INNOVATIVE ACCESS ARRANGEMENTS AND MANAGED ENTRY

WHAT CANADA CAN LEARN FROM EUROPE

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EXECUTIVE SUMMARY

Although Europe's healthcare systems – and pharmaceutical markets – are different from Canada's, their experience of managed entry and innovative access arrangements can offer some valuable lessons. All three countries focused on in the report have developed national managed entry strategies. A growing number of payers in many countries are looking to managed entry agreements (MEAs) and other innovative access arrangements (IAAs) to allow rapid access to medicines that address significant unmet needs. In some cases, these medications require additional evidence to fully access their value. There are numerous types of MEAs, but they can be categorized into three broad approaches serving different objectives: (1) financially based schemes to control budget impact; (2) outcomes-based agreements (OBAs) to manage variable drug response rates; and (3) coverage with evidence development to tackle uncertainty about a drug at launch.

Country profiles

Italy was one of the global pioneers of managed entry. The country's managed entry strategy is underpinned by an extensive national system of online registries created in 2004. Data from the registries are used to allocate funds to the regions to cover the cost of their prescriptions for innovative drugs. The system is also used to support MEA-related payments and refunds for individual patients.

England's National Health Service (NHS) was an early adopter of managed entry. In February 2021, NHS England published its Commercial Framework for New Medicines, which outlined its strategy for managed entry. Its aim is to "encourage faster market entry for new treatments and support uptake and adoption where these medicines are priced fairly and responsibly."

The NHS has negotiated dozens of what it calls "smart deals"—agreements that seek to align the needs of the healthcare system and drug manufacturers. 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 agreements in dyslipidemia and oncology.

NHS England is looking to develop long-term partnerships with pharmaceutical companies and is willing to assist them with activities such as patient identification, drug roll-out, data collection, clinical trials and production. Companies are encouraged to approach NHS England with proposals for smart deals: the organization holds 30-40 commercial consultations per year and has a triage system to prioritize ideas.

If manufacturers are willing to offer competitive pricing, the NHS can give them rapid, broad access—in some cases within weeks or even days of marketing authorization. Earlier access will come at the price of a less mature evidence base. To compensate, NICE will make greater demands for post-marketing research, including real-world data collection.

Spain was a relative latecomer to managed entry: it negotiated its first MEA in 2010. Historically, managed entry activity was mainly regional or local. The managed entry environment was transformed by the launch in 2019 of the VALTERMED online registry platform.

A key objective of VALTERMED is "going from efficacy to effectiveness" by being able to record data from the real life of patients. The platform also makes it possible to reduce uncertainty in the actual use of drugs and will facilitate payment by results. In the future, patients will be able to enter information related to their quality of life, which will allow analysis of the cost-effectiveness of drugs and support the dual objectives of sustainability and access to health.

WHAT CAN CANADA LEARN FROM EUROPE?

When considering what lessons there are for Canada from the experience of these jurisdictions, it is helpful to look at markets that have functional similarities. Italy and Spain have highly regionalized healthcare systems—not unlike the Canadian model—but both have been able to coordinate managed entry at the national level. Spain also has extensive experience of regional and local agreements and is exploring ways to accommodate regional variations within national agreements.

Like Canada, the English healthcare system relies heavily on health economic evaluation, and Canada's Drug and Health Technology Agency (CADTH) and NICE have collaborated extensively in recent years. CADTH and NICE are also working with several other HTA agencies in the United Kingdom and Australia in the AUS-CAN-UK Collaboration Arrangement.

The experiences of Italy, England, and Spain show the importance of investing in a robust digital infrastructure—AIFA's registries in Italy, the SACT database in England, and VALTERMED in Spain—to collect the real-world data needed to support MEAs. This infrastructure will allow subsequent assessment of a medicine's real-world performance as required by managed entry and innovative access agreements.

A key element of managed entry is speed of access—making innovative medicines available to patients who need them as quickly as possible while limiting the risk to the healthcare system by gathering additional evidence to overcome uncertainty or restricting reimbursement to patients who meet outcomes targets.

