issues that were presented to the Expert Methods Panel as part of a survey are described, in addition to the results of the survey and changes to *Guidance for Reporting Real-World Evidence*, or any other actions. Details of this process are described fully in the *Guidance for Reporting Real-World Evidence* document in Appendix 1. Minor feedback outlining typographical errors, grammatical corrections, and sentence structure changes were made but were not described (Table 11).

Section 1: Major Themes

Table 2: Health System — Considerations for Regulators (Health Canada), HTAs (CADTH, INESSS), and Payers (Federal, Provincial, and Territorial; Private)

Feedback received	Response from Guidance for Reporting Real-World Evidence WG[1]	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Alignment of Health Canada, CADTH, and INESSS regarding *Guidance for Reporting Real-World Evidence* 2. Consistency with other Health Canada, CADTH, INESSS documents 3. Need for collaboration across decision-makers (regulators, HTA, and payers) 4. Use of special access program for RWE generation	Health system implementation feedback not addressed by Methods Authorship Team.	*Guidance for Reporting Real-World Evidence* was developed with the intention of promoting alignment on principles for reporting RWE, as well as consistency with other documents previously issued by either CADTH, INESSS, or Health Canada. INESSS agrees with the principles and best practices to report RWE in submissions. It is in line with previous and actual work being conducted within the organization. Note: The definition of RWE used in this document will be consistent with the definition as per Health Canada. Recognizing various definitions of RWE, the practical approach is to ensure a consistent definition in use by the Canadian regulator and HTA.	*Guidance for Reporting Real-World Evidence* was developed with the intention of promoting alignment on the principles for reporting RWE, as well as consistency with other documents previously issued by either CADTH, INESSS, or Health Canada. Health Canada continues to collaborate with both domestic and international partners to further advance alignment and harmonization in the RWE space wherever possible. While the principles captured in this guidance document are generally applicable to all situations where the goal is to generate high-quality RWD, regulatory decision-making requires additional and unique considerations that are beyond the scope of the guidelines. Early engagement with Health Canada during the development of any RWD or RWE protocol is important and recommended. Expansion of the special access program to analyze RWD is not currently planned but could be considered when more experience has been gained with more traditional RWD sources such as registries.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; RWE = real-world evidence; WG = working group.

[1]The Guidance for Reporting Real-World Evidence WG included the Methods Authorship Team, Leadership Review Team, and Expert Methods Panel.

Table 3: Data Considerations (Canada, International)

Feedback received	Response from Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Data sources 2. Data infrastructure resources 3. Data quality 4. Transparency (database, study design)	*Guidance for Reporting Real-World Evidence* is intended to establish which components of the data used for a given submission should be reported to maximize transparency and facilitate assessment. Because data availability, components, and quality can change over time, endorsing specific data or vendors would be challenging. Moreover, submissions using the same data source may also choose to use or manage data components differently for the particular question of interest and methods used. However, ongoing work with major Canadian data holders that can be leveraged to better understand the components and quality of data, and be referenced within a submission, is highlighted. The "Data Cleaning" section regarding the use of unstructured data has been updated, and current tools that can be leveraged when searching for best practices regarding data cleaning and quality of these data have been cited.	Principles for reporting of data are outlined in this iteration of *Guidance for Reporting Real-World Evidence*.	Principles for reporting of data are outlined in this iteration of *Guidance for Reporting Real-World Evidence*. Data should be fit-for-purpose, reliable, and of high-quality, and should be collected based on a prespecified, comprehensive procedure when submitted to Health Canada. Evaluating RWE in the context of regulatory decision-making depends not only on the evaluation of the methodologies used to generate the evidence, but also on the reliability and relevance of the underlying RWD. Early engagement with Health Canada is therefore encouraged. The Department continues to explore ways of promoting greater transparency in collaboration with international partners, as described in the International Coalition of Medicines Regulatory Authorities (ICMRA) statement on international collaboration to enable RWE for regulatory decision-making.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; RWE = real-world evidence; WG = working group.

