CADTH

ENVIRONMENTAL SCAN

Use of Real-World Evidence in Single-Drug Assessments

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Context

Traditionally, regulatory and health technology assessment (HTA) organizations rely on evidence derived from randomized controlled trials (RCTs) for the assessment of new drugs, given that RCTs are perceived as the gold standard to demonstrate efficacy and safety. However, patients in RCTs are highly selected and may not reflect the target population in whom the drug may be used. Actual recipients in routine clinical practice present with various comorbidities, co-medications, genetic profiles, behaviours, and perspectives. Long-term effects of drugs are also difficult to assess in RCTs designed to show efficacy in a narrow time window. Drug evaluators, such as regulators and HTA agencies, are therefore faced with making decisions based on incomplete or uncertain information on some aspects of effectiveness.[1]

In view of these limitations, drug evaluators are considering the use of real-world evidence (RWE) — clinical evidence emanating from real-world data (RWD) — to supplement and enrich the evidence in support of drug regulation and reimbursement. RWD may be defined as "data regarding the effects of health interventions (e.g., safety, effectiveness, resource use, etc.) that are not collected in the context of highly controlled RCTs" and may include "primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data" (Appendix 1).[2] Although no consensus exists on what RWD is, most organizations include data generated from observational studies (e.g., cohort, case-control, or case series) and from sources such as disease registries, administrative data, health surveys, electronic health records, or medical chart reviews.[1-3] For some agencies, RWD may also be generated from pragmatic studies (also known as large simple trials or practical clinical trials), where patients may be randomized to treatments but subsequent care and follow-up more closely resembles standard clinical practice than in a conventional RCT.[1,3] RWD may also be obtained from home medical devices or wearable technologies.[4]

RWE is routinely used to inform some aspects of drug development, such as the natural history and epidemiology of a disease, to provide data on treatment pathways and comparator interventions in clinical practice, safety surveillance, and to determine resources used and costs of health care.[1,4-6] In cost-effectiveness analysis, RWE is generally accepted and frequently used.[5-7] The growth of accessible data from electronic health records, administrative claims databases and registries, combined with advanced statistical methods, may facilitate greater use of observational data to draw causal inferences on the effectiveness of treatments.[4]

In keeping with these trends, drug review programs increasingly have to contend with non-RCT data submitted to demonstrate effectiveness and safety of single drugs. This Environmental Scan was developed to better understand how international regulatory and HTA organizations address this challenge. The information presented in this report may be of value to all organizations seeking to implement processes that take into consideration the role of RWE in single-drug appraisal.

Objectives

This Environmental Scan will identify, describe, and compare how regulatory frameworks and HTA processes in Canadian and international organizations incorporate RWE in single-technology assessment of drugs.

More specifically, this Environmental Scan will aim to meet the following objectives:

- Describe the eligibility criteria for inclusion of RWE for the purpose of establishing drug effectiveness and safety in single-drug technology assessments performed by international HTA and regulatory organizations.

- Describe how international HTA and regulatory organizations use RWE of effectiveness and safety that is included as part their single-drug technology assessments.
- Describe the impact of RWE on single-drug technology assessments performed in various organizations.

This Environmental Scan will focus on the initial assessment of drugs for reimbursement or regulatory approval as part of relative effectiveness assessments and will not address the use of RWE in managed access programs or conditional approval processes.

Methods

The findings of this Environmental Scan are based on responses to the Use of RWE in Single-Drug Assessments survey (Appendix 2) and a limited literature search.

A limited literature search was conducted on key resources including Ovid MEDLINE, PubMed, HTA agencies, domestic and international ministries of health websites, and a focused Internet search. No methodological filters were applied to limit retrieval by publication type, but conference abstracts were excluded from the search results. The search time frame was limited to English and French language documents published between 2012 and 2017 (five-year time frame). Regular alerts were executed until project completion. Reference lists of relevant articles were reviewed. Websites for regulatory and HTA organizations were searched for relevant guidelines or policy papers.

The organizations listed in Table 1 were selected due to commonalities with the Canadian context, including geography and regulatory, HTA or reimbursement processes. Due to feasibility issues such as time constraints, other organizations with some relevance to the Canadian context were excluded.

Table 1: National and International Regulatory and HTA organizations

Country	Regulatory Agencies	HTA Organizations
Canada	Health Canada[a]	CADTH (CDR, pCODR), INESSS[a]
US	FDA	US Department of Veterans Affairs
Europe	EMA	EUnetHTA
UK		NICE, SMC
France		HAS
Germany		IQWiG
Netherlands		ZIN
Sweden		TLV
Finland		PPB
Norway		NoMA
Australia	TGA	PBAC[a]
New Zealand	Medsafe	PHARMAC[a]

CDR = CADTH Common Drug Review; EMA = European Medicines Agency; EUnetHTA = European Network for Health Technology Assessment; FDA = Food and Drug Administration; HAS = Haute Autorité de Santé; HTA = Health Technology Assessment; INESSS = Institut national d'excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE = National Institute for Health and Care Excellence; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee; pCODR = CADTH pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency; PPB = Pharmaceuticals Pricing Board; SMC = Scottish Medicines Consortium; TGA = Therapeutic Goods Administration; TLV = Dental and Pharmaceutical Benefits Agency; ZIN = Zorginstituut Nederland.

[a] Organizations surveyed.

Following a preliminary review of the available literature, gaps in knowledge were identified for a subset of agencies hosting drug review programs. To fill those information gaps, a survey was distributed electronically to the identified agencies. Survey respondents were asked to consent to the reporting of the information they provide by electronically signing a form attached to the questionnaire. The survey included dichotomous (e.g., Yes/No), nominal (e.g., list of options), and open-ended questions. A summary of the results of the survey were merged with related information from the literature review. Surveys received up to January 30, 2018 were included. See Appendix 2 for the complete survey questionnaire.