While the focus of managed entry tends to be on new medicines, deals may also be beneficial for mature products. It may be advantageous to negotiate new financial terms and relax prescribing restrictions to significantly expand the use of drugs that can have major impact on population health.

MEAs and IAAs also provide opportunities for healthcare systems and pharmaceutical companies to develop meaningful partnerships that can help address the challenges of adopting new health technologies by redesigning services and supporting healthcare professionals. Improving patients' quality of life by giving them timely access to promising medicines is, after all, the common goal of all healthcare systems and drug manufacturers.

WHY ARE MANAGED ENTRY AGREEMENTS AND INNOVATIVE ACCESS ARRANGEMENTS ON THE INCREASE?

We are fortunate to live in an era of unprecedented pharmaceutical innovation, which has played a major role in extending life expectancy and improving the quality of life for people around the world. These advances have made a significant difference to the lives of millions of patients and their families, but they also benefit society in general by boosting productivity and easing pressure on overstretched healthcare systems. Given that many of these interventions address significant unmet clinical needs, regulatory authorities are licensing increasing numbers of new medicines through accelerated approval routes. For example, from 2019 through 2021, 22% of new drugs that were given a favourable recommendation by the European Medicines Agency received a conditional marketing authorization, approval under exceptional circumstances or accelerated assessment.[1] In the United States, 37 of the 50 novel drug approvals in 2021 (74%) used one or more expedited programs—specifically, Fast Track Designation, Breakthrough Therapy Designation, Priority Review, and/or Accelerated Approval.[2]

Earlier marketing authorization can, however, mean that many drugs are approved on a relatively limited evidence base, including small study populations, single arm trials, and immature data. Increasingly, regulators mandate confirmatory post-marketing studies, which may take several years to complete. In the meantime, healthcare systems—which may have different priorities and favour different endpoints from regulators—have to decide whether to reimburse these new drugs fully, impose restrictions on their use, or exclude them from coverage altogether. Uncertainty about the cost-effectiveness of innovative therapies can make healthcare payers hesitant to reimburse some promising new treatments.

Assessing the value of therapies that are potentially curative is especially difficult. These treatments may be administered in a single course of therapy, or even a single dose, demanding a high price—especially if they treat rare or ultra-rare diseases. However, the duration of their effect is not always certain. In addition, allocating costs for these types of treatments can be challenging, not least because patients may not stay with the same public drug plan and may relocate to another jurisdiction within Canada.

A growing number of payers are looking to managed entry agreements (MEAs) and other innovative access arrangements (IAAs) to allow rapid access despite questions. There are numerous types of MEAs, but they can be categorized into three broad approaches serving different objectives. Table 1 summarizes the most common forms of MEAs. The common denominator is that they give patients timely access to innovative therapies by sharing the risk between payers and drug developers.

Table 1: Major categories of managed entry agreements

Broad approach	Primary objective	Type of arrangement	Level of activity	Key characteristics
Financially based schemes	Control budget impact	Price-volume agreements	Population	A drug's price is inversely linked to prescription volume
		Discounts/ rebates	Population	Manufacturer offers a concession on a drug's list price in return for (favourable) reimbursement
		Free stock	Population/ patient	Manufacturer provides some stock without charge
		Budget caps	Population	Total expenditure on a drug is limited; manufacturer covers excess costs
		Utilization/ time caps	Patient	Manufacturer covers treatment costs beyond a specified duration or level of usage
		Fixed cost per patient	Patient	Cost per patient is the same regardless of drug consumption
Outcomes-based schemes (OBAs)	Manage variable drug response rates	Outcomes guarantees	Patient	Manufacturer refunds part or all of the cost of treatment if patients do not meet specified outcomes targets; may be linked with instalment payments
		Patient eligibility controls	Patient	Access to a drug is restricted to patients who satisfy strict eligibility conditions, possibly controlled by enrolment in patient registries
		Conditional treatment continuation	Patient	Continuation of treatment is contingent on patients' meeting specified outcomes milestones
		Process of care	Patient	Reimbursement is linked to defined treatment protocols (e.g., therapeutic plans, disease management programs)
Coverage with evidence development (CED)	Tackle uncertainty	Coverage with evidence development	Population	Price and reimbursement terms are subject to review based on postmarketing trials or real-life data

More than any other region of the world, Europe has pioneered the use of MEAs and IAAs. Healthcare systems vary enormously across Europe, as do their approaches to managed entry and innovative access. Historically, the European Union played a relatively limited role in healthcare policy, but the COVID-19 pandemic has prompted a dramatic increase in EU activity in matters related to health, including high-profiles initiatives related to real-world data collection—a practice that will increasingly shape access decision making in the future.

