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Overview of Health Technology Assessment Processes for Time-Limited Recommendations

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Table 1: Comparison of TLR Processes Identified Across International HTA Agencies 19

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AIFA	Italian Medicines Agency
CED	Coverage with Evidence Development
CMS	Centers for Medicare & Medicaid Services
CTG-CRM	Commission for Reimbursement of Medicines
EMA	European Medicines Agency
G-BA	Federal Joint Committee
HAS	Haute Autorité de Santé
HTA	health technology assessment
ICER	Institute for Clinical and Economic Review
INESSS	Institut national d'excellence en santé et en services sociaux
LSDP	Life Savings Drug Program
MEA	managed entry agreement
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance
NOC/c	Notice of Compliance with Conditions
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
RCT	randomized controlled trial
RWD	real-world data
RWE	real-world evidence
SMC	Scottish Medicines Consortium
TC	Transparency Committee
TLR	time-limited recommendation
TLV	Dental and Pharmaceutical Benefits Agency
ZIN	Dutch National Health Care Institute

Key Messages

- Several regulatory agencies have implemented processes to facilitate timely access to innovative therapies for patients with rare or life-threatening diseases with high unmet medical needs, typically with additional data-generation requirements to address important uncertainties in the existing evidence base at the time of regulatory approval. Many health technology assessment (HTA) agencies have adapted their processes to include time-limited recommendations (TLRs) for such therapies, which allows patients access to these medications while additional data are collected to verify the clinical efficacy, real-world effectiveness, or economic value of the new therapeutic. The objective of this Environmental Scan is to identify what HTA agencies have processes in place for TLRs and to describe these processes, if applicable.
- HTA agencies in North America, Europe, Australia, and New Zealand were considered for this report based on commonalities to the Canadian context in terms of geography and relevant regulatory or HTA and reimbursement processes. Seven HTA agencies (the National Institute for Health and Care Excellence, the Scottish Medicines Consortium, France's Haute Autorité de Santé, the Dutch National Health Care Institute, the Italian Medicines Agency, the Belgium National Institute for Health and Disability Insurance, and the Australian Pharmaceutical Benefits Advisory Committee) that have implemented formal TLR processes, through managed entry agreements, special access funds, or other related programs were identified. Most TLR programs are referred to as managed access or entry agreements, but other types include interim acceptance, conditional inclusion, assessment contingent on additional evidence development, and additional specialized programs or pathways.
- TLRs are primarily used for promising (and sometimes high-cost) medicines intended to treat a condition with an important unmet medical need; some specify that the disease must be serious and life threatening (regardless of prevalence), others indicate that the process is used for orphan drugs intended to treat rare conditions, and others consider multiple criteria or do not have prerequisite criteria for eligible indications.
- Evidence generation requirements for TLRs vary across HTA agencies and are often dependent on the nature of the clinical and economic uncertainties identified in the initial assessment; sources include later follow-up from ongoing clinical trials, new clinical trials, real-world data, or a combination of both clinical and real-world studies. Additionally, most TLR processes have explicit maximum durations for the time-limited period, which range from 2 to 7 years across the included HTA agencies (although some allow for time adjustments or renewals); however, the French and Scottish HTA agencies determine the duration of the time-limited period on a case-by-case basis.
- Overall, this report provides an overview of HTA processes for TLRs across HTA agencies in Europe and Australia, many of which may be useful to inform the implementation of future TLR processes in Canada, as well as to refine existing ones.

Background

Several regulatory agencies have implemented processes to facilitate timely approval of and access to innovative medical therapies, including Health Canada, the US FDA, and the European Medicines Agency (EMA).¹⁻⁴ Such programs allow for earlier approval of drugs that have limited evidence available to support conclusions regarding efficacy and safety, but show sufficient promise in addressing important unmet medical needs. In these cases, there is generally a requirement that a confirmatory trial with an appropriate design to address key data gaps and uncertainties either be ongoing or initiated shortly after regulatory approval.

In countries with pricing and reimbursement processes that depend on recommendations from health technology assessment (HTA) agencies, including Canada, the UK, Australia, and many European countries, accelerated or conditional regulatory approval does not guarantee timely access to treatments for patients.⁵⁻¹¹ In order for a drug with regulatory approval to be launched in regions with a centralized HTA process, it must also be deemed to have sufficient support to warrant a recommendation in favour of public reimbursement.^{1,5,7-11} As HTA agencies evaluate the comparative effectiveness and safety, budget impact, and cost-effectiveness of a new drug relative to currently available treatment options, drugs receiving regulatory approval through conditional processes may have challenges demonstrating sufficient evidence of clinical benefit and economic value through standard HTA review processes.⁸⁻¹¹

Many HTA agencies have implemented different types of recommendations and agreements in response to the changing regulatory environment, recognizing the need to balance limited health care budgets with stakeholder expectations of earlier access to innovative therapies for patients with high unmet medical needs. These programs and processes allow drugs receiving conditional approvals to be marketed under conditions that share the risk associated with uncertainties regarding the financial impact or performance of a drug.^{1,12-18} Such agreements are called managed entry agreements (MEAs), risk-sharing agreements, or managed access programs.^{1,12-20} MEAs are typically categorized as either financial-based agreements or performance-based agreements (which can also include financial components). Financial-based agreements are more common than performance-based agreements in Organization for Economic Co-operation and Development (OECD) countries overall, although the latter are also used.²¹ In some cases, reimbursement recommendations may also be contingent on the imminent availability of additional data, either through new or ongoing clinical trials or real-world evidence (RWE) activities, that will sufficiently address the gaps in the drug's evidence within a prespecified time frame.^{17,21-26} Such time-limited recommendations (TLRs) are 1 way that HTA agencies and payers can manage uncertainty regarding the evidence supporting a drug with promising preliminary data, allowing its use in patients with serious conditions and a high unmet medical need while additional evidence is collected to verify the clinical benefit.