Findings

From the literature search, 45 articles were identified that provided information relevant to this Environmental Scan. Surveys were distributed to four agencies (Appendix 3) and responses were received from all groups.

The literature search identified sufficient information to forego the need to survey European HTA agencies. Information from regulatory agencies was deemed to be secondary, thus except for Health Canada, the regulatory agencies were not surveyed and only data from the literature review were used to inform the Environmental Scan. No relevant or English or French language information was identified for the regulatory agencies in New Zealand (Medsafe) and Australia (Therapeutic Goods Administration), and the US Department of Veterans Affairs.

Eligibility Criteria of Inclusion of RWE

Regulatory Agencies

In the US, the statutory requirement for marketing approval of new drugs for both common and rare disorders is "substantial evidence" of the drug's claimed effect.[8] Substantial evidence has been defined as data from adequate and well-controlled studies that are able to "distinguish the effect of a drug from other influences, such as spontaneous change in the course of a disease, placebo effects, or biased observation."[8] The guidance also lists specific study design aspects including a valid comparison with a control, which may be concurrent, or in limited circumstances, historical.[8] A requirement for at least two adequate and well-controlled trials has been accepted as the evidentiary standard to determine effectiveness, although flexibility has been used in applying these standards, and the FDA has outlined situations where effectiveness of a new indication may be extrapolated from existing efficacy studies, where a single adequate and well-controlled clinical investigation and confirmatory evidence may be accepted, and situations where a single multi-centre study without supporting data may be sufficient.[9] What may be accepted as "substantial evidence" takes into consideration the clinical context, including the severity of the disease (and thus patients' willingness to accept risk) and the availability of alternative treatments.

As part of the 21st Century Cures Act (2016), the FDA had been directed to develop a regulatory framework to evaluate how RWE can potentially be used to support approval of new indications for approved drugs or to support or satisfy post-approval study requirements.[10] The Act defined RWE as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials."[10] The framework shall include information on the sources of RWE, gaps in data collection activities, and the standards and methodologies for collection and analysis of RWE.[10] In 2017, the FDA issued guidance on the use of RWE to support regulatory decision-making on medical devices.[11]

Health Canada accepts all relevant data in support of a drug's efficacy and safety, including RWD, with no limits by study design or data source (see summary of survey, Appendix 4). All regulatory agencies accept

RWD to supplement clinical trial data on the safety of pharmaceuticals (both pre- and post-approval), and real-world studies may be conducted in order to meet post-authorization data requirements requested by regulators.[6,12,13] The FDA and the European Medicines Agency (EMA) have developed accelerated or conditional approval mechanisms, whereby drugs may be approved based on phase II studies or surrogate outcomes, with subsequent evidence to be developed that confirms efficacy and safety. In addition, the EMA is exploring adaptive pathway processes, which use an iterative approach to drug development allowing for early and progressive patient access to a medicine combined with RWD generation, in specific patient populations with high unmet medical need.[14]

HTA Agencies

Table 2: Evidence Accepted by Key HTA Organizations

Country (Agency)	Efficacy and Safety	Safety (additional evidence)[a]	Sources
UK (NICE)	All clinical data: RCTs, observational studies	Non-comparative trials, post-marketing surveillance data	17
Scotland (SMC)	Active-controlled RCTs, meta-analyses; in absence of active-controlled RCTs, other RCTs or uncontrolled studies accepted	Data from regulatory authorities	18
France (HAS)	Meta-analysis, clinical trials, observational studies	PSUR, pharmacovigilance and regulatory data	15,19
Germany (IQWiG)	RCTs; observational studies (in exceptional circumstances)	Observational studies, pharmacovigilance and regulatory data	20
Netherlands (ZIN)	Clinical trials, observational studies, meta-analyses, systematic reviews	Voluntary reports	21
Sweden (TLV)	RCTs, systematic reviews, comparative studies, other evidence		7,15,22
Finland (PPB)	RCTs (EPAR, published articles), other relevant studies, epidemiological studies, meta-analyses, reviews articles	PSUR, EPAR	15,23
Norway (NoMA)	RCTs, observational studies		15
Europe (EUnetHTA)	Systematic reviews, RCTs, indirect treatment comparisons, randomized pragmatic designs, other study designs	Epidemiological studies, registries or other RWD, pharmacovigilance data, data from manufacturer or regulatory agencies	24-26
Australia (PBAC)	RCTs (NRS accepted if no direct or indirect evidence available from RCTs or other exceptional circumstances)	PSUR, NRS, pharmacovigilance studies	Survey[27]
New Zealand (PHARMAC)	All study types accepted	Surveillance data	Survey[28]
Canada (CADTH)	All study types accepted		29,30
Canada (INESSS)	At least one RCT, unless in exceptional circumstances. Additional study types accepted as supporting data		Survey[31]

EMA = European Medicines Agency; EPAR = European public assessment report; EUnetHTA = European Network for Health Technology Assessment; HAS = Haute Autorité de Santé; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE = National Institute for Health and Care Excellence; NRS = non-randomized study; PBAC = Pharmaceutical Benefits Advisory Committee; pCODR = CADTH pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency; PPB = Pharmaceuticals Pricing Board; PSUR = Periodic Safety Update Report; RCT = randomized controlled trial; SMC = Scottish Medicines Consortium; TGA = Therapeutic Goods Administration; TLV = Dental and Pharmaceutical Benefits Agency; ZIN = Zorginstituut Nederland.

