Canada's Drug Agency
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Drugs **Health Technologies** Health Systems

Canada's Drug Agency Position Statement on the Use of Artificial Intelligence in the Generation and Reporting of Evidence

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Key Messages

What Was the Issue?

Canada's Drug Agency (CDA-AMC) is aware that artificial intelligence (AI) methods are increasingly being explored for purposes relating to health technology assessment (HTA), including in the generation and reporting of evidence. Concerns regarding the appropriateness, transparency, trustworthiness, and ethics exist with respect to AI methods.

What Did We Do?

CDA-AMC used work conducted by the National Institute for Health and Care Excellence (NICE) to develop this position statement, which provides clarity on how we will consider the use of AI methods in the generation and reporting of evidence to be evaluated within our programs.

What Did We Find?

CDA-AMC requires transparency, rigour, and trust are maintained when AI methods are used. Any use of AI should be done judiciously, leveraging the strengths of AI to support and enhance the generation and reporting of evidence only when it is suitable and when it adds value.

What Does This Mean?

Greater transparency about the role of AI in evidence generation and reporting will facilitate evidence appraisal and will allow CDA-AMC deliberative committee members and other external assessment groups to understand and appraise evidence using AI methods.

Purpose of This Position Statement

CDA-AMC is a pan-Canadian health organization responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions.

We anticipate that evidence considered by regulators and HTA bodies will soon be informed by AI methods that exhibit some level of adaptivity and autonomy[1] — from well-established machine learning approaches to newer and more complex generative AI. A wide range of types of AI, and uses for AI, are being developed for or are already implemented in health care.[2] In recent years, we have turned our attention to improving our understanding of AI as well as its potential impact on our organization and the broader health ecosystem.

Despite the potential benefits of AI methods, issues regarding the appropriateness, transparency, trustworthiness, and ethics exist. Thus, guidance is needed on how to present evidence that has been informed by AI methods to ensure potential benefits are balanced against anticipated and/or known concerns.

This CDA-AMC position statement leverages work already conducted by NICE. It gives our perspective on the use of AI methods in the generation and reporting of evidence submitted for evidence appraisal to CDA-AMC. This statement also points to relevant Canadian regulations, best practices, standards, and guidelines to follow when using AI methods. Greater transparency about the role of AI in evidence generation and reporting will facilitate evidence appraisal and will allow CDA-AMC deliberative committee members and other external assessment groups to understand and appraise evidence using AI methods.

How This Position Statement Was Developed

This position statement was developed based on the NICE position statement on the use of AI in evidence generation. We reviewed the position statement to determine where there was alignment and where adaptations would be needed to contextualize the content to CDA-AMC and the HTA environment in Canada.

We have aligned our position statement with all the positions outlined by NICE, with minor additions and modification. The following key changes have been made to ensure this statement is fit for purpose for the CDA-AMC context:

- the definition of AI has been updated to reflect the Canadian standard
- additional points on ethical considerations have been added
- relevant federal, provincial, and territorial legislations (where available) have been added.

This position statement focuses on the use of AI methods in the generation and reporting of evidence submitted for evidence appraisal. It does not consider health technologies that use AI methods to perform their function (AI-enabled technologies).

Definitions

There is no universally accepted definition of AI. In this position statement, we use the description of AI in the proposed Canadian *Artificial Intelligence and Data Act* (*AIDA*): AI "enables computers to learn to complete complex tasks, such as generating content or making decisions and recommendations, by recognizing and replicating patterns identified in data."[3]

The following are additional definitions that are referred to or covered by this position statement and are aligned with the NICE position statement for consistency:

AI methods: Methods that exhibit some level of adaptivity and autonomy.

Deep learning: A subset of machine learning that uses artificial neural networks for complex learning tasks, such as recognizing patterns in data and providing an output (e.g., a prediction).

Generative AI: An AI model that generates data, such as text, in response to user prompts.

Large language models: A type of model that is trained on vast amounts of text to understand and generate human speech and text and infer new content.