Table 4: Standards (Principles) and Methods

Feedback received	Response from Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Methods-related comments, including study design, data	Responses for the Methods-related theme are addressed by the Expert Methods Panel in section 2.	This first iteration of *Guidance for Reporting Real-World Evidence* is intended to outline	Evaluating RWE in the context of regulatory decision-making depends

Feedback received	Response from Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
generation and analysis, reporting, and interpretation of results		the principles to report RWE studies. This guidance applies to all stakeholders who report on RWE studies to support decision-making, including academic partners and CADTH's own programs. If a design method was not specifically addressed in this guidance document, issues raised in the received feedback will be explored further, as part of future work on CADTH's RWE guidance documents. Future CADTH work will include the development and implementation of HTA appraisal methods for submitted RWE to support interpretation of the studies.	not only on the evaluation of the methodologies used to generate the evidence but also on the reliability and relevance of the underlying RWD. Early engagement with Health Canada is therefore encouraged. If feedback is not specifically addressed in this document, the issues raised will be explored further as part of future work. Health Canada continues to participate in a variety of initiatives related to the development of RWE principles and methodology.
2. Application of principles to non-drugs (devices) and rare diseases	The current broad scope of the guidance is purposeful as the guidance is designed not only for drugs, but also for devices, technologies, and other interventions, recognizing that they each present their own unique methodological challenges. Many of these methodological challenges are related to treatment of rare diseases, and as such, the framework of the guidance is flexible to allow for further advancement or expansion in future efforts. Additionally, an "Implementation Recommendations" section has been included to outline considerations for implementation of the guidance (e.g., flexibility of its use in various applications) and the development of methods extensions.	This document outlines principles and best practices to report RWE that applies to both drugs and devices.	No additional comments from Health Canada.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; RWE = real-world evidence; WG = working group.

Table 5: Implementation Considerations (Procedures, Processes)

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Use of RWE for regulatory, HTA, and payer decision-making 2. Comments or questions about regulatory and HTA processes 3. Questions or comments specific to payers	This document is a crucial first step toward the end goal of integrating RWE into decision-making in Canada. To start tackling these important next steps, it is essential that standards for reporting and methodological considerations be established to develop trust in RWE as a source of evidence. This trust must be established to develop the appropriate integration of RWE into decision-making. The introduction highlights how and where this document can be used now and in the future. Although many of these suggestions were included in various sections in the original draft, these are now also included in a new section titled "Implementation Recommendations."	The current document outlines principles and best practices. CADTH will develop implementation procedures for how RWE will be appraised, and how committees will use RWE in decision-making, with appropriate submission templates and other tools in collaboration with patients, sponsors, and committees. INESSS has recently updated its Drug Submission Guidelines to reflect the increasing interest toward RWE. Implementation work is still ongoing and will build on the RWE Guidance with a particular attention to the Quebec context. CADTH will collaborate with INESSS on understanding and aligning implementation activities.	The current document outlines principles and best practices. Health Canada continues to encourage high-quality RWE submissions that aim to expand evidence-based indications for populations often excluded from clinical trials; for drugs or diseases where clinical trials are unfeasible; and/or where clinical trials are unethical, as described in the "Optimizing the Use of RWD to inform Regulatory Decision-Making" notice to industry. The quality of the RWE will inform the extent to which Health Canada considers such information sources in regulatory decision-making. There are factors to consider when evaluating quality of evidence, including data reliability and validity, scientific questions of interest, study design, statistical methods and analyses, and interpretation of results. An overview of protocol elements and data quality that should be considered when collecting data and evaluating the quality of RWE can be found in Health Canada's "Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle" document. When RWD or RWE is intended for regulatory purposes, early consultation with Health Canada is encouraged so that critical elements — such as the reliability and relevance of the proposed RWD and the methodologies proposed to generate the evidence — are

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
			discussed and agreement in principle can be obtained.
4. Evidentiary "bar" for different types of RWE, depending on evidence gap or research question	There is agreement with feedback from stakeholders that RWE studies are not just limited to studies exploring the effectiveness and safety of health technologies. Importantly, safety and effectiveness studies are often the most complex, and thus the considerations for reporting and methodological issues are more extensive. To maximize usability of the document, it was written for the highest level of complexity of RWE while allowing flexibility for less complex RWE.	For RWE studies and designs not focused on safety and effectiveness outcomes, many of the sections in this document may not apply. To communicate how this guidance may be leveraged in practice, a section entitled "Implementation Recommendations" has now been included. In this section, it is explicitly stated that various designs (e.g., drug utilization studies, burden of disease studies) may not require reporting of all sections and adherence to all recommendations of this guidance. This and other implementation considerations are planned for future work on CADTH's RWE guidance documents.	No additional comments from Health Canada.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; RWE = real-world evidence; WG = working group.