COUNTRY PROFILES

ITALY—A TRAILBLAZER IN MANAGED ENTRY

Italy was one of the global pioneers of managed entry. The country's managed entry strategy is underpinned by an extensive national system of online registries, which the Agenzia Italiana del Farmaco (AIFA; Italian Medicines Agency) began to develop not long after its formation in July 2004.

The very first disease-specific registry was launched in November 2004 to support a national strategy for psoriasis and evaluate the standard of care around the country. In 2006, AIFA initiated the first outcomes-based managed entry agreement (MEA) linked to registries to address uncertainty for some cancer therapies. This action was a response to the growth in the numbers of cancer therapies receiving accelerated regulatory approval from the European Medicines Agency (EMA) that had the potential to have a significant impact on the national healthcare budget. Registries in other therapeutic areas were added in the following years.[3]

In 2017, the Italian government introduced a new process for evaluating the degree of innovation of promising new medicines based on unmet clinical need, additional therapeutic value and quality of evidence. Drugs that were deemed to be fully innovative were eligible for coverage by two new funds for innovative oncology and non-oncology medicines (recently consolidated into a single fund) for up to 36 months, with the possibility of an extension. In addition, all of Italy's regions were required to include these products in their formularies. The list includes some gene and cell therapies.

Products that are deemed to be fully innovative, based on the aforementioned evaluation process, are included in an AIFA registry that monitors their appropriate use and "makes it possible to access treatment in a homogeneous manner throughout the national territory."[4] The registries are also "a support tool for the evaluation of drug efficacy and for renegotiation" of access terms.[5]

In 2019, AIFA introduced a modification to its established payment-by-results model—payment-at-results. First used for cell and gene therapies, the crucial difference with payment-at-results MEAs is the addition of instalment payments to the design to avoid the need for the healthcare system to pay the full cost of therapy at administration. To date, three drugs on the list are the only drugs to be subject to payment-at-results. For two of these drugs, the instalments are all paid within a year of treatment, but the timeframe for the deal for one of them is five years. Table 2 summarises the different approaches to managed entry used in Italy.

Table 2: Managed entry approaches used 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. PbR is used to manage a high degree of uncertainty for drugs that are perceived to have an unfavourable 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 instalment 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 in cases of uncertainty regarding the potential financial impact of a new medicine (as opposed to uncertainty regarding its 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 spending on a given drug in its 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 in the form of a price reduction or a refund to the regions.

Pharmaceutical companies pay AIFA a fee of €30,000 for three years for a registry on the platform, which is controlled by the agency.[6] In 2021, 73 companies owned at least one registry on the AIFA platform.[7]

At present, AIFA operates 192 appropriate prescribing registries, 8 financially based registries and 10 outcomes-based registries.[8] 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.[9]

Data from the registries are used to allocate funds to the regions to cover the cost of their prescriptions for innovative drugs. The system is also used to support MEA-related payments and refunds for individual patients.

The Italian government has pledged to increase the fund for innovative medicines from €1 billion in 2021 to €1.3 billion by 2024 as part of a general boost to healthcare spending. Further changes to the Italian access environment are planned to make the country more attractive to drug manufacturers.