Machine learning: A type of AI that allows a system to learn and improve from examples without all its instructions being explicitly programmed. They learn by finding patterns in training datasets and translating those findings into a model (or algorithm).

Natural language processing: An approach to programming computer systems to understand and generate human speech and text by looking at linguistic patterns and word and sentence structures.

Synthetic data: Artificial data that is generated from original data and a model that is trained to reproduce the characteristics and structure of the original data, and are generated using AI-based methods, including machine learning algorithms and other approaches.[4]

Part 1: Potential Uses of AI Methods in HTA

This position statement first outlines how AI methods could be applied to aspects of evidence considered by CDA-AMC. The following sections summarize potential uses of AI methods and opportunities for HTA-related purposes. Since AI is a rapidly developing field, the listed possible uses are neither exhaustive nor endorsements or acceptance of those methods. The methods proposed are being developed, tested, and validated.

Systematic Review and Evidence Synthesis

A systematic review involves identifying, appraising, and synthesizing all empirical evidence according to prespecified eligibility criteria to answer a specific research question.[5] Conventional review processes are primarily undertaken manually and typically require substantial time and resources.

1. AI methods have the potential to automate various steps in these processes.

2. Machine learning methods and large language model prompts may be able to support evidence identification by generating search strategies, automating the classification of studies (e.g., by study design), screening of primary and full-text records to identify eligible studies, and visualizing search results.
3. Large language models could be used to automate data extraction from published quantitative and qualitative studies by inputting prompts into the AI tool to generate the desired output. This is less well established than the uses described in paragraph 2.
4. Large language models could be provided with prompts to generate the code required to synthesize extracted data in the form of a (network) meta-analysis. This is less well established than the uses described in paragraph 2.
5. Cochrane is developing guidance on the responsible use of AI in evidence synthesis, and the Guidelines International Network has established a working group that will produce guidance and resources. These are likely to be useful sources of good practices for the submitter seeking to use such methods. To assist evidence synthesis producers to evaluate and make use of AI tools for information retrieval, CDA-AMC has also developed an evaluation instrument on AI search tools.[6]

Clinical Evidence

Clinical effectiveness evidence is typically informed by clinical trials on the intervention, clinical trials on the comparator(s), and real-world data (RWD). It may include evidence to quantify a treatment effect, establish a side effect profile, or assess the generalizability of trial data to the Canadian population.

6. AI can be used in trial design, such as defining the inclusion and exclusion criteria, and retention. Pattern recognition and machine learning may be used to avoid excluding people based on factors that do not affect the treatment response. Dosage levels, sample size, and trial duration can also be optimized using AI approaches. Natural language processing can be used to mine electronic health records; for example, it can be used to identify people who meet the trial criteria and have the highest potential for benefit and for side effect reporting.
7. AI approaches can also be used to identify and adjust for limitations in clinical data. For example, pattern recognition can identify relevant covariates that influence treatment response and adjust for these in the statistical analyses.
8. AI methods can account for complex, nonlinear relationships between covariates, producing models that have fewer structural assumptions compared with parametric models. This may be particularly useful for improving performance of predictions and reducing bias in causal inference, with benefits also for precision of the effect estimate and estimates of uncertainty.
9. AI approaches can be used to produce synthetic data and generate external control arms. This may be applicable when it is unethical to include a placebo arm in a trial. It can also be used to predict clinical effectiveness in different populations (e.g., by applying data from a clinical study to a population with different characteristics).

10. Natural language processing may be used to analyze large amounts of information. For example, this could be applied to generate an executive summary of the clinical evidence. It may also be used to simplify technical language for the purpose of creating a lay summary.
11. When AI is used in clinical evidence generation, reporting should be transparent and make use of relevant tools (e.g., checklists to justify its use and to explain AI model development). Any AI approach used (e.g., a cohort selection model) should be considered part of the clinical trial, and full details should be provided within a submission.