Table 6: Patient Engagement

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Need for more, and better, patient engagement to ensure patient perspective is included in *Guidance for Reporting Real-World Evidence*.	This *Guidance for Reporting Real-World Evidence* document is a technical document about the principles on how to report RWE.	The current document outlines principles and best practices to assist sponsors and methodologists to ensure they are transparent in the reporting of RWE in submissions to Canadian health technology assessment agencies and regulators. Future work will include more in-depth engagement with the patient community to better understand patient perspectives on the integration of RWE into decision-making.	Health Canada is taking steps to support patient involvement initiatives, with the aim of developing a Patient Involvement Strategy that includes structured methods for patients to work alongside Health Canada on various topics. As Health Canada gains additional experience with RWD and RWE, patient involvement will be further explored.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; RWE = real-world evidence; WG = working group.

Table 7: International Alignment and Harmonization

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. International alignment; harmonization	To ensure alignment with existing guidance and best practices from international regulators, HTA organizations, and other major bodies in the RWE space, existing recommendations in documents from these organizations were reviewed and extracted. The guidance was reviewed by numerous international panels, groups, and experts, and has been strongly supported by all parties.	The methodology to develop *Guidance for Reporting Real-World Evidence* included processes to ensure harmonization with guidance and best practices of other HTA bodies. This document is consistent with other principles previously issued by CADTH, INESSS, and Health Canada. As such the guidance is not more restrictive, nor more demanding than current global standards.	Health Canada collaborates with international regulatory partners to further advance alignment and harmonization in the RWE space wherever possible. This includes regulators such as EMA and FDA, and forums such as the International Coalition of Medicines Regulatory Authorities where Health Canada contributed to the development of a statement on international collaboration to enable RWE for regulatory decision-making and through Health Canada's participation in the development of ICH guidelines such as guideline M14, "General Principles on Plan, Design, and Analysis of Pharmacoepidemiological

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
			Studies That Utilize Real-World Data for Safety Assessment of Medicines."

EMA = European Medicines Agency; FDA = FDA; HTA = health technology assessment; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; RWE = real-world evidence; WG = working group.

Table 8: Clarity; Readability, Accessibility, and Other Factors to Facilitate Adoption

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Readability, accessibility, and other factors to facilitate adoption	Repetition across the guidance ensures clarity and reinforces key points that investigators should consider in the reporting of their RWE submissions. Repetition within sections also increases usability because it ensures that investigators will not need to repeatedly refer to other sections for specific recommendations or context; thus, each section is able to stand alone. Furthermore, certain sections were consolidated into common themes based on stakeholder feedback: Participants and Participant Characteristics sections were combined into a revised section entitled Participants. Variables section was integrated into a new section entitled Data Sources, Data Dictionary, and Variables. Separate sections were developed to facilitate flexibility in implementation. Providing distinct sections allows investigators the opportunity to consider only the components of the guidance that apply to their RWE. This is particularly true for investigators reporting studies not focused on safety and effectiveness for which only a subset of guidance recommendations may apply. In terms of layout, the sections are labelled by design and the current flow of the guidance aligns with how reviewers wish to view a submission	No additional comments from HTA perspective.	No additional comments from Health Canada.

Feedback received	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
	which differs from the layout of a scientific report or publication. After reviewing comments and suggestions on the overall readability of the guidance, a number of changes were made, including: clarification about who the guidance is for, changing "medical technologies" to "health technologies," and the addition of a glossary. A checklist has also been created to allow for transparent reporting.		
2. Clarity in language	To allow for flexibility in study designs, data availability, and many other factors in submissions involving RWE, we chose not to establish a gradient system for recommendations (i.e., language that conveys which components are required vs. optional). Rather, the document recommendations and suggestions ask for or strongly encourage specific reporting components and sections, with the flexibility of opting out if a component is not applicable, with sufficient justification. This has been clarified within the introduction.	No additional comments from HTA perspective.	No additional comments from Health Canada.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWE = real-world evidence; WG = working group.

Table 9: Consent, Privacy, and Confidentiality

Feedback	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Consent; privacy of patient health information 2. Confidentiality of business information	No additional comments.	These considerations are addressed within the document, from a principles perspective. This document does not supersede or contradict any legislative requirements or other guidance regarding consent or privacy of health information or the presentation of commercial in confidence information.	These considerations are addressed within the document, from a principles perspective. Consent, privacy, and confidentiality should be addressed by the sponsor or researcher when collecting and utilizing RWD.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; RWD = real-world data; WG = working group.