MEAs are becoming increasingly popular globally,²¹ and TLRs may continue to play an important role in HTA for drugs with conditional regulatory approval. Even in the absence of formal procedures for implementing TLRs, some HTA agencies are using such approaches for drugs approved through conditional regulatory processes or under other conditions.²²⁻³¹ In March 2023, CADTH initiated stakeholder consultation on a proposed process for implementing TLRs in the reimbursement review procedure.³² This initiative is being

undertaken to help ensure timely access to promising new pharmaceutical therapies for serious conditions with unmet medical needs, that CADTH recommendations accurately reflect the available evidence when drugs have received conditional regulatory approval from Health Canada, and to increase the confidence in CADTH reimbursement recommendations through improved reporting and consideration of evidence gaps and post market clinical studies designed to address uncertainties in the clinical evidence, as identified in the conditional regulatory approval.³² Given CADTH's TLR initiative, it is necessary to understand what processes other HTA agencies have developed and implemented for TLRs. This Environmental Scan explores the processes for TLRs and related recommendations used by a number of other HTA agencies.

Objectives

The objective of this Environmental Scan was to identify which HTA agencies have processes in place for TLRs, and to describe these procedures, where applicable. This Environmental Scan aimed to address the following questions:

1. What HTA agencies have processes in place for TLRs?
2. What are the processes used at HTA agencies to conduct TLRs?

Methods

Literature Search Strategy

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the International HTA Database, and the websites of Canadian and major HTA agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH) terms, and keywords. The main search concepts were time-limited or conditional recommendations and drugs. The search was completed on March 10, 2023, and limited to English-language documents published since January 1, 2013. Regular alerts updated the database literature searches until the publication of this final report. In addition, the report author conducted supplemental targeted internet searches using Google Scholar and PubMed (MEDLINE), as well as searches of HTA websites. Search concepts included those relevant to the key themes of the report (e.g., time-limited or conditional recommendations, MEAs, performance-based agreements, coverage with evidence development).

Study Selection

One author screened the literature search results and reviewed the full-text articles of potentially relevant studies. HTA agencies in North America, Europe, Australia, and New Zealand were included in this report based on commonalities to the Canadian context in terms of geography, relevant regulatory or HTA and reimbursement processes, and having sufficient information available in English. Sources were considered for inclusion if they provided evidence or supportive information for HTA processes related to TLRs.

Findings

The results of the literature search for TLRs and related processes at HTA agencies are presented by country throughout this section. A comparison of some components of these processes is provided in [Table 1](#).

Canada

In Canada, early regulatory approval is facilitated through the Notice of Compliance (NOC) with Conditions (NOC/c) policy.^{3,33} Market authorization under this policy allows Health Canada to approve promising new drugs for the treatment or prevention of serious, severely debilitating, or life-threatening diseases that have an unmet medical need, particularly if there are no or few treatments currently available or when the new drug may potentially provide a significant improvement compared with existing treatment options. However, an NOC/c requires that the sponsor undertake additional clinical trials to confirm the clinical benefit of the drug and will abide by strict post approval monitoring and restrictions on advertising and labelling.

CADTH does not currently have a formal framework for TLRs. However, at the time of this report, CADTH has been considering implementing TLRs in the reimbursement review procedures, as noted by the request for stakeholder feedback published in March 2023.³² The current proposal is that TLRs with additional evidence requirements will be limited to a subset of products approved through the NOC/c policy.

In July 2018, the Institut national d'excellence en santé et en services sociaux (INESSS) published their updated approach to the evaluation of drugs for listing purposes in Quebec.³⁴ One of the recommendation options includes a conditional listing that may be dependent on clinical monitoring requirements. This condition may be recommended if INESSS deems that the drug offers a desired therapeutic value, but additional clinical data are required to do a re-evaluation, or that the drug is associated with a risk of nonoptimal use and that monitoring real-world data (RWD) is necessary to support a subsequent re-evaluation.³⁵ The conditional listing with clinical monitoring requirement is applied to drugs with therapeutic value promise, a mechanism INESSS intends to use to make progress in promoting equitable and reasonable access to medications that are often the only therapeutic option for patients.³⁶ The specific criteria regarding what attributes a drug must have to receive this classification currently remain to be defined.³⁷ Although not restricted to this scenario, it could be used in certain exceptional situations for a drug intended to treat a very rare or ultra-rare disease with a poor prognosis in terms of function or lifespan, for which clinical data are difficult to obtain and limited, and when there is an important unmet medical need.³⁷ In such situations, it is recognized that there is likely to be uncertainty in the clinical data at the time of initial evaluation and that a traditional clinical trial design is unlikely to provide answers to all questions raised during a reimbursement review.³⁷ The clinical monitoring of the drug during the conditional reimbursement period requires the collection of RWD from various sources (e.g., international or Quebec-specific registries), which must be targeted to remove uncertainties about the drug's effectiveness by including clinically significant markers of disease progression, quality of life, life expectancy, and patient function.³⁷ Although this process is relevant to the present topic, no standard time limit or indication of a case-specific time restriction was identified for additional data collection in conditional recommendations with clinical monitoring in publicly available documents from INESSS; however, recent drug recommendations by INESSS may offer some insight on

this topic. In the published recommendation for Galafold (migalastat) for Fabry disease, a minimum period of 5 years was indicated in the clinical monitoring requirement.³⁷ In the recommendation for Spinraza (nusinersen) for spinal muscular atrophy 5q, it was noted that clinical follow-up over several years was required, but a specific time limit for reassessment was not noted.³⁸

United States

In the US, the FDA Accelerated Regulatory Approval program allows for earlier approval of drug products that treat serious conditions and address unmet medical needs based on data for a surrogate end point from clinical trials.² Confirmatory studies are required to confirm the clinical benefit of a drug. If confirmed, the FDA grants the product traditional approval. If clinical benefit is not confirmed, the drug may be withdrawn from the market.

