INNOVATIVE MEDICINES CANADA

Developing a Canadian managed entry approach for new innovation:

What can Canada learn from Europe?

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Objective:
This study explores international examples of successful innovative access agreements, RWE data infrastructure and reimbursement systems by detailing the experiences of countries that have similar systems to Canada.

Backgrnd:
Many new therapies coming to the market are not well served by the traditional drug reimbursement approaches currently employed by Canada's public plans. Given that many of these therapies address significant unmet clinical needs, a growing number of European regulatory authorities have been using novel managed entry agreements (MEA) and innovative access agreements (IAA) to accelerate approval times and improve availability to patients.

Methods:
An environmental scan was conducted detailing international trends in innovative agreements that have similar systems to Canada in terms of HTA market or health care system. The study also explores how RWE data is operationalized in other countries and provides examples of reimbursement agreement types throughout the product life cycle.

1 Managed Entry Agreements and Innovative Access Agreements

The numerous types of MEAs and IAAs are categorized into three main approaches serving different objectives: 1) financially-based schemes; 2) outcomes-based schemes; and 3) coverage with evidence development. The common denominator is that they provide patients timely access to innovative therapies by sharing the risk between payers and drug developers while additional evidence is gathered on outcomes.

Table 1. Major categories of managed entry agreements

Managed entry approach	Primary objective	Arrangement types	Level of activity
Financially-based schemes	Control budget impact	Price-volume agreements, discounts/rebates, free stock, budget caps, utilization/time caps, fixed cost per patient	Population/patient
Coverage with evidence development (CED)	Tackle uncertainty	Coverage with evidence development	Population
Outcomes-based agreements (OBAs)	Manage variable drug response rates	Outcomes guarantees, patient eligibility controls, conditional treatment continuation process of care	Patient

Europe has pioneered the use of managed entry agreements and innovative access agreements, however healthcare systems vary widely enormously across Europe, as do their approaches to managed entry and innovative access. Historically, the European Union (EU) has played a relatively limited role in healthcare policy, but the COVID-19 pandemic has dramatically increased EU activity (see Table 4), including initiatives related to real-world data collection.

2 Country profiles

Italy – a trailblazer in managed entry

- One of the global pioneers in managed entry agreements with an extensive national system of online registries operated by Italian Medicines Agency (AIFA).
- First registry launched in November 2004 and first outcomes-based managed entry agreement launched in 2006.
- AIFA introduced a new system of evaluating innovation in 2017.
- Pharmaceutical companies pay AIFA a fee of €30,000 for three years for a registry.
- In 2021, 73 companies owned at least one registry.
- Currently, AIFA operates 192 appropriate prescribing registries, 8 financially based registries and 10 outcomes-based registries.
- Nearly three quarters of active registries are for cancer therapies. However, 51% of the 3.3 million patients included in AIFA registries are enrolled for treatments for cardiovascular disorders, 16% for cancers, and 10% for eye diseases.
- The Italian government has pledged to increase the fund for innovative medicines from €1 billion in 2021 to €1.3 billion by 2024.

Table 2: Managed entry approaches in Italy

Level of activity	Type of approach	Managed entry agreement	Key features
Patient	Outcomes-based	Risk sharing	Pharmaceutical companies refund part of the treatment cost for non-responders.
		Payment by results (PbR)	Manufacturers repay in full the treatment cost for non-responders. Used for drugs with perceived unfavorable benefit/risk ratio at launch. Virtually all of the active outcomes agreements are PbR schemes.
		Payment at results (PaR)	As for PbR but with the addition of installment payments.
	Financially-based	Cost sharing	Provides for a discount on the cost of the first cycle of treatment, or the entire course of therapy, for all eligible patients. Generally used when the potential financial impact of a new medicine is uncertain (as opposed to uncertainty of effectiveness).
		Capping	Sets a ceiling on expenditure on a drug per patient, beyond which the manufacturer covers all remaining costs.
Population	Financially-based	Product-specific expenditure ceilings	AIFA's Comitato Prezzi e Rimborso (CPR; Pricing and Reimbursement Committee) negotiates a national limit for drug spending in the first 12 or 24 months on the market. If this limit is exceeded, the manufacturer must refund excess costs to regional administrations.
		Price-volume agreements	Provide for incremental discounts on list prices in response to growing prescription volume. The discounts may be a price reduction or a refund to the regional administrations.