[a] In general, the same study types were eligible for the assessment of efficacy and safety. Those listed specifically for safety were in addition to other data.

Two articles reviewed the evidence requirements of European HTA agencies for assessments of new pharmaceuticals.[7,15]

The European Network for Health Technology Assessment (EUnetHTA) reviewed the evidence requirements for HTA of new pharmaceuticals from individual European national agencies responsible for reimbursement.[15] In total, 29 countries provided data which included their manufacturer submission template or submission guidelines in use up to June 2013. The study types accepted to determine clinical effectiveness were specified by 23 countries and included all clinical research (1 country), RCTs and/or clinical trials (21 countries), or comparative studies (3 countries). In addition, eight countries specified observational studies and five specified meta-analyses or systematic reviews. Five countries accepted additional study types for safety data including non-comparative trials, post-marketing surveillance data, case reports, patient registers, observational studies, or pharmacoepidemiological studies.[15]

Makady et al.[7] examined the policies of six HTA agencies on the use of RWE. This included a literature search and interviews with representatives from six HTA agencies: Swedish Dental and Pharmaceutical Benefits Agency (TLV), UK National Institute for Health and Care Excellence (NICE), German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), French Haute Autorité de Santé (HAS), Dutch Zorginstituut Nederland (ZIN), and the Italian Medicines Agency (AIFA). The agencies accepted all available evidence for initial drug assessments, including RWE. Although most agencies did not specify which RWD sources or methods should be used, three (NICE, IQWiG, ZIN) provided suggestions for specific RWD sources and guidance on the suitability of these sources to answer different questions.[7]

Using data from the two reports described above, survey responses and individual agencies guidance or policy documents, a summary of the study types accepted by the HTA agencies specified in the Environmental Scan protocol was compiled (Table 2 and Appendix 4). The agencies accepted both randomized and non-randomized clinical data as part of the initial drug submission. There were four agencies that requested RCTs to demonstrate the efficacy and safety of a new drug, but were willing to accept non-RCT data in certain circumstances (IQWiG, Scottish Medicines Consortium [SMC], Pharmaceutical Benefits Advisory Committee [PBAC], Institut national d'excellence en santé et en services sociaux [INESSS]). Most agencies requested additional non-RCT safety data, such as Periodic Safety Update Reports (PSURs) or other pharmacovigilance data. Information on evidence requirements for resubmissions was found for seven agencies (INESSS, CADTH, HAS, SMC, ZIN, PBAC, and Pharmaceutical Management Agency [PHARMAC]). Of these, CADTH listed specific criteria for new evidence, including data from one or more RCTs (preferred), and non-randomized studies, which may be particularly useful if there was uncertainty regarding the persistence of efficacy or if long-term safety or efficacy data were required, if RCTs were not possible due to a limited number of patients or for ethical reasons, if RCT data lacked relevant comparators, there was uncertainty regarding the dosage in clinical practice, or if RCTs had limited external validity.[16]

Use of Real-World Evidence

Regulatory Agencies

Three articles were identified that examined the frequency with which regulatory bodies used non-RCT data in their deliberations.[32-34] Hatswell et al.[32] investigated the number of EMA or FDA approvals of drugs based on evidence other than RCTs. Data available from EMA and FDA websites were reviewed for all drugs approved between January 1999 and May 2014 (excluding generic drugs, biosimilars, vaccines, fixed-dose combinations of existing drugs, antimicrobial drugs, and blood products). The number of indications approved based solely on uncontrolled studies, without either the pivotal or supporting studies being RCTs, was reported. In this review, uncontrolled studies were described as single-arm observational studies,

historically controlled studies or randomized dosing studies (patients randomized two or more regimens of the experimental drug). In total, EMA issued 795 approvals, of which 44 indications (5.5%) were based on uncontrolled trials.[1] Eight approvals were extensions of indications and 36 were for products with no RCT data in an approved indication. Nine applications based on uncontrolled data were either rejected by the EMA or were withdrawn by the manufacturer.[32] Between 1999 and 2014, the FDA approved 774 indications including 60 (7.8%) approved based on uncontrolled studies (48 new drugs; 12 extensions of indications).[32] One application based on uncontrolled data was not approved by the FDA.[32] The majority of indications approved based on uncontrolled studies were in oncology (66%), with 20% of indications approved for rare metabolic disorders.[32]

The National Organization for Rare Disorders conducted a review of the evidence used by the FDA to approve orphan drugs.[33] Publicly available documents for non-cancer orphan drugs approved by the FDA between 1983 and 2010 were reviewed, and those approved based on evidence other than the conventional standard of "two adequate and well-controlled studies" were noted. Of the 135 drugs approved 90 (67%) were based on evidence that did not meet conventional standards, although the report did not quantify to what extent approvals were based on a single well-controlled trial versus other forms of evidence including RWE.[33]

Davis et al.[34] reviewed the evidence available for cancer drugs approved by the EMA between 2009 and 2013. During that time, EMA approved 48 drugs for 68 cancer indications, of which eight indications (12%) were approved based on uncontrolled studies.[34]

The survey respondent from Health Canada stated that sufficiently large well-constructed RCTs are considered the least biased source of efficacy and safety data to inform risk-benefit assessments, and although RWD is accepted, the weight of this evidence in regulatory decisions varies depending on the situation. For example, RWE may provide significant added value when assessing drugs for populations not well studied in RCTs, where there is significant unmet need, for innovative medicines or priority reviews, and when RCTs are not feasible (ultra-rare conditions) or unethical situations (pregnancy). RWE may provide supportive data that has greater external validity, as well as providing information on subpopulations, off-label use, misuse, adherence, and to validate surrogate outcomes. The Therapeutics Products Directorate is currently in the early stages of exploring the enhanced use of RWE to support pre-market regulatory decisions (Appendix 4).