In March 2023, the FDA published draft guidance for industry regarding clinical trial considerations to support accelerated regulatory approval of oncology therapeutics.³⁹ In brief, the guidance emphasizes randomized controlled trials (RCTs) as the preferred approach over single-arm studies to support accelerated approval, the latter of which have become increasingly more common in oncology submissions; however, the FDA recognizes that there may be circumstances where a single-arm trial is appropriate, such as when there are substantial concerns about the feasibility of an RCT. Two options for trial designs to support accelerated approval are presented for manufacturers; one is to submit initial data from a single-arm trial followed by data from a confirmatory RCT that should be well under way, and ideally fully enrolled, by the time an accelerated approval submission is made; the other is to conduct 1 single RCT, initially submitting data for end points sufficient to support accelerated approval (e.g., response rate), followed by data to verify actual clinical benefit (e.g., progression-free survival and overall survival). The guidance document notes that sponsors should engage in early discussions with the FDA before initiating and while conducting trials intended to support accelerated approval.

Although the HTA process is not required for market access of new pharmaceuticals in the US, the Institute for Clinical and Economic Review (ICER) and the Agency for Healthcare Research and Quality (AHRQ) conduct HTAs and develop evidence reports for new technologies to assist public- and private-sector organizations in improving the quality of health care in the US.^{40,41}

No formal framework for TLRs was identified at ICER or AHRQ. As part of their 2020 to 2023 value assessment framework, ICER initiated a pilot program intended to generate new RWE to inform reassessments of therapies approved through the FDA accelerated approval program; however, no time limit was placed on the evidence development for reassessment.⁴² The AHRQ provides technology assessments for the Centers for Medicare & Medicaid Services (CMS) to help inform national Medicare coverage decisions.³⁸ The CMS Coverage with Evidence Development (CED) policy is intended to allow Medicare beneficiaries to access promising therapies that have insufficient evidence to support coverage decisions while additional data are collected to determine whether the technology provides an actual benefit for patients.^{38,43} In a 2022 topic refinement report, an evidence-based practice centre on behalf of AHRQ prepared recommendations for revisions to the CMS CED process, including a recommendation that there is a written plan describing the schedule for completion of key study milestones to ensure timely completion

of the CED process;³⁸ however, this does not constitute a formal TLR process and a set time limit was not specified in this new recommendation.

United Kingdom

England

The National Institute for Health and Care Excellence (NICE) may recommend managed access for a promising new treatment that requires more evidence to address uncertainties around its clinical or cost-effectiveness.²³ When managed access is recommended by NICE, an agreement is developed between the National Health Service (NHS) England and the drug manufacturer. Managed access agreements are time-limited and include the conditions under which people will have access to the NHS-funded treatment, and how additional data will be collected to address the uncertainties in the clinical and cost-effectiveness data identified in NICE's review. The agreements consist of 2 elements: first, a data collection agreement, which lasts for the shortest amount of time to collect sufficient data to address evidence uncertainties (up to a maximum of 5 years), second, a commercial access agreement between NHS England and the manufacturer that lays out the commercial terms of NHS funding and mitigates any recognized uncertainties during the managed access period. During this time, managed access oversight groups meet regularly to assess the data generated from the additional evidence generation activities. These groups include NICE and NHS England employees, clinicians and clinical experts, representatives from patient organizations, manufacturer representatives, and NHS data custodians. The groups convene to discuss the progress of data collection, analysis plans, access or treatment service issues, clinical assessment issues, and safety issues reported by patients or clinicians. Data are collected until the end date specified in the managed access agreement, at which point the guidance and recommendations related to routine use of the treatment in the NHS are updated.

Treatments under managed access in England are paid for by the NHS Cancer Drugs Fund and the NHS Innovative Medicines Fund.²⁷ A study of the first 24 drugs exiting the Cancer Drugs Fund reported that 87.5% of reappraisals resulted in recommendations for the drug to be routinely commissioned.¹⁸ The uncertainty in evidence available at the time of the original assessments of most drugs was assessed by later follow-up data from clinical trials, with only limited use of RWD.¹⁸

Scotland

In 2018, the Scottish Medicines Consortium (SMC) introduced an interim acceptance decision option based on the Scottish government's review of access to new medicines, which recommended that the SMC accept a medicine with terms requiring ongoing evaluation and future reassessment.²⁵ An interim acceptance decision may be issued if the evaluation committee determines that the new medicine may be cost-effective and additional data are expected that may address the uncertainties in the existing evidence base. This decision option applies for medicines that have been given a Great Britain Conditional Marketing Authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA), have received an MHRA Early Access to Medicines Scheme positive scientific opinion, and have been included in the Innovative Licensing and Access Pathway. This approach better aligns with early regulatory pathways for promising medicines that are expected to address an important unmet need but where considerable uncertainty exists

in the available evidence base, allowing earlier and increased access to these therapies while using an established process to assess ongoing clinical effectiveness and provide reassurance that a final decision will be made once further clinical data are available. An interim decision from the SMC is valid until the time at which the pharmaceutical company is required by the MHRA to provide the additional data from clinical and real-world studies to address the existing uncertainties. For medicines included in the Early Access to Medicines Scheme and Innovative Licensing and Access Pathway, the SMC and the manufacturing company establish regular points of contact to discuss the updated evidence and agree upon an acceptable date for a full HTA resubmission. Therefore, interim acceptance decisions administered by the SMC are time-limited, although the time frame varies on a case-by-case basis.