Table 10: Research Ethics Approval

Feedback	Response from the Guidance for Reporting Real-World Evidence WG	Response from HTA perspective (CADTH, INESSS)	Response from regulatory perspective (Health Canada)
1. Clarification regarding requirement for Research Ethics Board approval	Research Ethics Board approvals are required when the content of the submission is considered research. The definitions of research and human subjects research can differ by institution and research ethics boards.	There are no additional comments from the HTA perspective.	No additional comments from Health Canada.

HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; WG = working group.

Section 2: RWE Reporting–Specific and Methodological Feedback and Responses

Table 11: Feedback, Survey Response, and Changes to the Guidance Document

Number	Summary of feedback and suggestions	Expert Methods Panel Survey response and changes to the guidance document
1	Provide examples for an "appropriate" public platform for protocol registration.	Agreement to include (88%). Given changes in protocol registration and available platforms for studies of RWE over time, it is challenging to recommend specific platforms for protocol registration. However, examples have been included of protocol registration platforms that have the recommended characteristics (permanent registration, assigns a unique study identifier, and is maintained

Number	Summary of feedback and suggestions	Expert Methods Panel Survey response and changes to the guidance document
		by a third party) at the time of the development of this version of the guidance within section 1 (Research Questions and Study Design).
2	Remove the need to report the costs associated with data sources and modify to recommend reporting whether other researchers can access the data and whether costs are associated with the data access in general.	Agreement to include (89%). The text in section 3 has been modified (subsection: Data Access) as suggested.
3	With regard to reporting all codes or algorithms used in the RWE submission (e.g., for inclusion, exclusion, outcome measures), we received feedback to revise the wording to "codes/algorithms should be provided *where possible*." Further, it was suggested to acknowledge that some codes and algorithms are proprietary and cannot be shared.	Agreement to include (71%). The text and relevant checklist items in sections 5 (Population) and 8 (Outcomes) have been modified to acknowledge that codes and algorithms should be provided "when possible." However, the guidance highlights that the submission should acknowledge when this information cannot be provided, especially for inclusion or exclusion criteria, the primary exposure measure(s), and the primary outcome measure(s). It has been highlighted that this guideline's recommendations related to reporting codes and algorithms align with international standards and guidance identified in the Environmental Scan.
4	Some feedback highlighted that the use of more than one RWD source can add value by providing insight and validation of results, rather than detract from the study due to the heterogeneity of data sources.	Agreement to include (78%). Phrasing has been added in the Overview subsection of section 2 (Setting and Contexts), which highlights that conducting studies to replicate findings from one RWD source to another can support validation of findings, depending on the degree of heterogeneity between databases. It is recognized that some degree of heterogeneity is unavoidable.
5	Multiple stakeholders to add mention of common data models and the Observational Medical Outcomes Partnership (OMOP).	Agreement to include (71%). Some discussion about common data models has been added and examples provided within section 3 (Data Specifications, Access, Cleaning Methods, and Linkage). A recommendation has been added that submissions should acknowledge whether a common data model was used to organize data components.
6	Provide a list of "acceptable databases" in the guidance.	Agreement to include (89%). Whether a database is "acceptable" is dependent on the level of data access, current version of the database, and other factors that may change over time; thus, recommending specific RWD sources is outside the scope of this document. Text has been added to the Overview subsection of section 2 (Setting and Context) that emphasizes these considerations. The importance of transparency in understanding the data that were available and how all key measures were created and analyzed is highlighted, rather than providing a blanket statement on whether a data source is acceptable.