HTA Agencies

Makady et al.[7] examined the policies of six European HTA agencies on the use of RWE for initial drug submissions, using data from a literature review and interviews with representatives from NICE, TLV, IQWiG, HAS, ZIN, and AIFA. With regard to the evaluation of effectiveness, the authors found that all agencies used evidence hierarchies that placed RWD on a lower level of quality and reliability than RCTs.[7] Thus the agencies affirmed that RWE may be used to confirm or supplement, not replace, the findings from RCTs on the treatment effects of drugs.[7] Under specific circumstances only would RWD be used to demonstrate treatment effects. The examples provided included the following: in the absence of RCT data (NICE, ZIN, IQWiG); in the absence of head-to-head RCTs, RWD may be used to inform indirect treatment comparisons (NICE, ZIN); or to supplement RCT data if data on specific subpopulations or long-term follow-up were lacking (NICE, ZIN). Makady et al.[7] reported that in all cases, the agencies required an explicit justification why RWD were used and clear discussion of the biases associated with the RWD and its consequences on treatment effect estimates.[7] Any conclusions on treatment effects that were based on RWE would more circumspect than those based on evidence from RCTs.

A subsequent study[5] by members from this research team evaluated the use of RWD for reimbursement decisions by five HTA organizations in Europe (NICE, SMC, HAS, IQWiG, and ZIN) for seven drugs indicated

for melanoma (ipilimumab, vemurafenib, dabrafenib, cobimetinib, trametinib, nivolumab, pembrolizumab). In total, 52 HTA reports published between 2011 and 2016 were included in the review, and of these, 28 (54%) included RWD. RWD were used to estimate the incidence or prevalence of melanoma in all 28 reports, and to inform drug efficacy and safety in seven (13.5%) and six reports (11.5%), respectively. The study designs providing evidence for efficacy included six observational studies, six non-randomized phase I or II trials, and one registry study. For safety, four non-randomized phase I or II trials and three observational studies were included. In most instances where RWD were used there was no reported appraisal on the validity of the data (33%) or validity was reported as unknown (51%). A negative appraisal of the validity of the RWD or its source was reported in 12% of cases and this was largely due to decision-makers perceptions of the low reliability of RWD to estimate effectiveness because of the potential for bias with observational studies.[5]

Makady et al.[5] noted differences between the HTA organizations in their use of RWD, although given the relatively small number of reports available for some agencies these trends should be interpreted with caution. All 10 NICE reports and both ZIN reports included RWD, whereas RWD were included in 3 of 13 SMC reports (23%). RWD were included in 62% of HAS reports (total N = 8) and 53% of IQWiG reports (total N = 19).5 Melanoma incidence and prevalence was the most common reason for including RWD in relative effectiveness assessment reports, accounting for 6% (SMC) to 100% (ZIN) of the agencies' use of RWD. IQWiG and ZIN did not use RWD to inform safety or efficacy in any report. SMC used RWD for safety or efficacy in 6% to 12% of cases, HAS for 9%, and NICE for 22% of cases.[5] The authors stated that the use of RWD were consistent with the agencies policies toward RWE based on previous work.[5,7]

The review of policy and guidance documents for Canadian, Australian and New Zealand HTA agencies, and the EUnetHTA showed similar findings as in the first Makady report.[7] The agencies stated a preference for RCTs, specifically head-to-head RCTs, with greater weight assigned to well-designed RCTs over other forms of evidence (Appendix 4). RWD could provide complementary data to RCTs, but as the sole source of data is unlikely to represent conclusive evidence of treatment benefits. The agencies listed a number of situations where RWE would provide particular value to decision-making including the following: conditions that without intervention would be fatal within a short period of time ("dramatic effect"); significant unmet need; impractical to conduct RCTs due to the limited number of patients; unethical to conduct RCTs (e.g., during pregnancy); and to identify serious, long-term or rare adverse effects (Appendix 4). Some survey respondents also cited examples where RWE was used to provide efficacy and safety data versus an active comparator for drugs where only placebo-controlled trials were available. In the presence of RCT data, RWE may be used to address applicability issues, or address other outstanding uncertainties from RCTs such as persistence of effects, adherence, dosing, and utilization in clinical practice.

A report by Griffiths et al.[35] examined the role of non-comparative evidence in HTA decisions. Between 2010 and 2015, a total of 549 appraisals were extracted from three HTA agencies: NICE (118 appraisals); IQWiG (169) and CADTH (262). Non-comparative evidence was considered in 38%, 12% and 13% of NICE, IQWiG and CADTH appraisals respectively, and was the only evidence presented in 4%, 4% and 6% of appraisals respectively.[35] This non-comparative evidence consisted most frequently of single-arm studies (included in 13% to 24% of appraisals per agency), single-arm extension studies (3% to 14%), randomized dosing studies (5% to 13%), or other studies (3% to 8%; case series, individual patient data, audits).[35] The disease states where non-comparative data were accepted most frequently included neoplasms (43 appraisals), followed by infections (21 appraisals). Thirteen appraisals that included non-comparative data were for orphan diseases.[35]

The non-comparative data were used to inform efficacy or safety in 30% to 33% of NICE appraisals, and 28% of CADTH reviews, but only 3% of IQWiG appraisals.35 Although CADTH and NICE were critical of the lower quality of the non-comparative evidence, these agencies were willing to consider the non-comparative evidence in the absence of higher quality data. IQWiG, in contrast, was less willing to consider

non-comparative data, and it deemed non-comparative data to be acceptable in only one review for a drug for hepatitis C. The agencies stated that non-comparative evidence may be acceptable in situations where effective treatment alternatives are lacking or there is high unmet clinical need, in small patient populations where an adequately powered comparative trial may not be possible, if the anticipated magnitude of the treatment effect is sufficiently large that it would be unethical to conduct a comparative trial (e.g., hepatitis C), or the disease was life threatening and thus it would be unethical to compare against a less efficacious treatment.[35]