In addition, the SMC implemented a process in 2018 for ultra-orphan medicines intended to treat extremely rare conditions.^{26,44} The pathway for assessment of ultra-orphan medicines consists of 4 stages: first, the drug must be validated as an ultra-orphan medicine according to SMC criteria; second, a full submission, including a Patient Access Scheme, must be made to the SMC for initial assessment of clinical and cost-effectiveness of the drug; third, the submitting company must agree to collect data to meet evidence generation requirements over a period of up to 3 years to increase SMC confidence in the clinical and cost-effectiveness during reassessment; and fourth, a full update of the submission should be made after the 3-year data collection period for reassessment, at which point the SMC will make a decision regarding whether the medicine should be accepted for routine use in NHS Scotland. During the 3-year data collection period of the ultra-orphan medicine pathway, pharmaceutical companies are required to develop an evidence generation plan to capture clinical outcomes and patient-reported outcomes that address the uncertainties in clinical and cost-effectiveness identified in the initial SMC assessment report. The plan is expected to draw on additional follow-up data from existing clinical studies, new data collection activities (e.g., registries from other parts of the UK and beyond), and opportunities to collect RWD for patient-reported outcomes and other relevant information, including patient and caregiver quality of life, productivity, social and societal functioning, and indirect costs.⁴¹ During the data collection period, pharmaceutical companies are responsible for determining whether the data being collected are adequately assessing and achieving the outcomes identified in the evidence generation plan.

Europe

The EMA introduced its conditional marketing authorization in 2006 for medicines (including orphan medicines) that address unmet medical needs by treating, preventing, or diagnosing seriously debilitating or life-threatening diseases, but have less comprehensive clinical evidence than normally required for consideration.⁴ A conditional marketing authorization may be granted if the following criteria are met: the benefit-risk balance for the medicine is positive, it is likely the pharmaceutical company will be able to provide comprehensive data after authorization, the medicine fulfills an unmet medical need, and the benefit of immediate access to the medicine for eligible patients is greater than the risk associated with the limited data available. Conditional marketing authorizations are valid for 1 year and can be renewed annually. Specific obligations, including completing ongoing or new studies or other data collection activities, must be fulfilled by the authorization holder within prespecified timelines.

The EMA may also grant a marketing authorization for medicines without comprehensive data under exceptional circumstances.⁴⁵ Unlike conditional marketing authorizations, the EMA can grant authorizations under exceptional circumstances when comprehensive data cannot be obtained even in the postmarketing period. This may be because the indication for the product is so rare that comprehensive evidence cannot be reasonably generated, or the information cannot be collected in the present state of scientific knowledge or within the principles of medical ethics.

France

France's Haute Autorité de Santé (HAS) Transparency Committee (TC) doctrine (updated in 2020) recognizes that clinical benefit assessments may sometimes be necessary for products with major data uncertainties.²⁴ This is specifically in situations when not reimbursing a product with preliminary data is likely to result in a lost opportunity for patients who have a serious disease (regardless of its prevalence) with a high unmet medical need, particularly when the initial data suggest clinical utility for patients and additional evidence presented in the short-term may eliminate the uncertainties in clinical benefit. In such cases, a clinical benefit assessment may be completed contingent on the presentation of a development plan that includes clinical or real-world studies that must be predefined at the time of the initial assessment. There is a time-limited component of such recommendations; the TC stipulates the period in which the pharmaceutical company is required to meet the additional data requirements needed to eliminate the uncertainties within its initial opinion. Once the required evidence to sufficiently assess clinical benefit is submitted to the TC, a reassessment is conducted.

Of note, HAS has a mandatory legal requirement to reassess medicinal products listed on France's national health insurance every 5 years, or when new evidence warrants it.¹⁰ Therefore, all positive recommendations for pharmacy or outpatient medicines provided by HAS are TLRs in a sense, notwithstanding the previously noted process for medicines with major data uncertainties intended to treat serious diseases with a high unmet medical need.

Germany

No formal process for TLRs was identified at the Federal Joint Committee (G-BA) or the Institute for Quality and Efficiency in Health Care. Germany is unique among countries considered in this document in that all pharmacy or outpatient medicines with a marketing authorization from the EMA can immediately be launched in the German market at a price set by the manufacturer for a period of 1 year under the Act on the Reform of the Market for Medicinal Products.^{46,47} At the time of market launch, the manufacturer must submit a dossier with all available evidence necessary to prove an additional benefit of the new product over the appropriate comparator specified by the G-BA; exceptions include drugs with annual expenditures below €1 million or orphan drugs with expenditures below €50 million. The G-BA must conduct the benefit assessment within 3 months of market authorization, a task which is typically delegated to Institute for Quality and Efficiency in Health Care. The result of the assessment is published online for comment by stakeholders. Within another 3 months (6 months after marketing authorization), the G-BA publishes a binding resolution of the extent of additional benefit of the new drug, the eligible patient population, and the cost of treatment starting in the second year after market authorization (i.e., 6 months after the final

resolution document is published). Next steps for determining the reimbursement price are dependent on whether the G-BA determines that the new drug has an additional benefit over the appropriate comparator.