ENGLAND MAKES INCREASING USE OF COVERAGE WITH EVIDENCE DEVELOPMENT AND "SMART DEALS"

England's National Health Service (NHS) was an early adopter of managed entry. In 2002, a risk-sharing scheme was initiated to provide outcomes-based reimbursement for multiple sclerosis therapies following an unfavourable assessment by the National Institute for Health and Care Excellence (NICE). However, the MEA was later judged to be a failure because of the administrative burden, slow recruitment of patients, flawed study design, poor choice of comparator and outcomes measure, and difficulties enforcing the link between outcomes and price.[10]

In response, the NHS shifted away from OBAs to patient access schemes based on simple discounts, which remain the NHS's preferred approach to managed entry in England, accounting for more than 70% of deals.[11] In 2016, however, NHS England undertook a major reassessment of its access strategy. The Cancer Drugs Fund (CDF) was reformed to provide interim funding for promising oncology medicines pending collection of real-world data for reassessment by NICE. The CDF relies on data from Public Health England's Systemic Anti-Cancer Therapy (SACT) database, which can be used to inform outcomes analyses, financial and service planning, and policy development.

The UK government also commissioned an Accelerated Access Review (AAR), which proposed "novel risk-sharing arrangements between the NHS and the innovator that enable both parties to benefit from a product's success." In addition, the UK could adopt flexible pricing methods that have been implemented in other countries, such as price-volume agreements, conditional reimbursement, deferred payments or annuity-based pricing, outcomes-based payments, and product-service bundling.[12]

In its Life Sciences Vision, the government sets a strategic goal to "make the UK the best place in the world to discover, develop, test, trial, launch and adopt new treatments and technologies, by creating a forward-thinking commercial environment where the NHS can strike flagship deals and where proven, clinically and cost-effective innovations are rapidly adopted and spread across the country to bolster the health of the nation, deliver greater value for the taxpayer and stimulate economic growth."[13]

In January 2021, the government launched the new Innovative Licensing and Access Pathway (ILAP), which offers promising new drugs early access to a range of key stakeholders in the UK healthcare system, including the Medicines and Healthcare Products Regulatory Agency (MHRA), NHS England, NICE and the Scottish Medicines Consortium. Successful applicants are awarded an Innovation Passport, which gives them access to a product-specific team of experts to help them to outline a target development profile that will "define key regulatory and development features, identify potential pitfalls, offer access to specialist toolkits and create a roadmap for delivering early patient access." Companies can submit an application any time from the pre-clinical trial stage through to the mid-development program point but are encouraged to apply as early as possible to derive maximum benefit from the arrangement.

In February 2021, NHS England published its Commercial Framework for New Medicines, which outlined its strategy for managed entry (Table 3). Its aim is to "encourage faster market entry for new treatments and support uptake and adoption where these medicines are priced fairly and responsibly."

Table 3: NHS Commercial Framework for New Medicines

Type of scheme	Key features
Simple patient access schemes (PASs)	• Most common option: faster access because of 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

Coverage with evidence development (CED) is an important element of the Commercial Framework for New Medicines in the form of managed access arrangements, which require data collection. A recent analysis found that, in six years, 22 technologies had thus far been re-evaluated by NICE following a period of managed access. All but two of these products were cancer therapies. The MAAs for 19 drugs (86%) had involved real-world data collection, with a median duration of 18 months. All but three of the 22 technologies were recommended for routine use in the NHS following managed access. The authors concluded that, "without managed access, these technologies would most likely not have been recommended for routine use within the NHS in England."[14] Managed access will become increasingly important in the future, when a new Innovative Medicines Fund (IMF)—the non-oncology equivalent of the CDF—is launched with an annual budget of £340 million to match the CDF. The IMF will have eight guiding principles:

1. It will cover non-cancer medicines to ensure equal opportunity to benefit from promising but uncertain medicines.
2. It will cover the most promising medicines for which there is significant remaining clinical uncertainty.
3. Drugs should have plausible potential to be cost-effective and be priced responsibly (reflecting uncertain clinical benefit).

4. Managed access should be for the shortest time necessary to collect data to resolve any uncertainties identified by NICE.
5. The entire eligible patient population (as determined by NICE) should have access to drugs included in the IMF.
6. All medicines in the IMF must be re-evaluated by NICE to determine whether they should be routinely available on the NHS.
7. Patients will have the option to continue treatment (at the company's cost) even if a drug is not recommended in re-evaluation.
8. Participating companies will proportionally repay spending in excess of the fund's £340 million annual budget.