The review by Griffiths et al.,[35] found that few submissions were granted a positive appraisal based solely on non-comparative evidence. NICE issued positive decisions (recommend or recommend with restrictions) in 38 of 45 (85%) appraisals that included non-comparative data, and 3 of 5 (60%) based on non-comparative evidence only.[35] For CADTH, positive recommendations were reported for 22/34 (65%) of appraisals that included non-comparative data, and 11/16 (69%) of those based solely on non-comparative evidence.[35] Positive recommendations were reported for 7/21 (33%) of IQWiG appraisals that included non-comparative data, and 1/6 (17%) based solely on non-comparative data.[35] Among all submissions reviewed, 3%, 0.6%, and 4% were approved based solely on non-comparative evidence by NICE, IQWiG, and CADTH respectively.[35] Of note, not all drug evaluators may consider evidence from non-comparative trials as fulfilling their definition of RWE. Indeed, many non-comparative studies are conducted in the same stringent context as RCTs and are thus no more reflective of the "real world."

With respect to rare diseases, there were discrepancies noted among agencies' policies regarding the use of RWE. In the paper by Makady et al.[7] three agencies (TLV, NICE, and ZIN) stated that non-RCT data could be used for decision-making in situations where RCT data were sparse, but one stated that non-RCT data presents a greater risk to validity of conclusions and should thus be avoided (IQWiG). In their General Methods document,[20] IQWiG stated that there is no convincing argument to deviate from the evidence hierarchy when assessing drugs for rare conditions; however, in case of extremely rare diseases, the requirement for parallel comparative trials may be inappropriate. In these situations, use of historical patient data may be required to assess the expected course of disease without the new treatment.[20] Three other non-European HTA agencies (CADTH, INESSS, PBAC) expressed a willingness to use non-RCT data in some cases where RCTs were not feasible due to the limited number of patients (Appendix 4).

Nicod et al.[36] conducted an analysis of reimbursement decisions of four HTA agencies for 10 orphan drugs. Representatives from NICE, SMC, TLV, and HAS were interviewed on a number of themes including evidentiary requirements for orphan drugs and dealing with uncertainty. None of the agencies had minimum requirements for evidence, but phase III comparative trials were preferred by all.[36] The level of evidence accepted differed within the context of the clinical claim for two of the agencies. TLV required higher scientific and methodologic standards be met for interventions claiming superior efficacy with a price premium, and accepted greater uncertainty for noninferior efficacy and low price or for treating otherwise untreatable diseases.[36] HAS judged the quality of evidence depending on the prevalence of the disease and availability of recruitable patients, and the relative improvement in clinical benefit rating (Amélioration du service médical rendu).[36] The agencies stated that registry data and historical controls may be acceptable in certain situations: if no other data were available (NICE) or if it was the best available data (SMC, TLV); to provide long-term data on safety and efficacy, or on disease progression if no alternative treatments existed (HAS); for economic modelling (NICE); or when the disease was rare or in other exceptional circumstances (SMC).[36]

Impact and Implications of RWE

Although stakeholders generally agree on many uses of RWD that may contribute valuable information for regulatory and reimbursement decision-making, the use of RWE to answer questions or relative effectiveness of interventions is controversial and some question the possible impact of increased reliance on these data. At the regulatory level, acceptance of a "lower standard" of evidence and accelerated approvals may allow unsafe or ineffective products to reach the market.[37,38] The authors of one paper stated that drugs approved based on data with greater uncertainty, such as non-randomized studies, uncontrolled studies or surrogate outcomes, will be a challenge for HTA organizations in making relative effectiveness assessments.[39] Modelling cost-effectiveness based on such data will be subject to high uncertainty, and this uncertainty should not be underestimated by decision-makers and payers.[39] Others argue that a cultural shift is necessary so that the evidence developed is not so heavily weighted toward generating precise answers to narrow questions.[40] Recognition that the evidence needed to support regulatory approval and the evidence needed to inform treatment decisions are part of a single continuum will provide incentive to manufacturers and sponsors to evaluate treatment effects in real-world conditions.[40] Integrating these two processes will allow progressive demonstration of a therapy's safety and efficacy (which may include the use of RWE), and will yield a comprehensive understanding of how to use medical products in practice.[40]

Among the advantages listed for using RWD, external validity is frequently mentioned.[6] However, some HTA agencies have challenged the assumption that RWD has inherently greater generalizability.[41] Country-specific observational studies or pragmatic trials may be affected by local clinical practice patterns, thus their external validity should be examined carefully.[5,24] Moreover, the purported external validity advantage of RWE is meaningless if the internal validity of the data is in question.[41] It has been argued that despite advances in the methods to adjust for bias in non-randomized studies, it is unclear which methods are most appropriate in any given circumstance and the risk of confounding cannot be eliminated.[39] Incomplete or invalid data is a major problem for many sources of RWD which may limit the ability to gather meaningful data.[6,41,42] For example, in the Netherlands, RWD were used to evaluate bortezomib in patients with advanced multiple myeloma as part of conditional reimbursement scheme.[43] RWD were useful to determine who received bortezomib and how it was administered in daily practice but it was limited in generating robust evidence of real-world safety and effectiveness, due to missing data from patient charts (for prognostic factors, efficacy measures, and harms) and due to treatment variations and dynamics in care during the new drug's uptake in practice.[43] In other examples, however, RWD were of sufficient quality to provide supporting evidence on efficacy and safety, which were of value to the regulatory and reimbursement decisions for deferiprone in Canada.[44,45] Another issue raised was the potential for publication bias, which is as much a problem for real-world studies as for RCTs.[41]