The Netherlands

The Dutch National Health Care Institute (ZIN) has 2 arrangements for promising drugs that do not have sufficient scientific evidence to prove added or equal value and meet the established criteria for the medical science and medical practice for reimbursement: the Potentially Promising Care program and the conditional inclusion of orphan drugs, conditionals, and exceptionals.⁴⁸ Both of these programs include TLRs.

ZIN introduced the Potentially Promising Care program in February 2019, in collaboration with ZonMw on behalf of the Ministry of Health, Welfare and Sport.²⁹ The intent of the program is to increase the quality and accessibility of the health system in the Netherlands by offering temporary funding for promising but relatively expensive interventions that are not reimbursed under the Dutch standard health care package, based on a lack of the high-quality data needed to establish, at the very least, comparable effectiveness between the new therapy and the existing standard of care. In this program, funding for a new therapy may be granted for up to 6 years under the condition that high-quality research data are collected during the subsidy period to assess the clinical and cost-effectiveness, as well as the national budget consequences, of the intervention-indication combination in the future. Within 6 months of the end of the subsidy period, ZIN conducts a reassessment using the new research data and provides a recommendation on whether the treatment can be reimbursed under the standard health package.

The conditional inclusion of orphan medicinal products, conditionals, and exceptionals policy was introduced by ZIN in October 2019.²⁸ This policy was developed in recognition of the fact that promising medicines for serious, often rare, diseases may not have sufficient data for a full effectiveness assessment at the time of registration for several reasons (e.g., the patient population is too small or too heterogeneous, or the condition is slowly progressing and requires long follow-up times to assess outcomes), but not allowing access would leave patients with an important unmet medical need without effective treatment. The policy focuses on orphan drugs (i.e., drugs for rare diseases), medicines with conditional marketing authorization, and medicines authorized under special circumstances. ZIN accepts submissions under this process either before an initial drug evaluation or after a negative opinion due to insufficient evidence has been administered. To be eligible for conditional authorization, medicines must meet the following criteria: first, the drug must have conditional or exceptional marketing authorization from the EMA, or must have marketing authorization with orphan drug status, for the indication in question; second, there must be an unmet medical need according to the EMA definition; third, the main submitter of the dossier must be the registration holder, with cosubmitters including professional associations, patient associations, and an independent research institute; and fourth, it must be possible that the drug could meet the criteria for medical science and medical practice based on the new data collected at the end of the study period. The registrant is required to design and carry out their research in collaboration with professional groups, patient associations, and an independent research institute. Because the drugs considered under this policy generally have special characteristics that may preclude the typical research methods of randomization and blinding, alternative research study methods may be agreed upon in consultation with ZIN. The study

period from research to reassessment must be indicated at the time of submission; the starting point is a maximum of 7 years, but in some cases a longer period, up to a maximum of 14 years, may be acceptable. During this time, the medicine is conditionally accessible to all eligible patients through basic insurance; however, patients must agree to participate in the study to be reimbursed. Reassessment by ZIN is initiated no later than 6 months before the end of the predefined conditional authorization period. ZIN then provides a final opinion based on the assessment of data collected during the study period, and the Ministry of Health, Welfare and Sport decides whether a medicine warrants coverage under basic insurance.

These policies follow a long history of MEAs including CED schemes for expensive hospital drugs and orphan medicines in the Netherlands, which were previously managed by the Dutch Healthcare Insurance Board (now ZIN) and originally instituted from 2006 to 2012 as conditional financing agreements.⁴⁹⁻⁵⁴ These previous CED schemes were used for inpatient products in which positive coverage decisions were conditional upon the collection of evidence for all patients receiving the drug, and reassessments were conducted after 4 years to determine whether coverage would be continued or withdrawn.^{49,50} Drugs eligible for this retired program included those with a budget impact above €2.5 million per year, a proven additional therapeutic benefit relative to appropriate comparators, and a well-defined proposal for outcomes research that uses RWE to address uncertainties in the clinical and cost-effectiveness.^{49,50}

Italy

Italy was 1 of the earliest countries to implement MEAs and is among the European countries with the largest number of such agreements.^{17,22,30,52} The Italian Medicines Agency (AIFA), with support from the Technical-Scientific Commission and the Pricing and Reimbursement Committee, assesses the innovation status of new high-price or orphan medicinal products according to 3 criteria: unmet need, clinical added value, and robustness of evidence.^{22,30,55} Scores are assigned on a 5-point scale (from absent to maximum) for unmet need and clinical added value, and on a 4-point Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) score (very low to high) for robustness of evidence.^{22,30} Generally, if the product scores highly on the first 2 points, it may be considered for an MEA, even if it has a lower quality of evidence. Innovation status and its consequent benefits have a maximum duration of 36 months; for conditionally or potentially innovative products, a re-evaluation at least 18 months after status assignment is mandatory and may lead to a change in status and associated benefits for the remainder of the original period.^{22,30} MEAs implemented by AIFA are unique in that all such agreements, regardless of whether they are performance based or financial based, require additional data collection through AIFA's distinct system of national registries. These registries are governed by AIFA but financially supported by the pharmaceutical companies, and are mandatory for pharmaceutical governance and for managing clinical or financial uncertainties.³⁰ Registries are established for each new product or indication by the Technical-Scientific Commission, which determines the place in therapy, reimbursement class, innovation status, and data necessary to address the uncertainties in the existing evidence.²² If the MEA is outcome based, clinical experts and the pharmaceutical company will be involved in the establishment of the registry.²²

All MEAs administered by AIFA are time-limited. Although most re-evaluations are planned for 24 months after MEA initiation, the duration can be adjusted on a case-by-case basis and there is often a delay beyond the 24-month period.^{30,52}

Sweden

Inclusion of outpatient drugs in the pharmaceutical benefits scheme in Sweden is determined by the Dental and Pharmaceutical Benefits Agency (TLV) (the HTA agency and reimbursement authority), which uses a value-based pricing system in its reimbursement decisions.^{56,57} Health economic guidance from TLV is also used to inform recommendations for hospital products by the New Therapies Council, although TLV does not have formal decision-making power for these products. However, the Swedish health care system is decentralized, so the 21 regions of the country are responsible for delivery of care and management of pharmaceutical budgets within their own populations.