The NHS has also negotiated dozens of what it calls "smart deals"—agreements that seek to align the needs of the healthcare system and drug manufacturers. 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 agreements in dyslipidemia and oncology (See Appendix).[15]

NHS England is looking to develop long-term partnerships with pharmaceutical companies and is willing to assist them with activities such as patient identification, drug roll-out, data collection, clinical trials and production. Companies are encouraged to approach NHS England with proposals for smart deals: the organization holds 30-40 commercial consultations per year and has a triage system to prioritize ideas.[16]

Increasingly, England is the first market in Europe, if not the world, to provide access to new medicines—and uptake is also becoming much faster.

Earlier access will come at the price of a less mature evidence base. To compensate, NICE will make greater demands for post-marketing research. The NICE Strategy 2021-2026 states that "the meaningful use of real-world data and evidence will play an increasingly important role in health care decisions and in measuring the actual impact of those decisions in practice. The ability to link real-world evidence with evidence-based practice will drive a shift from recommendations being produced at a single 'static' point in time to more dynamic, living guidance, and from health technology assessment to health technology management."[17]

In June 2022, NICE published a Real-World Evidence Framework that has two key objectives:

- "Identifying when real-world data can be used to reduce uncertainties and improve guidance
- Clearly describing best-practices for planning, conducting and reporting real-world evidence studies to improve the quality and transparency of evidence."

Ultimately, NICE believes the use of RWD will help to "resolve gaps in knowledge and drive forward access to innovations for patients."[18]

SPAIN BUILDS A MULTI-PURPOSE ONLINE PLATFORM TO SUPPORT NATIONAL MANAGED ENTRY

Spain was a relative latecomer to managed entry: it negotiated its first MEA in 2010.[19] Historically, managed entry activity was mainly regional or local, led by the comunidades autónomas (autonomous communities) of Andalusia, the Balearic Islands, and Catalonia, as well as hospitals in Barcelona, Granada, Madrid, and Valencia. One manufacturer, for example, negotiated risk-sharing deals for more than 20 drugs with more than 100 hospitals.[20] Catalonia has been the autonomous community most active in managed entry: the regional administration published detailed guidelines on the implementation of risk-sharing agreements.[21]

In 2013, one multinational became the first manufacturer to negotiate a national MEA, when it offered the Ministry of Health a treatment initiation agreement for a treatment for multiple sclerosis (MS).[22] In February 2018, the company concluded another risk-sharing deal with the Ministry of Health, this time for a treatment of spinal muscular atrophy.[23]

One study identified 39 MEAs in Spain as of May 2016. Twenty-six (67%) of these deals were risk-sharing agreements, while the remaining 13 (33%) were expenditure ceilings. MEAs had been negotiated in ten autonomous communities, predominantly at the hospital level. However, all but one of the expenditure ceiling contracts were negotiated nationally.[24]

The managed entry environment was transformed by the launch in 2019 of the VALTERMED platform—the Information System to Determine the Therapeutic Value in Real Clinical Practice of Medications with a High Health and Economic Impact in the SNS. The objective of the system is to provide optimal information for appropriate decision making at different levels of pharmaceutical provision and different stages of the drug life cycle.

- Physicians can use data from VALTERMED to discharge patients, register variables and consult and use records for their patients.
- Hospital pharmacists can do the same as physicians but also consult and use the records of all patients.
- Autonomous communities are able to consult and use anonymized data for all patients in hospitals in their territory (including referrals from other regions).
- The Ministry of Health can consult and use records from healthcare system centers, manage users, and set terms for medicines and protocols.