Despite growing interest in the use of RWE in decision-making, Makady et al.[5] found no substantial change in the use of RWD over time in their review of drugs for melanoma, although these findings should be interpreted with caution given the limited scope of the review and small number of reports included. The authors suggested possible reasons for the limited impact of RWD in decision-making. Robust RWD may not be available at the time when initial HTAs are conducted.5 Others have also noted this issue.[6,24] Another factor suggested was the absence of guidance on systematic approaches for the inclusion, analysis, and interpretation of RWD in HTA.[5] The authors noted that collaborations such as IMI GetReal and EUnetHTA are working to address some of these issues, and that further dialogue is needed among HTA agencies.[5] Another potential factor is the presence of cultural barriers against the use of RWD in which adherence to evidence hierarchies automatically assesses RWE as being of lower quality or lower value.[6] Two HTA agencies noted the limitations of strict adherence to evidence hierarchies, and stated that adoption of a hierarchy should not preclude the use of valuable non-RCT data.[7] Makady et al.,[7] commented that guidance from HTA agencies is generally lacking on the potential relevance of pragmatic trials, and as a result these may be excluded from decision-making.

Limitations

The intent of the Environmental Scan was to provide a snapshot on the acceptance and use of RWE, rather than a comprehensive review. It was based on a limited literature search, and results were screened for inclusion by a single researcher. Included articles were limited to those available in English and French, thus some relevant references may have been missed or were excluded (e.g., the current version of the IQWiG General Methods paper v. 5.0, available in German only,[46] or ZIN guidelines on orphan drugs).[47] The scan focused on initial regulatory or reimbursement decisions and did not address the use of RWE in managed access programs or conditional approval processes where drugs are approved based on early evidence with the requirement that additional evidence to be collected to resolve existing uncertainties. In addition, the scan did not consider use of RWE in the proactive reassessment of single drugs, in class-based evaluations of multiple drugs by HTA organizations, in cost-effectiveness assessments, or in the assessment of hospital-only medical products. Given the interest in the use of RWE among HTA and regulatory agencies, their policies in regard to RWE may be evolving, and some material summarized here may be out of date.

There was no consistent definition of RWD or RWE among organizations, with some agencies not using these terms in their submission or guidance documents. A number of the included articles examined the use of uncontrolled clinical trial data in decision-making. While these are non-RCT data, they may not meet the definition of RWD. The lack of a clear and consistent definition of RWD/RWE may complicate comparisons of policies and practices between agencies.

Conclusion

Regulatory and HTA agencies assessing single drugs can manage the influx of RWE either at the level of study eligibility, where evidence is accepted or declined for review; or at the review stage, where evidence is appraised to draw conclusions. Findings in this Environmental Scan indicate that RWE is accepted for inclusion in single-drug technology assessments by the agencies discussed in this report; however, the way in which RWE is used and its value to decision-making depends on the clinical context, the availability or feasibility of conducting RCTs, and the agencies' policies and practices.

The evidence hierarchies which are used by regulatory and HTA agencies place RWE at a lower level of quality or value than RCTs. Thus, RWE is used to confirm or supplement, rather than replace, the evidence from RCTs on the safety and efficacy of drugs. There was recognition of specific situations where RWE may be of particular value, such as: when RCTs are not feasible (very rare conditions) or are unethical (pregnancy), there is significant unmet need or in life-threatening conditions, and to identify serious, rare or long-term adverse effects. HTA agencies stated that the sole use of RWE to determine the comparative effects of a drug requires a prudent approach and any conclusions based on RWE alone would be more circumspect.

Recent reviews showed that non-RCT data were used infrequently to inform relative benefit assessments by regulatory bodies or HTA agencies; although for certain conditions, such as oncology, RWD use was more common. Regulatory bodies are exploring ways that RWE could play a larger role in initial market access decisions, extension of indications, or in situations where there is considerable unmet need. There is also interest in how RWE can support or satisfy post-approval study requirements.

As more information on the impact of RWE on drug marketing approval and reimbursement becomes available, the place of RWE in single-drug assessments will become more clear, which may be translated into the development of new processes and standards across the globe.

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Appendix 1: Key Definitions

	IMI GetReal	ISPOR
RWD	"An umbrella term for data regarding the effects of health interventions (e.g., safety, effectiveness, resource use, etc.) that are not collected in the context of highly controlled RCT's. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes (PRO) and health-related quality of life (HRQoL). RWD can be obtained from many sources including patient registries, electronic medical records, and claims databases." Page 27	Data used for decision-making that are not collected in conventional RCTs. Sources of RWD include: • registries • administrative data • health surveys • electronic health records or medical chart reviews • supplements to RCTs (additional data gathered on PROs, resource use and costs) • large simple trials or pragmatic clinical trials.
RWE	"Real-world evidence (RWE) is the evidence derived from the analysis and/or synthesis of real-world data (RWD)." Page 27	
RWS	"Studies investigating health interventions whose design does not follow the design of a highly controlled RCT and aims to reflect health intervention effectiveness in routine clinical practice. Real-world studies do not typically include randomisation of trial subjects, but there are exceptions (e.g., pragmatic clinical trials). For the purposes of GetReal, real-world studies include, but are not limited to, the following: pragmatic clinical trials, non-interventional/ observational studies, drug utilisation studies, post-authorisation efficacy/safety studies. RWS, by definition, generate RWD, which can subsequently be analysed and/or synthesised to produce RWE. (See also: "real-world data," "real-world evidence," "effectiveness study," "drug utilisation study," "pragmatic clinical trial," and "non-interventional/ observational study")." Page 27	

IMI = Innovative Medicines Initiative; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; RWS = real-world studies.
Source: Goettsh W and Makady A.,[2] Garrison et al.[3]

Appendix 2: Use of RWE in Single-Drug Assessments Survey

Survey Questions

Context and Definitions

1. What type of organization do you represent? Choose an item.
2. Does your organization have a standard definition for "real-world evidence?"