England – increasing use of coverage with evidence development and "smart deals"

- Early adopter of managed entry. In 2002, outcomes-based reimbursement for multiple sclerosis therapies was initiated.
- In 2016, the Cancer Drugs Fund (CDF) was reformed to provide interim funding for promising oncology medicines pending collection of real-world data for reassessment by the National Institute for Health and Care Excellence (NICE). The UK government also commissioned an Accelerated Access Review, which proposed novel risk-sharing arrangements between the NHS and the manufacturer.
- Since 2021, the new Innovative Licensing and Access Pathway (ILAP) offers promising new drugs early access.
- In February 2021, NHS England published its Commercial Framework for New Medicines, which outlined its strategy for managed entry.
- The NHS has also negotiated dozens of "smart deals". The list includes several cutting-edge cell and gene therapies, reserve antibiotics, hepatitis C treatments, a portfolio of cystic fibrosis drugs, and population health management deals in dyslipidemia and oncology.
- In October 2021, NHS England signed a first population health management deal in cancer with a biotech start-up contingent on regulatory approval and recommendations by NICE. Population health deals maximize the potential patient population in return for significantly lower prices to contain the budget impact.
- NHS England has pioneered a subscription model – also known as "delinked payment" – that guarantees the developers of selected antibiotics a fixed sum, regardless of how often the products are prescribed. The contract will have a maximum value of £10 million per antibiotic per year and will last for 3 years, with an option to extend it to up to 10 years.
- Increasingly, England is the first market in Europe to provide access to new medicines.
- In June 2022, the NICE published a Real-World Evidence Framework. Ultimately, NICE believes the use of real-world data (RWD) will help to "resolve gaps in knowledge and drive forward access to innovations for patients".

Table 3. NHS Commercial Framework for new medicines

Type of scheme	Key features
Simple patient access schemes (PASs)	• Most common option: faster access due to minimal administrative burden • Fixed price or percentage discount applicable to all indications (no blended or indication-specific pricing)
Complex patient access schemes	• Considered only with a strong rationale for their use and clear explanation of how risks will be shared • Details are not confidential (to ensure value to NHS is achieved)
Commercial access agreements (CAAs)	• Option for technologies with an incremental cost-effectiveness ratio (ICER) of less than £20,000 per quality adjusted life year (QALY) or where a product launch would be particularly challenging or commercially unviable • Examples include budget caps, price-volume agreements, cost sharing, stop-start criteria, and outcomes-based agreements/payment by results
Managed access agreements (MAAs)	• Considered for drugs that are plausible candidates for routine commissioning but subject to uncertainty • Data collection is combined with a PAS (simple or complex) or a CAA • Key requirement for approval of an MAA is feasibility of collecting relevant health outcomes • To date, MAAs have generally been used in the Cancer Drugs Fund or for highly specialised technologies, but they need not be limited to these programs • Statutory funding requirement (NHS coverage within 90 days of NICE approval) does not apply to MAAs
Budget impact schemes	• For drugs with a potential net budget impact of more than £20 million in any of the first three years on the market, the NHS will engage in commercial discussions to reduce the cost

Spain builds a multi-purpose online platform to support national managed entry

- Relative latecomer to managed entry, negotiating its first regional MEA in 2010. Historically, activity was mainly regional or local with the first national MEA in 2013.
- One study identified 39 MEAs in Spain as of May 2016. 26 (67%) were risk-sharing agreements, 13 (33%) were expenditure ceilings.
- The managed entry environment was transformed by the launch of the VALTERMED online registry platform in 2019.
- VALTERMED online registry platform will enable analysis of the cost-effectiveness of drugs and support the dual objectives of sustainability and access to health.

France signs a framework agreement that provides for greater use of managed entry

- France makes extensive use of managed entry, but the agreements are predominantly financially-based.
- In 2021, MEAs saved the French healthcare system a record €4.5 billion, an increase of 39% over the preceding year and tenfold since 2012.
- In 2012, price-volume agreements accounted for 80% of savings but this share declined to 30% in 2021. In contrast, simple discounts' share of MEA savings grew from just 3% in 2012 to 64% in 2021.
- Outcomes-based agreements (known as performance contracts in France) are used only where there is an unmet medical need.
- In 2021, the Economic Committee for Health Products (CEPS) signed a three-year framework agreement with Leem, the leading French pharmaceutical industry association, that includes provision for greater use of managed entry.
- The Social Security Finance Act 2023 includes provisions to promote the use of outcomes-based agreements with installment payments for cell and gene therapies.