Number	Summary of feedback and suggestions	Expert Methods Panel Survey response and changes to the guidance document
7	Submission should include the specific version of the database used and the date of the last update of the database.	Agreement to include (100%). Language has been added to section 4 (Data Sources, Data Dictionary, and Variables) in accordance with the feedback received.
8	Investigators should consider whether a data source can appropriately address the study populations, exposure(s), outcome(s), and key covariates, particularly as this relates to the provenance of the data source.	Agreement to include (90%). In section 4 (Data Sources, Data Dictionary, and Variables), language has been added to emphasize that investigators should briefly discuss whether the RWD source can appropriately address the variables of interest. We also highlight that understanding data provenance (data collection, coverage, and governance), accuracy, completeness, curation, linkage, and relevance are key to understanding how well the data capture the necessary information. Current guidance is cited for the terminology (e.g., data provenance) used rather than discussing each definition in detail.
9	Reporting on duplicate records.	Agreement to include (89%). In the Data Cleaning subsection of section 3 (Data Specifications, Access, Cleaning Methods, and Linkage), a recommendation has been added to specify that investigators should also report how duplicate records were identified and managed.
10	Flexible in allowing some space for causal inference.	Agreement to include (78%). To allow more flexibility or opportunity for causal inference, a paragraph has been added to the Overview subsection of section 1 (Research Questions and Study Design) that highlights that using RWE for causal inference is challenging but in certain situations can be appropriate. It is highlighted that in-depth discussion of causal inference methods and assumptions is beyond the scope of the document and interested readers are referred to other texts and publications.
11	Include comment on machine learning methods, which can be appropriate and useful even for causal inference studies.	Agreement to include (71%). This feedback and survey response was flagged for further discussion with the Expert Methods Panel. Result from Expert Methods Panel discussion: 100% agreed to exclude discussion of machine learning methods, as the choice of method to use in a RWE submission (such as machine learning methods) is at the discretion of the investigators. Response: Within the Overview subsection of section 11, additional discussion has been included to indicate that certain methods are not being prescribed but that investigators should justify chosen methods based on the specific research question, data source, and other specifics of the submission.

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12	Guidance was too specific to more advanced analyses (i.e., comparative effectiveness and safety) and makes it challenging to apply to other methods. To address this, it was suggested to add a new Implementation section, where we suggest that while some recommendations are for the most complex submissions, some sections can be specifically omitted for some designs and methods.	No agreement (< 70%). Result from discussion: 100% agreed to include. Response: A new section entitled Implementation Considerations has been added, which outlines, at a high level, the principles that should guide successful implementation of this document to form a submission. This can be found in the Introduction section of the guidance. In this section, it is highlighted that reporting of some of the sections and recommendations may not apply to some types of RWE (e.g., burden of disease studies, drug utilization studies).
13	The guidance document should discuss pragmatic randomized trials as a source of RWD.	Agreement to include (100%). It has been acknowledged that the RWD sources are separate from the different designs that are suited to producing RWE (e.g., cohort, pragmatic trial) within section 1 (Overview). It is emphasized that certain study designs are not preferred over others, rather that transparency in reporting and justification of study design choices are most critical for a submission.
14	Include in-depth discussions on how to conduct pragmatic trials or compare the strengths and limitations of pragmatic trials and other designs used to generate RWE.	Reject this recommendation (100%). The discussion of trial design is out of scope for the document and, as such, no in-depth guidance on the implementation or conduct of pragmatic trials is included.
15	Citation of the PRECIS and PRECIS 2 tools when discussing pragmatic trials.	Agreement to include (83%). In section 1 (Overview), the PRECIS tools are cited in relation to pragmatic trials.
16	Add the following details to the exposures subsection: • reporting on the validity of exposure data • reporting of start and stop windows for assessing exposures • encouraging the use of sensitivity analyses for exposures with regard to misclassification.	Agreement to include (100%). The Exposures subsection of section 6 now contains suggestions on these aspects.
17	Change reporting the validity of outcome measures to “strongly recommend.”	Agreement to include (91%). The text in section 8: Outcomes has been modified, accordingly.
18	Acknowledge whether a sample of outcomes has been manually verified for validity, to describe the sampling strategy and methods used to ascertain validity.	Agreement to include (100%). The text in section 8: Outcomes (subsection Outcome Definitions and Validity) has been modified accordingly.
19	Studies should report whether they explored linking other sources of data to provide additional information on missing potential confounders.	Agreement to include (71%). Text has been added to section 8 (Bias, Confounding, and Effect Modifiers or Subgroup Effects) that discusses reporting whether data linkage was explored