The government sees VALTERMED as an important source of data to plug evidence gaps from clinical trials—for example, in rare diseases. In December 2021, Dolores Fraga, the Deputy Director General of Pharmacy in the Ministry of Health, described the platform as "an information system that determines the therapeutic value of drugs in real practice" and allows "long-term follow-up." She thinks "it will allow the evaluation of results not measured during the standard clinical development process and complete all the data of the drug life cycle." VALTERMED can also help to "accelerate access" to treatments with additional clinical value over established therapies."[25]

Fraga believes VALTERMED "will make it possible to assess the prevalence of a disease or clinical situation to know the true budget impact and carry out an adequate cost-effectiveness analysis and, above all, improve the efficiency of the National Health System."[26]

VALTERMED provides support for OBAs, including an innovative payment-by-results agreement with regional pricing variations for a novel treatment for diffuse large B-cell lymphoma. In the first stage of the deal, the manufacturer will receive a partial payment on account that will be adjusted based on the results in each patient and in each of Spain's 17 autonomous communities. Using data from VALTERMED, autonomous communities will periodically evaluate the results to calculate the payments that are due. In the second stage, the Ministry of Health will review the response rates and procedures annually with a view to calculating the cost of therapy that the manufacturer must bear and potentially negotiating adjustments to the deal, if necessary.[27]

OBAs with instalment payments have been crucial to Spain's CAR-T-cell programme, in the view of some thought leaders. For example, Manuel Molina, Managing Director of the Virgen del Rocío University Hospital in Seville, believes that the risk-sharing model—half the cost of treatment is paid at the time of infusion, the balance if the patient continues in remission—has been an important factor in coverage of CAR-T-cell therapy by the Spanish healthcare system. Álvaro Bonet, Managing Director of the Hospital Clínico Universitario de Valencia, agrees that risk sharing "is a very reasonable system that guarantees sustainability."[28]

A gene therapy used to treat spinal muscular atrophy is also the subject of an MEA that includes a payment-by-results deal and a price-volume agreement. Monitoring committees in each region verify compliance with the reimbursement conditions and communicate the results to the Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia (DGCYF; Directorate General for the Common Portfolio of NHS Services and Pharmacy) to determine whether the price needs to be reviewed. If sales exceed the company's forecasts, the drug's price will be reduced. Expenditure will be tracked by means of SEGUIMED—a computer application that manages data related to drug transactions between manufacturers, wholesalers and pharmacies—or a similar process. The manufacturer will be required to report sales data on a monthly basis.[29]

A key objective of VALTERMED is "going from efficacy to effectiveness" by being able to record data from the real life of patients. The platform also makes it possible to reduce uncertainty in the actual use of drugs and will facilitate payment by results. A new patient area on the platform will make it easier for them to contribute directly to data collection by completing quality of life questionnaires throughout their treatment. According to the Ministry of Health, the objective is "to carry out an evaluation of the quality of life from the beginning of the treatment; to analyse the correlation of the quality of life reported by the patient with the clinical variables of response to the treatment; as well as to carry out an evaluation and follow-up of adherence to treatment."[30] Patients will be able to enter information related to their quality of life, which will allow analysis of the cost-effectiveness of drugs and support the dual objectives of sustainability and access to health.[31]

The Ministry of Health is working to integrate VALTERMED into the IT systems of the 17 autonomous regions to allow for large-scale data sharing and to avoid duplication. In the future, it will also be possible to cross-reference VALTERMED records with health cards, which should improve the monitoring of patients.[32]

WHAT CAN CANADA LEARN FROM EUROPE?

Canada's access environment for innovative medicines is set to undergo significant changes in the coming years. Health Minister Jean-Yves Duclos has recognized the "need to have in Canada a strong pharmaceutical industry, especially given the lesson that we have seen through COVID-19."[33] The National Strategy for Drugs for Rare Diseases is expected to be supported by funding of $500 million per year for therapies for these conditions.[34] The government has also recently reaffirmed its intention to proceed with the pharmacare program to ensure access to needed medicines for all Canadians.[35]

Although Europe's healthcare systems—and pharmaceutical markets—are very different from Canada's, their experience of managed entry and innovative access arrangements can offer some valuable lessons. All three countries have developed national managed entry strategies. Italy and Spain have highly regionalized healthcare systems—not unlike the Canadian model—but have been able to coordinate managed entry at the national level. Spain also has extensive experience of regional and local agreements and is exploring ways to accommodate regional variations within national deals.