In 2014, a process for implementing risk-sharing agreements between Swedish regional health care payers, TLV, and pharmaceutical companies was introduced to facilitate early and more equal access to new therapies in regions across the country.^{54,56} However, studies assessing MEAs implemented in Sweden since 2015 have identified that risk sharing has largely taken the form of refunds based on volumes and use, with no or few identified recommendations or agreements with requirements for additional data collection within a specified time frame.^{52,56} This is noteworthy because at least up until 2010, and perhaps up until the introduction of the risk-sharing agreement process in 2014, CED schemes that included time-limited requirements (usually 2 or 3 years) for additional RWD collection to address cost-effectiveness uncertainties were common in Sweden.^{51,52,54,56}

No current formal process for TLRs with evidence generation components was identified at TLV. However, not all information on the TLV website was available in English, and detailed descriptions of processes were not identified. Therefore, it is possible that relevant processes exist but were not captured in this report.

Belgium

MEAs were formally introduced in Belgium in 2010 as “conventions” agreed upon between the pharmaceutical companies and the National Institute for Health and Disability Insurance (NIHDI) (also called INAMI in French and RIZIV in Dutch) via the Commission for Reimbursement of Medicines (CTG-CRM), in consultation with the Minister of Social Affairs and Public Health.^{51,58,59} In the original legislation, applicants for class 1 drugs (products for which there is a claim of added therapeutic value) could request to negotiate conventions when the CTG-CRM either was unable to formulate a final proposal within 150 days of submission or if a negative recommendation was provided.^{51,56} Negotiation processes are motivated by an excessive reimbursement claimed by the applicant in terms of the therapeutic- or social-added value or by budget impact uncertainties.⁵¹ Other pharmaceuticals applicable under the 2010 legislation included orphan drugs (defined based on severity and rarity of the condition, unmet need, and degree of therapeutic benefit), specialties for a new indication for which there exists a therapeutic or societal need, or specialties for which the CTG-CRM-determined reference product is under a convention.⁵⁶ An evaluation of MEAs in Belgium signed between 2010 and 2015 (n = 71) found that number of MEAs implemented per year increased year after year. Cancer drugs represented the largest proportion of MEAs (32%), and most were concerned with

cost-effectiveness aspects or budget uncertainty. Additionally, it was found that 16 MEAs had expired by the time of analysis, and, for these expired MEAs, no new clinical studies were provided and uncertainty with these therapies was still present. In this same study, the following topics were identified as issues with the MEAs: lack of incentives to generate evidence, problems with delisting reimbursed pharmaceuticals, the impact of price confidentiality on reference pricing and performing economic evaluations, the accountability of policy decisions, short-term advantages of MEAs versus their long-term consequences, the potential snowball effect of MEAs, price setting problems with generics or biosimilars, problems with the chosen type of MEA, and a discussion about the duration of MEAs. The authors of this study also made recommendations to optimize the potential of MEAs, which included providing the correct incentives to deliver good evidence, establishing a correct link between identified uncertainties and the type and content of the MEA, reducing the risk of making the system nontransparent, providing transparent information to patients and prescribers about the temporary nature of the funding, and internal collaboration.⁵⁶

The legislation was updated to 2014, allowing the CTG-CRM to directly propose a convention in its provisional or final proposal with a two-thirds majority vote (even with negative advice), and removing the possibility for the applicant to propose a convention when the CTG-CRM provides negative advice within the prespecified time frame.⁵⁶ Furthermore, the list of authorized products for conventions was expanded to include class 2 drugs (products for which there is a claim of similar or analogous therapeutic value) for which the reference product is under convention.⁵⁶ Regardless of the situation, the final decision as to whether to request a convention negotiation with NIHDI rests with the applicant.^{51,56} Among other things, a finalized convention includes the price and reimbursement basis; the possible modalities for compensation of the budgetary risks, linked to the proposed reimbursement basis or the estimated drug use volume; terms related to scientific reporting and evaluation necessary during the convention period (i.e., additional evidence development to address uncertainties in existing data); the consequences of noncompliance with the convention; and the modalities regarding the implementation, potential revision, or extension of the convention.⁵⁶ Conventions are valid for 1 to 3 years and may be renewed periodically for up to a maximum of 3 years (though only for conventions with an initial period of less than 3 years), during which time data on drug performance and budget impact are collected for later reassessment.^{51,56,58} At the earliest 6-month time point before the convention expires, NIHDI and the associated assessment groups evaluate any new information and explore options to either prolong the convention with or without modifications, terminate the convention and remove the product, or propose that a new application be submitted.