3 Real-world data sources and their applications

Managed entry and innovative access agreements require a robust digital infrastructure to collect real-world data.Table 4 summarizes key real-world data sources in the four countries considered in this analysis, as well as in the European Union, which is actively promoting wider use of real-world evidence.

Table 4. Real-world data sources in Europe

Geography	Real-world data sources	Application
European Union	European Medicines Regulatory Network (EMRN)	Filling pre-authorization evidence gaps; post-authorization safety monitoring
	European Health Data Space (EHDS): electronic health records, wellness apps, and other health and medical software products	Improving health outcomes for patients and the broader public; support for health technology development
	Data Analysis and Real World Interrogation Network (DARWIN EU)	Improved understanding of the natural history of diseases; higher standards of care; insights on the design, feasibility and representativeness of studies
	European Health Data & Evidence Network (EHDEN)	Support for regulatory approval, HTA, and payer needs; development of a standardized process to facilitate decision making in personalized medicine
	GetReal Institute (GRI)	Reducing barriers to the use of data generated in routine clinical practice in healthcare decision making; bridging the gap between RWE and randomized clinical trial (RCT) approaches; addressing the evidence needs of "downstream" decision makers-HTA bodies, payers, clinical guideline developers, clinicians, and patients-as well as regulatory agencies
United Kingdom	RWD in clinical studies	Regulatory decision making by Medicines and Healthcare Products Regulatory Agency
	Systemic Anti-Cancer Therapy (SACT) dataset	Coverage with evidence development
	Patient health records, administrative records, patient registries, surveys, observational cohort studies and digital health technologies	Coverage with evidence development; outcomes-based agreements
Italy	AIFA appropriate prescribing registries	Coverage with evidence development
	AIFA outcomes-based registries	Outcomes-based agreements
Spain	VALTERMED platform	Coverage with evidence development; outcomes-based agreements
Germany	GBA registries	Coverage with evidence development
	Health insurance fund claims data	Outcomes-based agreements
	Health Data Hub	Optimization of the management of diseases by better monitoring drug effects
France	National network of hospital health data warehouses	Data sharing with public and private actors to support research and innovation
	Manufacturer-sponsored real-world data	Outcomes-based agreements
Sweden	Patient Register, Prescribed Pharmaceuticals Register, Swedish Cancer Register, Cause of Death Register, regional health records, data from Swedish Social Insurance Agency, data from Statistics Sweden	Coverage with evidence development; outcomes-based agreements
Netherlands	Registries (existing or bespoke)	Coverage with evidence development; outcomes-based agreements; hybrid OBA and CED deals for orphan drugs

4 Outlook for managed entry in Europe

- Not all types of MEA will be suitable for all markets.
- Coverage with evidence development is likely to be increasingly important for drugs that are promising but have an immature evidence base at launch.
- Personalized medicine and genetic profiling should improve response rates for some new drugs, potentially reducing the need for outcomes-based agreements.
- The expected growth in the number of tumor-agnostic and multi-indication oncology drugs will require manufacturers and payers to work more closely together to facilitate patient access.
- For at least some drugs, there is likely to be a transition from the current practice of health technology assessment to health technology management.
- Technology and the overhaul of the IT infrastructure will facilitate many aspects of managed entry.

5 What can Canada learn from Europe?

- Although Europe's healthcare systems and pharmaceutical markets are different from Canada's, their experience of managed entry and innovative access arrangements can offer valuable lessons for Canada to build its own pan-Canadian approach.
- Italy and Spain have highly regionalized healthcare systems – not unlike the Canadian model – and have been able to coordinate managed entry at the national level.
- The experiences of Italy, England, and Spain show the importance of investing in a robust digital infrastructure to collect the data needed to support innovative agreements. All three countries have developed national managed entry strategies.
- The experiences in Italy and England could be used to accelerate access to oncology drugs across Canada while post-marketing evidence to support long-term reimbursement is collected.

Conclusion:

Innovative reimbursement solutions provide opportunities for payers, pharmaceutical companies, and other stakeholders to develop long-term meaningful partnerships that can promote timely adoption of medicines by focusing on the value of new medicines through evidence.

Investments in data infrastructure can help facilitate the implementation of innovative agreements. Ultimately, this will benefit patients with timely access to treatments and can address uncertainty for payers.