☐ YES ☐ NO

If YES, please use the box below to provide the definition.

3. Can RWE be included in the assessment of single drugs by your drug evaluation program(s) to answer questions of clinical effectiveness and/or safety?

☐ YES ☐ NO

You can enter any additional comments in the box below

If you answered NO to this question, then this is the END of the survey. Thank you for your responses.

Eligibility

For the purpose of this section, please use your definition of RWE. If you do not have a definition, please include information on the eligibility of evidence generated from the outcomes of interventions provided outside the context of formal clinical trials.

4. For which type of drug submission and under which circumstances can RWE be submitted? (Check any that apply)

	Initial drug submission	Drug resubmission (for the same indication)
Rare condition	☐	☐
Priority review	☐	☐
Significant unmet clinical need	☐	☐
Ethical considerations preventing RCT conduct	☐	☐
Innovative/breakthrough medicine	☐	☐
Potentially large budget impact	☐	☐
NO specific circumstances (eligible in ALL submissions)	☐	☐
Other (please specify)	☐	☐
Other (please specify)	☐	☐

5. Please specify the RWE study designs eligible for inclusion in drug submissions. (Check any that apply)

	Initial drug submission	Drug resubmission
Cross-sectional studies	☐	☐
Case-control studies	☐	☐
Prospective cohort studies	☐	☐
Retrospective cohort studies	☐	☐
"Pragmatic" trials[a]	☐	☐
Uncontrolled studies	☐	☐
ANY study design	☐	☐
Other (please specify)	☐	☐

[a] Large simple trials designed to test the effectiveness of an intervention in broad routine clinical practice

6. What data sources can be utilized for the generation of eligible RWE? (Check any that apply)

	Initial drug submission	Drug resubmission
Health surveys	☐	☐
Disease registries	☐	☐
Administrative data	☐	☐
Electronic patient records	☐	☐
Other (please specify)	☐	☐

Are there circumstances that would allow exceptions to the acceptability of data sources?

7. Does your organization request RWE from manufacturers to complement single-drug technology assessments?

☐ YES ☐ NO

7a. If YES, are requirements for study design and data sources (if any) in terms of study design and data sources mandatory?

☐ YES ☐ NO

If yes, what are the consequences of non-conformity?

8. Where eligible RWE is accepted, does it need to be captured from individuals treated in your jurisdiction or country?
   ☐ YES ☐ NO

8a. If YES, what kind of advice, if any, is communicated to the drug sponsor to better align the RWE population to the target patient population? Examples include considerations of data sharing and connectivity.

9. Does your agency have any plans to change its current approach relative to RWE in the future?
   ☐ YES ☐ NO ☐ UNCERTAIN

9a. If YES, please share the rationale and briefly summarize any concrete plan of action

Use of RWE

10. What gaps can RWE of effectiveness and safety fill in the assessment of single drugs for marketing approval or reimbursement? (Check any that apply)

	New drug submission	Drug resubmission
Establish the effectiveness of the intervention	□	□
Supplement the RCT evidence on effectiveness of therapy	□	□
Establish the safety of the intervention	□	□
Supplement the RCT evidence of safety	□	□
Provide information on treatment adherence	□	□
Validate surrogate outcomes	□	□
Other purpose (please specify)	□	□

11. Please select the circumstances below in which RWE would likely bring significant added value and be given more weight, relative to conventional situations where the evidence base consists of RCT data of sufficient quality and quantity.

	New drug submission	Drug resubmission
Rare condition	☐	☐
Priority review	☐	☐
Population not well studied in RCTs (few and/or small RCTs)	☐	☐
Significant unmet clinical need	☐	☐
Innovative/breakthrough medicine	☐	☐
Potentially large budget impact	☐	☐
RWE with superior external validity relative to the population of interest	☐	☐
Not applicable: No circumstance can influence the weighting of clinical evidence	☐	☐
Other (please specify)	☐	☐

12. What are, according to your perceptions, the added benefits of using RWE for single-drug submissions, in comparison to, for example, RCT evidence?

13. What are, according to your perceptions, the limitations of using RWE for single-drug submissions? And what are possible solutions to such limitations?

14. How do you reconcile conflicting results from RWE and RCT evidence? Please describe decision-making processes, if any.

Case example

This last section will ask you to describe an example of a drug review in which RWE was included, appraised, considered and had some impact on the final decision.

15. Please provide information on a drug that was reviewed by your organization using RWE. Please limit to RWE submitted for the purpose of addressing questions of safety and/or effectiveness.

Drug brand name:
Generic name:
Manufacturer name:
Year of review:
Indication reviewed:
Type of submission:

What kinds study designs were submitted as evidence (including but not limited to RWE)? (Check any that apply)

- ☐ RCT
- ☐ Pragmatic trial
- ☐ Uncontrolled (single arm) studies
- ☐ Cross-sectional studies
- ☐ Case-control studies
- ☐ Cohort studies
- ☐ Other (please specify)

What data sources were used for the RWE? (Check any that apply)

- ☐ Registry data
- ☐ Administrative data (insurance claims, hospitalizations, etc.)
- ☐ Patient health records
- ☐ Survey data
- ☐ Other (please specify)

What aspect(s) of the drug review did the RWE help inform? (Check any that apply)

- ☐ Drug effectiveness relative to an inactive control or baseline health states
- ☐ Drug effectiveness relative to an active comparator
- ☐ Safety relative to an inactive control or baseline health states
- ☐ Safety relative to an active comparator
- ☐ Adherence to treatment
- ☐ Validity of surrogate outcomes
- ☐ Other (please specify)

In your opinion, in what way and to what extent did the RWE add value to the drug review and/or did it influence the final decision?