Notably, since 2022, NIHDI has been developing an innovative medicines policy and working with a variety of stakeholders to reform reimbursement procedures to promote rapid and sustainable access to promising medicines in Belgium.^{60,61} The objectives of the reform are to enable patients to better obtain pharmaceutical specialty drugs, provide health care professionals with the necessary channels through which they can access the specialty pharmaceutical market, create an attractive competitive environment for innovative therapies and off-patent drug alternatives, and improve the sustainable use of public resources.⁵⁷ In March 2023, NIHDI published a proposed roadmap for the modernization of drug reimbursement procedures, which is currently open for consultation with representatives of the pharmaceutical industry and other stakeholders.⁵⁸ Among relevant reforms noted in the proposal is the creation of an RWE platform, which

could play various roles in the context of convention (MEA) implementation, such as advising stakeholders on evidence requirements to address uncertainties in the clinical and economic data, supporting the development of and evaluation of research plans; engaging in early dialogue with stakeholders, and conducting quality control of applications and re-evaluations after convention periods. Other proposed reforms that are relevant to the theme of this Environmental Scan include promoting rapid and equitable access to promising drugs through a “fast access” program, as well as promoting better use of the existing MEA framework. For the latter point, 2 notable recommendations include involving the RWE platform in reassessment and limiting the maximum convention time limit to 6 years – an initial 3-year period, followed by a second 3-year period as decided by the CTG-CRM on an exceptional basis.

Australia

Australia has been implementing MEAs (with a TLR component) to enhance patient access to medicines since 2011 using the Managed Entry Scheme.^{31,35,62} With this program, the Australian Pharmaceutical Benefits Advisory Committee (PBAC) may recommend Pharmaceutical Benefits Scheme (PBS) coverage at a price justified by the existing evidence base, pending submission of more conclusive evidence of the drug’s cost-effectiveness at a later date to support listing at a higher price.³¹ The PBAC will provide advice in relation to sources of uncertainty and specific evidence required to support a subsequent application. This program is widely used in Australia.²⁰ Submissions to the Managed Entry Scheme are considered under the following circumstances: first, PBAC deems there is a high clinical need for the proposed drug in the indication requested by the sponsor, based on an assessment of the prevalence or severity of the disease, whether alternative therapies are available, and the extent to which the new drug meets the unmet need, and where the drug would otherwise not be recommended for listing at the proposed price because the clinical value or extent is uncertain; and second, there is an upcoming RCT (or alternative necessary non-RCT evidence in certain circumstances; for example, data collection to confirm cost offsets in an economic analysis) due to report within a reasonable time frame (a period covered by the deed of agreement, usually 4 years), the results of which PBAC is satisfied will resolve the identified areas of uncertainty.³¹ Implementation is done via a deed of agreement, which specifies the framework and conditions of managed entry (e.g., agreed initial price, areas of uncertainty of clinical effect, time frame for resubmission). Any subsequent PBAC review of evidence specified in the agreement would also include consideration of all other relevant data, including that mandated by the Australian regulatory body, the Therapeutic Goods Administration.³¹

In addition, the Australian government has implemented the Life Saving Drugs Program (LSDP), which provides eligible patients with rare or life-threatening diseases access to essential and very expensive medicines at no cost to the patient or family.³⁷ Although not specifically guided by an HTA body, PBAC plays a role in the process and there is a time-limited component of recommendations for medicines in the program. To be eligible for listing in the LSDP, the following criteria must be met: the medicine must have been approved by the Therapeutic Goods Administration to treat an ultra-rare disease; doctors must be able to identify the disease with reasonable diagnostic precision, and the disease must have been shown to reduce age-specific life expectancy; evidence must support the use of the medicine to prolong patients’ lifespans; PBAC must have accepted that the medicine is clinically effective but was rejected for PBS listing because it is not cost-effective; there must be no other medicine listed on the PBS, or available for public

hospital inpatients, that can be used as a life-saving treatment for the disease (aside from other medicines listed on the LSDP); there must be no suitable, cost-effective nondrug treatments available; and the cost of the medicine would be an unreasonable financial burden to patients or their families. In terms of process, a medicine that is accepted as clinically effective but rejected for PBS coverage by PBAC because it does not meet cost-effectiveness criteria may be proposed for inclusion on the LSDP by the Commonwealth Chief Medical Officer to the Minister for Health. The LSDP Expert Panel conducts an assessment and various other activities (meetings, stakeholder forum, and so forth) and provides advice to the Chief Medical Officer, who makes their recommendation regarding inclusion of the medicine on the LSDP to the Minister of Health. The use and cost of each medicine on the LSDP are reviewed after 2 years of listing to ensure it is being used according to the listing recommendations and is providing the expected results.

New Zealand

Although the New Zealand Pharmaceutical Management Agency has implemented multiple funding mechanisms for expensive medicines that treat rare disorders,⁶³ no processes for TLRs were identified at this organization.

Table 1: Comparison of TLR Processes Identified Across International HTA Agencies

Country	HTA agency	Type of process	Eligibility criteria (brief)	Sources for additional data collection	Duration of time-limited period
England	NICE	Managed access	Promising new cancer and noncancer treatments	Later follow-up from clinical trials, RWD	Shortest amount of time to collect sufficient data; maximum 5 years
Scotland	SMC	Interim acceptance decision	Promising medicines expected to address an unmet need and that will treat a life-threatening or seriously debilitating condition ^a	Data from ongoing or new clinical studies, plus additional relevant observational or RWD	Until the licence holder is required by the regulator to provide more data within the obligations imposed; case-by-case basis
		Ultra-orphan medicine pathway	Ultra-orphan medicines intended to treat extremely rare conditions, validated according to SMC criteria ^b	Data from existing and new clinical studies, new data collection activities such as registries, and other RWD for PROs and other types of data	Up to 3 years
France	HAS	Clinical benefit assessment contingent on additional evidence development	Medicines with initial data suggesting clinical utility for patients with a serious disease (regardless of prevalence) with a high unmet medical need	Clinical and/or real-world studies that will provide additional evidence in the short-term to eliminate uncertainties in clinical benefit	The period in which data requirements must be met to eliminate uncertainties is stipulated in initial opinion; case-by-case basis