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		to add additional measures on missing potential confounders.
20	Consolidate the Data Sources and Variables sections, since the Variables section primarily contains information on creating a data dictionary.	Agreement to include (88%). Original sections 4 and 9 have been consolidated in a new section entitled Data Sources, Data Dictionary, and Variables (new section 4).
21	Consolidate Participants and Participant Characteristics sections due to common material.	Agreement to include (88%). These sections have been consolidated into one section entitled Participants (new section 5).
22	Provide definitions of an external and historical comparator.	Agreement to include (100%). A short paragraph has been added to define external (historical) comparators.
23	Add a brief section in the subsection on cohort study designs that provides an overview of the ECA design and provide minimum reporting standards for ECAs in particular.	Agreement to include (86%). A short paragraph has been added to provide references to established texts on the proper implementation of external control arms.
24	Discuss QBA.	Agreement to include (89%). A brief overview of QBA and its benefits in relation to understanding the direction and magnitude of potential biases (Sensitivity Analyses subsection) has been added to section 8 (Bias, Confounding, and Effect Modifiers or Subgroup Effects). References to current literature on best QBA practices have been included rather than an in-depth discussion of their implementation.
25	Mention of the target trial approach or estimate framework as a more useful causal framework.	Agreement to include (78%). A brief paragraph has been added in the Study Design subsection of section 1 (Research Questions and Study Design) that highlights that studies asking causal research questions may wish to follow a modern causal inference framework, such as the target trial. Here, modern literature and best practices are cited rather than providing recommendations on implementation.
26	Emphasize that, although causation should not be inappropriately inferred from association, causal conclusions are often the main goal of RWE. Emphasize that if sufficient design choices and assumptions are met, causal inference can be a part of RWE and submissions.	Agreement to include (73%). To allow flexibility or space for causal inference, a paragraph has been added to the Overview subsection of section 1 (Research Questions and Study Design) that highlights that causal inference is challenging with RWE but, in certain situations, can be appropriately implemented. It is highlighted that in-depth discussion of causal inference methods and assumptions is beyond the scope of the document but interested readers are referred to additional texts should they want to learn more.

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27	Provide more specific suggestions on potential "guardrails" that can be used to limit investigator bias, as both the FDA and NICE have included similar recommendations in their guidance.	Agreement to include (100%). A subsection has been added to section 8 (Bias, Confounding, and Effect Modifiers or Subgroup Effects) that briefly discusses the following: • recommend conducting descriptive analyses before inferential analyses • disclose if diagnostic checks were conducted (baseline confounder balance; exposure or outcome distribution between groups and within defined strata if applicable) • consider blinding the analysts to the exposure groups or conducting feasibility analyses unstratified by exposure.
28	Acknowledge that the underinclusion of a patient group cannot always be accounted for, and instead recommend that submissions acknowledge this.	Agreement to include (100%). Section 11 (Interpretation and Generalizability) now recommends that submissions acknowledge whether some patient groups may not be well represented or may be over-represented and, if so, how under- or over-inclusion of these groups may affect the external generalizability of research findings.
29	Cite current CIHR guidelines (or most current best practices) specifically related to research conduct and reporting on sex and gender.	Agreement to include (100%). For reporting of sex and gender, investigators are directed to recommendations outlined by CIHR.
30	State which surrogate outcomes are acceptable or valid and provide some examples of surrogate markers, and an example of when they would be considered appropriate (e.g., dose reduction might be used as an appropriate surrogate marker of intolerance to treatment, if there is a study that validates that there is a strong relationship between the surrogate outcome and main outcome of interest, with a justification of why the main outcome of interest cannot be measured).	No agreement (< 70%). Result from discussion: Agreement to keep wording as-is (100%). During the Expert Methods Panel Meeting on March 1, 2023, experts agreed that stating which surrogate outcomes are acceptable and valid, with examples, is out of scope of the guidance. Experts voted to keep the wording as-is, with the understanding that: • there is well-established documentation of surrogate outcomes • surrogate outcomes are highly condition-specific.
31	Revise the recommendation to remove blanket requirements for subgroup analyses based on demographic or comorbidity variables. Instead, recommend that relevant subgroup analyses should be identified and conducted based on a prespecified rationale (such as previous studies or biologic rationale to suggest heterogeneity of effect).	Agreement to include (100%). The subsection of Effect Modification in section 8 (Bias, Confounding, and Effect Modifiers or Subgroup Effects) has been revised to remove the requirement for effect modification or subgroup analyses based on demographic or comorbidity variables. Text has been replaced with the recommendation that relevant effect modification or subgroup analyses should be identified and conducted based on prespecified rationale.