Like Canada, the English healthcare system relies heavily on health economic evaluation, and Canada's Drug and Health Technology Agency (CADTH) and NICE have been developing a growing collaboration in recent years. The two countries are both members of the Access Consortium, which seeks greater regulatory alignment but is also exploring HTA collaboration to expedite access to promising new medicines.[36] CADTH and NICE are also working with several other HTA agencies in the United Kingdom and Australia in the AUS-CAN-UK Collaboration Arrangement.[37]

The experiences of Italy, England, and Spain show the importance of investing in a robust digital infrastructure—AIFA's registries in Italy, the SACT database in England, and VALTERMED in Spain,—to collect the data needed to support MEAs. Such systems should be easy for healthcare professionals to use, and ideally able to accommodate inputs from patients to reflect the growing importance of patient-reported outcomes in evaluating drugs. Canada should therefore also consider investing in user-friendly digital infrastructure.

The funds for innovative medicines operated in both Italy and England rely heavily on managed entry. Their experience could be used to accelerate access to oncology drugs across Canada and could be helpful as the federal government develops the National Strategy for Drugs for Rare Diseases by providing dedicated funding for these therapies while post-marketing evidence to support long-term reimbursement is collected. A public consultation on rare disease therapies found that "many people felt the emphasis on the high-cost of drugs overlooked their value for patients, the health system and society as a whole." Pay-for-performance agreements were identified as one option that could be explored.[38]

While the focus of managed entry tends to be on new medicines, deals may also be beneficial for mature products. In England, the NHS negotiated a deal in 2019 with the manufacturers of hepatitis C virus (HCV) therapies to work with local health services, councils, and voluntary groups to find potential patients, test for infection and provide treatment to those who need it. According to Blake Dark, "having companies work with us to invest in finding patients, and at the same time putting that as part of the procurement around the actual acquisition cost of the medicine, is smart procurement because we're solving the problem and we're coming together, rather than just buying a drug."[39]

It may be advantageous in Canada to negotiate new financial terms and relax prescribing restrictions to significantly expand the use of drugs that can have a major impact on population health. A recent high-profile deal between NHS England and drug manufacturers will make four direct oral anticoagulants available to up to 610,000 more patients from 2022 through 2024, potentially averting an estimated 21,700 strokes and 5,400 deaths over the next three years.[40]

A key element of managed entry is speed of access—making innovative medicines available to patients who need them as quickly as possible while limiting the risk to the healthcare system by gathering additional evidence to

overcome uncertainty or restricting reimbursement to patients who meet outcomes targets. For example, NHS England negotiated a managed access agreement for a new T-cell immunotherapy within 10 days of the drug's marketing authorisation.[41] Without such deals, patients might be denied reimbursement or face long access delays pending the collection of post-marketing evidence.

MEAs and IAAs also provide opportunities for healthcare systems and pharmaceutical companies to develop meaningful partnerships that can help address the challenges of adopting new health technologies by redesigning services and supporting healthcare professionals. Improving patients' quality of life by giving them timely access to promising medicines is, after all, the common goal of all healthcare systems and drug manufacturers.

The following table summarizes the key lessons for Canada from the three individual countries that were discussed throughout the report.

Key Lessons for Canada from Europe

ITALY

- Build a national online registry system to support managed entry by collecting real-world data and supporting repayments for treatment failures
- Draw on the experience of the funds for innovative medicines in planning for the prospective new National Strategy for Drugs for Rare Diseases
- Consider the use of outcomes-based agreements linked to instalment payments for high-cost drugs that have one-time or short-term administration but long-term or potentially curative benefits (e.g., cell and gene therapies)

ENGLAND

- For promising drugs, make use of coverage with evidence development to allow very early access pending collection of additional data to support re-evaluation
- Use initiatives such as the Access Consortium and potential collaboration with England's National Institute for Health and Care Excellence (NICE) to expedite marketing authorization and health technology assessment
- Follow the model of NHS England by enabling developers of drugs that have the potential to fill unmet clinical needs to engage very early with key stakeholders in the Canadian healthcare system
- Encourage companies to propose innovative access solutions and be open to new approaches and willing to adapt methods from other countries
- Build a robust digital data infrastructure similar to England's SACT database
- Consider the use of innovative access arrangements for mature drugs that would offer broad population health benefits from much wider use
- Consider negotiating new financial terms and relax prescribing restrictions to significantly expand the use of drugs
- Develop partnerships with pharmaceutical companies at all levels of the healthcare system
- Evaluate the flexibility offered by health technology management and living guidelines driven by RWD