Country	HTA agency	Type of process	Eligibility criteria (brief)	Sources for additional data collection	Duration of time-limited period
The Netherlands	ZIN	Potentially Promising Care program	Promising but relatively expensive interventions not reimbursed under the Dutch standard health package based on data limitations	Clinical studies ^c	Up to 6 years
		Conditional inclusion of orphan drugs, conditionals, and exceptionals	Orphan drugs, medicines with conditional marketing authorization, and medicines authorized under special circumstances, where there is an unmet medical need according to the EMA's definition	Tailor-made research methods in consultation with ZIN and in collaboration with professional groups, patient associations, and an independent research institute; typically a primary clinical study and at least 1 secondary register study	Maximum of 7 years; in some circumstances, a maximum of 14 years may be acceptable
Italy	AIFA	MEA	New high-price or orphan medicinal products based on unmet need, clinical added value, and robustness of evidence	AIFA registries established by CTS	Typically 24 months; possible adjustment on a case-by-case basis
Belgium	NIHDI	Convention (MEA)	Class 1 drugs (claim of added therapeutic value) in certain circumstances, ^d orphan drugs, specialties for a new indication with a therapeutic or societal need, or specialties for which the reference product is under a convention	Unclear; in practical experience, mostly RWD to reduce budgetary uncertainty as opposed to clinical effectiveness uncertainty	Initially 1 to 3 years and may be renewed periodically up to a maximum of 3 years
Australia	PBAC	MEA	High clinical need for the drug based on assessment of the prevalence and/or severity of the disease, whether alternative therapies are available, and the extent to which the new drug meets the unmet need	Randomized controlled trial (or alternative necessary evidence, such as RWD to confirm cost offsets in an economic analysis)	Usually 4 years

AIFA = Italian Medicines Agency; CTS = Technical-Scientific Commission; EMA = European Medicines Agency; HAS = Haute Autorité de Santé; HTA = health technology assessment; MEA = managed entry agreement; NICE = National Institute for Health and Care Excellence; NIHDI = National Institute for Health and Disability Insurance; PBAC = Pharmaceutical Benefits Advisory Committee; PRO = patient-reported outcome; RWD = real-world data; SMC = Scottish Medicines Consortium; TLR = time-limited recommendation; ZIN = Dutch National Health Care Institute.

^aMedicines that have been given a Great Britain conditional marketing authorization by the Medicines and Healthcare products Regulatory Agency (MHRA), have received an MHRA Early Access to Medicines Scheme positive scientific opinion, and have been included in the Innovative Licensing and Access Pathway.

^bThe condition has a prevalence of ≤ 1 in 50,000 in Scotland, is chronic and severely debilitating, and requires highly specialized management; and the drug has Great Britain orphan marketing authorization from the MHRA.

^cLimited details are provided in English sources regarding study design and type for data collection activities.

^dMEAs can be proposed by the manufacturer if the CTG-CRM does not provide a decision within 150 days of submission, or by the CTG-CRM directly with a two-thirds majority vote.

Limitations

There are some limitations to this Environmental Scan. First, a limited literature search was conducted, and a pragmatic screening approach was used for TLRs and related processes at HTA bodies of interest; therefore, some relevant information may not have been captured. In addition, not all HTA agencies publish their full processes online, including arrangements that may potentially have confidential and variable components. Second, only resources with information available in English were reviewed for inclusion in the report. As several of the HTA agency websites reviewed had sections with English translations, but only provided technology assessment reports, guidance documents, or descriptions of processes in the country's primary language, it is possible that some relevant information was not captured. Third, the key concept of this report (TLRs) may be presented in a variety of ways; indeed, several relevant terms for such recommendations were identified during the development in this report, many of which required full review of associated processes (where available) to identify a time-limited component of the arrangements. Therefore, it is possible that additional programs exist within the countries covered in this report. Lastly, for reasons of practicality, not all countries with centralized HTA processes that may use TLRs were considered herein.

Conclusions

The use of TLRs in HTA allows patients to access promising therapies that address an unmet medical need, often for the treatment of a serious, rare, or life-threatening disease, while additional data are collected to address key uncertainties in the clinical or economic evidence at the time of initial assessment. In this Environmental Scan, many international HTA agencies, including NICE (England), SMC (Scotland), HAS (France), ZIN (Netherlands), AIFA (Italy), NIHDI (Belgium), and PBAC (Australia) have implemented formal processes that include TLRs, whether through MEAs, special access funds, or other programs. There was variability across HTA agencies in terms of the eligibility of medicines for processes involving TLRs; the types of agreements or programs used during the time-limited period; the methods by which the evidence required to address the uncertainties are collected; the stakeholders involved in assessing, reassessing, and funding the therapies during the time-limited period; the duration of the time-limited period; and whether the time-limited period is strict and consistent across files, or flexible and decided on a case-by-case basis. Formal HTA processes with TLRs were not identified in the publicly available information for CADTH or INESSS (Canada), ICER or AHRQ (US), G-BA and IQWiG (Germany), TLV (Sweden), or PHARMAC (New Zealand); however, some of these agencies did have MEAs or related processes in place without clear TLR components. Although a formal, active TLR process was not identified at CADTH, the agency recently published a proposed process for implementing TLRs in their reimbursement review procedure, which was open for stakeholder feedback at the time of this publication.

Overall, this report provides an overview of processes for TLRs across a variety of HTA agencies in multiple countries, many of which are highly relevant to inform implementation of future processes and refine existing ones.

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