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32	Provide both relative and absolute measures of effect for binary outcomes. Include examples of what absolute measures can be used in relation to a relative measure. For example, for hazard ratios (relative measures), submissions should consider providing mean survival or Kaplan-Meier estimates of the outcome over time as absolute measures.	Agreement to include (100%). An example of using both absolute and relative measures of effect for binary outcomes has been included in section 8 (Study Findings).
33	For the Outcomes section, recommend that investigators consider the use of a COS for standardized outcome reporting, if available for the condition the study is examining.	Agreement to include (80%). In section 7 (Outcomes), in the Outcome Selection and Surrogate Outcomes subsection, a recommendation has been included that investigators consider the use of a COS for standardized outcome reporting, if one is available for the condition of interest. As the development of condition-specific COSs for real-world studies is emerging, future versions of the guidance may further expand on this topic.
34	No guidance on reporting of missing data or intercurrent events is provided. While aspects of missing data are interspersed throughout the document, we are considering revising the Statistical Methods section to include more detail on how to handle missing data, such as complete case analysis, multiple imputation, and clarification that appropriateness of the method is dependent on many factors, like the quality of the models and study size. We are also considering giving an example of intercurrent events and methods used to handle them.	Agreement to include (90%). Additional detail has been included in section 9 (Statistical Methods) concerning methods for handling missing data, considerations for the appropriateness of the method(s) selected, reporting on methods used to handle missing data, and dealing with intercurrent events.
35	Provide further guidance on how validity can be assessed in the absence of a recognized gold standard, and provide some basic principles for how validity of an outcome can be assessed in (e.g., surrogate markers, internal validation) in this case.	Agreement to include (71%). It has been clarified in the Outcome Selection and Surrogate Outcomes subsection of section 7 (Outcomes) that, in the absence of a clinical outcome, a well-established and validated surrogate outcome should be selected, if available. If a surrogate outcome is used, investigators should cite the strength of the relationship between the surrogate outcome and the relevant clinical outcome, and in cases where a surrogate outcome is not validated, investigators are asked to justify its use.
36	Mention only major deviations from protocol, where major deviations are defined as any deviations that may result in a material change to the methods or conclusion.	No agreement (< 70%). Result from discussion: Agreement to keep wording on deviations as-is with review of terminology (100%). Experts agreed to keep the wording of deviations as-is to account for inclusive reporting of deviations, which errs on the side of a conservative approach.
37	Describe team members involved in the study and include statements about their conflicts of interest.	Agreement to include (100%). In section 1 (Research Questions and Study Design) under Other Recommendations and Additional Transparency, a strong recommendation for each team

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		member to disclose their conflicts of interest, has been included.
38	Highlight that team inclusion should align with ICMJE standards, but recognize the fact that some members may not be authors based on rules of organizations.	Agreement to include (100%). In section 1 (Research Questions and Study Design), under Other Recommendations and Additional Transparency, a statement has been included to indicate that team inclusion should align with ICMJE standards, with the caveat that some team members may not be authors, based on differing rules and regulations of organizations.
39	In the Non-Canadian Data Source subsection, in line with recently published considerations for the transferability of RWD, add a recommendation that submissions include patient demographics (e.g., age, sex, and race or ethnicity), prevalence and incidence of the disease, and confounders and/or effect modifiers in the justification for transferring non-Canadian RWD to the Canadian context.	Agreement to include (100%). In section 2 (Setting and Context), under Non-Canadian Data Sources, it is now recommended that submissions include participant demographics, incidence and prevalence of the disease, and effect modifiers and/or confounders in the justification for transferring non-Canadian data to the Canadian context.
40	Add importance of international alignment to improve the efficiency of evidence development and evaluation was highlighted. Given the similarities of this guidance with existing and well-established best practice guidance on reporting RWE studies (e.g., STaRT-RWE, NICE's Real-World Evidence Framework, HARPER template), we are considering a harmonized approach to align with international guidance to improve the efficiency of evidence development and evaluation. Aligning with the EMA's recent endorsement of the HARPER template, we are considering a harmonized approach and making statements to align.	Agreement to include (89%). In the Environmental Scan of the literature, these documents (e.g., START-RWE, NICE's RWE framework) were included in the review that informed the structure and content of the guidance. The Methods Authorship Team ensured alignment with available and relevant guidelines, other international guidance, best practices, and policy papers, and, as such, there is strong overlap between them, reinforcing harmonization.
41	In the subsection of Generalizability, add to the discussion considerations for quality of care, underrepresented populations, and access to the intervention.	Agreement to include (89%). These considerations have been included under the subsection of Generalizability in section 11 (Interpretation and Generalizability).
42	Reporting on participant characteristics — including demographics and social determinants of health, along with participant follow-up requirements including the number of participants at each stage and reasons for loss to follow-up — is not feasible for many RWD sources. Add a statement noting that if this information is not available, submissions should explain why.	Agreement to include (100%). A statement has been included in the subsection of section 5 (Participants) that if participant data as described are not available or feasible to obtain and report, an explanation should be provided.
43	Provide stronger wording with respect to patient and/or caregiver involvement in the interpretation and generalizability of the study results. Following the recommendation, revise lines to state, "Finally, patient and/or caregiver involvement should be considered to support the interpretation and generalizability of study findings to a Canadian context."	Agreement to include (88%). In section 11 (Interpretation and Generalizability), the wording has been updated to reflect the suggested change.