SPAIN

- Build a coherent national managed entry strategy but allow scope for regional, or even local, agreements
- Study the VALTERMED model of a platform that meets the needs of multiple stakeholder groups (physicians, pharmacists, regional authorities, the national Ministry of Health), can record quality-of-life data from patients, and facilitates payment by results

APPENDIX: Smart deals negotiated between NHS England and pharmaceutical companies

Date	Drugs	Companies	Technology	Indication
September 2018	Kymriah	Novartis	CAR-T-cell therapy	B cell precursor acute lymphoblastic leukemia
October 2018	Yescarta	Gilead Sciences	CAR-T-cell therapy	Diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma
November 2018	Biosimilar adalimumab	AbbVie, Amgen, Biogen, Mylan/Fujifilm Kyowa Kirin, Sandoz	Monoclonal antibody	Multiple indications
April 2019	Hepatitis C therapies	Gilead Sciences, Merck Sharp and Dohme, AbbVie	Direct-acting antivirals	Hepatitis C
May 2019	Spinraza	Biogen	Anti-sense oligonucleotide	Spinal muscular atrophy
May 2019	Ocrevus	Roche	Monoclonal antibody	Multiple sclerosis
September 2019	Luxturna	Novartis	Gene therapy	Retinal dystrophy
October 2019	Orkambi, Symkevi, Kalydeco	Vertex Pharmaceuticals	CTFR modulators	Cystic fibrosis
February 2020	Ilaris	Novartis	Monoclonal antibody	Periodic fever syndromes
August 2020	Kaftrio	Vertex Pharmaceuticals	CTFR modulators	Cystic fibrosis
December 2020	Fetcroja, Zavicefta	Shionogi, Pfizer	Antibiotics	Drug-resistant infections
January 2021	Tecartus	Kite Pharmaceuticals	CAR-T-cell therapy	Relapsed or refractory mantle cell lymphoma
March 2021	Zolgensma	Novartis	Gene therapy	Spinal muscular atrophy
April 2021	PHESGO (pertuzumab + trastuzumab)	Roche	Monoclonal antibodies	HER2-positive breast cancer
September 2021	Leqvio	Novartis	Small interfering RNA molecule (siRNA)	Familial hypercholesterolemia
October 2021	Adakveo	Novartis	Monoclonal antibody	Sickle cell disease

Date	Drugs	Companies	Technology	Indication
October 2021	Oncology pipeline drugs	EQRx	Miscellaneous	Miscellaneous cancers
November 2021	Eliquis, Pradaxa, Xarelto, Lixiana	Pfizer, Boehringer Ingelheim, Bayer, Daiichi Sankyo	Direct oral anticoagulants	Atrial fibrillation and stroke prevention
November 2021	Evrysdi	Roche	mRNA splicing modifier	Spinal muscular atrophy
December 2021	sapropterin dihydrochlor-ide	Teva	Synthetic form of cofactor BH4	Phenylketonuria
December 2021	Palforzia	Aimmune Therapeutics	Oral immunotherapy	Peanut allergy
February 2022	Libmeldy	Orchard Therapeutics	Gene therapy	Metachromatic leukodystrophy
February 2022	Jemperli	GlaxoSmithKline	PD-1 inhibitor	Endometrial cancer
March 2022	Darzalex	Janssen	Monoclonal antibody	Multiple myeloma
March 2022	Lumykras	Amgen	KRAS G12C inhibitor	Non-small-cell lung cancer
June 2022	Fetcroja, Zavicefta	Shionogi, Pfizer	Antibiotics	Infections resistant to other antibiotics
October 2022	Rukobia, Vocabria, Rekambys	ViiV Healthcare,	Antiretrovirals	HIV

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