Real-World Data and Analysis

RWD are data that provide information on patient status and/or the delivery of health care and can be drawn from a vast number of sources, including but not limited to electronic medical records, clinical and disease registries, administrative databases, and other prospective sources (e.g., pragmatic and hybrid trials). Real-world evidence (RWE) is evidence on the use, safety, effectiveness, and cost of health technologies that is derived from RWD.[7]

12. RWD may become increasingly suited to AI approaches as the accessibility and standardization of large datasets reflecting routine care and real-world populations improve. AI approaches have several potential roles for supporting RWE across numerous stages of evidence generation.
13. AI methods may have a role to play in data processing before the development of RWE. For example, natural language processing approaches are being used to generate structured data from unstructured RWD. Approaches such as multimodal data integration can combine different data sources into a cohesive dataset, and aspects such as data matching and linkage, deduplication, standardization, data cleaning, and quality improvement (e.g., error detection and imputation of missing data) are increasingly being automated and are scalable to process large volumes of data.
14. AI approaches may support the efficient selection of relevant populations and observations from large datasets for the purposes of addressing specific research.
15. AI methods can support estimation of comparative treatment effects (causal inference), primarily through using feature selection methods which select from a subset of relevant features for use in model construction. Additionally, analytical methods using AI approaches can provide more targeted estimates of causal effects, sometimes harnessing predictive capabilities of multiple valid machine learning algorithms.

Cost-Effectiveness Evidence

Cost-effectiveness evidence is typically informed by economic models. Developing an economic model is a resource-intensive multistep process involving model conceptualization, parameter estimation, construction, validation, analysis, and reporting steps. AI methods may have a role in several of these steps.

16. AI methods are capable of interrogating complex or different datasets in new ways. This may generate new or deeper insights into cost drivers and health outcomes, such as disease progression, surrogate relationships, and clinical pathways. This information could inform the conceptualization

and parameterization of an economic model (e.g., in terms of included health states, transitions and events, and reducing structural uncertainty).

17. Methods using large language models could be used to automate the construction and calibration of new economic models and the generation of model reports. Following human-led model conceptualization and parameter estimation steps, large language model prompts can be designed to generate the code for the economic model. This may permit the construction and comparison of multiple models to assess structural uncertainty.
18. Large language models can be provided with prompts to reflect new information in an economic model, such as clinical data or comparators, facilitating updates and adaptations. In the future, AI methods may support economic models being updated in real time.
19. Large language model methods can support the replication and cross validation of existing economic models.
20. Machine learning methods can be used for simulation optimization. In the context of economic modelling, this could reduce, and ideally minimize, the computational time that a simulation model takes to run. By increasing the efficiency of economic models, more complex models that use fewer simplifying assumptions may become more practical to use, including for probabilistic sensitivity analysis.

Part 2: User Responsibilities When Using AI Methods in Evidence Generation and Reporting

It is important that the potential benefits to using AI methods in HTA are balanced against potential risks, such as algorithmic bias, cybersecurity, reduced human oversight, transparency, and accessibility to nonexperts. Considering the potential risks and the rapidly evolving nature of AI methods, these methods should only be used when risks are adequately mitigated. The following statements represent the CDA-AMC position on the use of AI in evidence generation and reporting.

21. The use of AI methods may introduce added complexity. It is important that the user considering using these methods for evidence generation and reporting ensure the rationale for doing so is clear. If more explainable and/or more common methods are potentially robust, those should be the primary approach, with supplementary use of other AI approaches. The user should clearly justify the use of these methods and outline assumptions (using appropriate tools) and consider the plausibility of their results.
22. Users considering using AI methods should engage early with CDA-AMC to discuss their plans. This could be sought through CDA-AMC Scientific Advice. At later stages of evidence development, users should discuss their plans with the appropriate CDA-AMC technical team.
23. All uses of AI should align with Canada's Voluntary Code of Conduct on the Responsible Development and Management of Advanced Generative AI Systems and, once available, the Canadian *AIDA*, which is expected to become law in 2025.[8,9] It is the user's responsibility to

determine which legislation applies, including data protection laws and ethical standards. When relevant, these should be clearly documented.