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44	Guidance does not consider laboratory (in vitro) evidence. Briefly mention that some in vitro evidence generated in both clinical laboratories and in research laboratories has the potential to influence clinical care but is not considered RWE.	No agreement (< 70%). Result from discussion: Agreement that in vitro evidence is out of scope (100%). Experts unanimously agreed that the addition of in vitro evidence is out of scope of the guidance.
45	Need for clarity about the definition of RWE. Align the provided definition of RWE with Health Canada's definition of RWE.	Agreement to include (90%). The definition of RWE has been aligned with Health Canada's definition, which can be found in the Introduction in the "What Is RWE?" subsection.
46	At different points throughout the guidance, investigators are asked to justify their choices; however, it is unclear what an appropriate level of justification would be. Use consistent terminology ("provide justification" or "provide rationale") and provide 1 or 2 examples of what an adequate justification may look like.	Agreement to include (70%). Experts discussed that providing examples of what adequate justification may look like would be challenging, as it varies case by case. As can be imagined, some are simple while others may be broader and more complex. This may also shift based on established methodological standards and novelty of analysis. As is seen throughout the document, justification must ensure that the methods are transparent and reproducible. It must also allow enough details to ensure a reviewer understands the justification and it is well supported with appropriate citations.
47	Remove terms such as "intention-to-treat" or "per protocol" and instead use exposure-based terminology, as this language only applies to interventional studies.	Agreement to include (83%). These terms have been removed from the guidance as suggested.
48	Add a recommendation to the Outcomes section to include justification of the rationale for why certain outcomes were chosen (e.g., was the outcome chosen simply because that data point was available? Or, is it clinically relevant?).	Agreement to include (100%). Wording has been modified in section 7 (Outcomes) under Outcome and End Point Definitions and Validity recommending providing rationale for why the study outcomes were selected and to provide evidence to support the rationale, if available.
49	Provide guidance on how to mitigate risk. NICE guidance has elaborated several approaches that investigators or sponsors should use to mitigate risk of bias, misclassification, and population heterogeneity. We are unclear how this may be perceived in the guidance and whether it will improve readability and/or usability.	No agreement (< 70%). Result from discussion: Experts discussed that mitigation of risk was relevant to the Interpretation section. In response, a statement has been included for investigators to discuss approaches undertaken to mitigate risk of potential biases, misclassifications, and/or heterogeneity throughout the study (e.g., how was risk accounted for?), and how this may affect the interpretation of the study results.
50	Conclusions should include language of certainty (specifically, "highly uncertain," "moderately uncertain," or "low level of uncertainty" to provide evidentiary guidance).	No agreement (< 70%). Result from discussion: Agreement to keep section as-is (100%). Offering specific language for levels of certainty (e.g., "highly uncertain," "moderately uncertain") may result in over- or under-estimation of the true certainty

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		of the findings. Experts agreed that investigators should report the results of their studies as accurately and transparently as possible while accounting for limitations and/or caveats of the findings.
51	Combine sections 12 to 14 into a "Study Findings, Generalizability, and Limitations" section.	No agreement (< 70%). Result from discussion: Agreement to keep sections as they are (100%). During the Expert Methods Panel Meeting on March 1, 2023, experts agreed to keep the Study Findings, Generalizability, and Limitations sections distinct, as this facilitates readability.

CIHR = Canadian Institutes of Health Research; COS = core outcome set; ECA = epidemiologic catchment area; EMA = European Medicines Agency; HARPER = HARmonized Protocol Template to Enhance Reproducibility; HTA = health technology assessment; ICMJE = International Committee of Medical Journal Editors; NICE = National Institute for Health and Care Excellence; PRECIS = PRagmatic Explanatory Continuum Indicator Summary; QBA = quantitative bias analysis; RWD = real-world data; RWE = real-world evidence; STaRT-RWE = Structured Template and Reporting Tool for Real-World Evidence.