24. It is the user's responsibility to ensure that all algorithms, models, datasets, and data processing pipelines used are in alignment with relevant Canadian regulations and guidance for AI use in a medicinal product life cycle, and are consistent with relevant ethical, technical, scientific, and regulatory standards.
25. There remains a need to build trust in the application and use of AI in decision-making. Therefore, any use of AI methods should be based on the principle of augmentation, not replacement, of human involvement (i.e., having a capable and informed human in the loop). Users should conduct careful technical and external validation when AI methods are used and present the results.
26. When AI is used, the user should clearly declare its use, explain the choice of method and report how it was used, including human input (refer to paragraph 25). The user remains accountable for the content included in any submission.
27. It is the user's responsibility to ensure compliance with any appropriate licensing agreements. This includes but is not limited to:
    - copyright considerations, such as whether the organization is authorized to use copyrighted or licensed materials in the AI tool, how the AI tool handles copyrighted or licensed materials, and compliance with copyright law or user licences
    - whether a business licence is required for any third-party AI tools that are used
    - who owns the intellectual property produced by the AI tool and is the organization authorized to share it with CDA-AMC.
28. The use of AI methods, particularly "black box" models, can introduce challenges for transparent reporting of evidence. When their use is justified, the user should consider how these methods can be accessibly presented, including appropriate referencing (e.g., of the AI tools used and suitability assessments) and the use of lay language. When available, consider using tools to support the explainability of AI methods and increase transparency of their application.
29. The use of AI can introduce new risks. These risks should be mitigated by adhering to established guidance and checklists (refer to the NICE position statement[1]) during the development, application, and reporting of AI, and using AI only in the context of following other relevant best practice guidance (such as the CDA-AMC Guidance for Reporting Real-World Evidence and the CDA-AMC Methods Guide).
30. When using AI methods, the user should report the risks they identified from using AI (e.g., concerns about transparency and bias) and the steps taken to address those risks.
31. The use of novel AI methods presents cybersecurity risks, such as manipulation of data ("data poisoning") or injecting malicious content into prompts ("prompt injection attacks"). These risks should be considered alongside other risks posed by AI systems. When using AI methods, the user should provide evidence of the steps taken to ensure robust security measures are in place to prevent such unauthorized access and manipulation.

32. The use of AI methods to estimate comparative treatment effects (causal inference) represent a potentially very influential and therefore higher-risk application of AI. These methods should be accompanied by sensitivity analysis, checked against other suitable methods, and the results should be presented in the context of available clinical evidence ("triangulation"). Ideally, the use of machine learning methods should be accompanied by prespecified outcome-blind simulations, conducted independently, to demonstrate their statistical properties in similar settings (e.g., different data types or populations) and the accuracy of their implementation.
33. AI methods used for RWD extraction and curation must be reported, in detail, as part of the data suitability assessment, making use of reporting tools when possible (refer to the CDA-AMC Guidance for Reporting Real-World Evidence).
34. Alongside the previously mentioned principles, AI methods should uphold ethical principles for the use of AI in health. These include promoting human well-being and safety, fostering responsibility, ensuring inclusiveness and equity, and promoting responsiveness and sustainability.

What Is Next?

As AI is a rapidly evolving discipline, this position statement will be regularly reviewed and updated as significant new evidence emerges on the use of AI methods in evidence submissions. Updates concerning AI methods may be considered as part of the framework for modular updates to the CDA-AMC Methods Guide. CDA-AMC will monitor any future use of AI methods in our evaluations and consider whether their use poses challenges to or opportunities for CDA-AMC processes. Going forward, CDA-AMC is committed to expanding capacity and capabilities across related disciplines that support the adoption of AI in our evaluations, including the upskilling and training of staff and committee members.

If you have any questions or comments about this position statement, please contact us at requests@cda-amc.ca.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.