End of Survey — Thank you for your help.

Appendix 3: Information on Survey Respondents

Country	Organization Represented by Survey Respondents
Canada	Health Canada
Quebec, Canada	INESSS
Australia	PBAC
New Zealand	PHARMAC

INESSS =Institut national d'excellence en santé et en services sociaux; PBAC = Pharmaceutical Benefits Advisory Committee; PHARMAC = Pharmaceutical Management Agency.

Appendix 4: Summary Table

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
HTA Agency			
Canada — CADTH	All evidence accepted; head-to-head comparison clinical trials with principal comparators of particular interest. For drug resubmission, new evidence of improved efficacy or safety from one or more RCTs is the preferred form of new clinical information. Non-randomized studies may also be submitted as new evidence. The evidence must address the specific issues identified by the expert review committee.	Any study design may be considered; however, the expert committee will evaluate the level of uncertainty in trial results introduced by different study designs. Non-RCTs may be particularly useful as follows: • when evaluation requires long-term follow-up • there is uncertainty regarding the persistence of efficacy due to short-term clinical trials • RCT is impractical due to limited number of patients • unethical to conduct a RCT • RCTs lack relevant comparators (e.g., indirect treatment comparison conducted evaluating new drug versus appropriate comparators) • there is uncertainty regarding the dosage of drug used in clinical practice • when RCTs have limited external validity	Submission guidelines and procedures[16,29,30,48]
Canada — INESSS	At least one published RCT is required and an explanation must be provided if this condition cannot be met. Other supporting studies may be submitted. For drug resubmissions, new clinical data are required (no specification provided).	NR	Submission guidelines[31]
	At least one published RCT is required and an explanation must be provided if this condition cannot be met. Double-blind studies are preferred. Additional data including RWE may be accepted with no limits on study designs or data sources. Same evidence accepted for resubmissions as initial drug submissions.	RWE may be used to support RCT data, for example to provide efficacy data versus an active comparator for drugs where only placebo-controlled trials were available. Circumstances where RWE may bring significant added value include: rare conditions, populations not well studied in RCTs (few or small RCTs), significant unmet need, or innovative medications.	Survey

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
Europe — EUnetHTA	**Efficacy:** systematic reviews, randomized controlled studies, randomized pragmatic designs, other study designs. For the assessment of pharmaceuticals, RCTs are usually possible and feasible, thus RCTs should be considered for benefit assessment. Head-to-head comparisons against the gold standard are preferred. Indirect evidence may be considered if no direct evidence is available. Non-randomized intervention studies or observational studies can be considered in cases where an RCT is not feasible, or as complementary data to RCTs. **Safety:** RCTs, observational studies, case series, epidemiological studies, register or other RWD sources, pharmacovigilance systems or spontaneous adverse event reports, and data from manufacturer or regulatory bodies. A broad range of study types may be included as they bring different and complementary data on harms.	**Effectiveness:** A relevant, comprehensive, methodologically robust systematic review may be sufficient. "Following the hierarchy of study designs [13], reviews on efficacy/effectiveness are generally limited to randomised designs. To assess their generalisability to routine clinical practice, it might be relevant to distinguish between efficacy (explanatory) and effectiveness (pragmatic) RCT. A set of criteria has been suggested to differentiate between these two [14]. In addition, registry data which reflects clinical routine care is helpful in judging whether study populations, interventions and outcomes in RCT are comparable to clinical practice. It may be necessary to broaden the inclusion criteria to incorporate other designs, if data from randomised trials are not available or are insufficient (e g. because they provide only short-term data or surrogate end points). Key elements of a benefit assessed under routine conditions are that (a) effective interventions should be directly compared, and (b) studies should include patients who are typical in day-to-day health care settings [5]. Benefit compared to placebo should have been proven before or parallel to the direct comparison of active treatments. Although data about the relative benefits under routine conditions are preferred for a relative effectiveness assessment, they are rarely available at the usual timing of a rapid assessment (soon after marketing authorisation or start of usage). Where sufficient good quality head-to-head studies are available, direct comparisons are preferred as the level of evidence is high. Should substantial indirect evidence be available, then it can act to validate the direct evidence. When there is limited head-to-head evidence, or more than two treatments are being considered simultaneously, it may be helpful to use indirect methods…." HTA Core Model[24] Pages 148 to 149 "The results of pragmatic trials and country-specific observational studies are usually affected by local clinical practices. Consequently, the transferability and generalisability of the results may suffer and should be considered carefully. For more details see section 2.1 of the WP5 guideline Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals." HTA Core Model24 Page 155	HTA Core Model;[24] HTA Core Model for Rapid Relative Effectiveness;[25] Methodological standards[26]

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
		"For diseases that would be fatal within a short period of time without intervention, for example, several consistent case reports may provide sufficient certainty of results that a particular intervention prevents this otherwise inevitable course ('dramatic effect')." HTA Core Model24 Page 155 **Safety:** RCTs are methodologically most solid, and alone may be the most appropriate source of evidence for some questions about harms (although adverse event reporting in RCTs may be heterogeneous and inadequate). New, serious, rare or long-term adverse effects may be found in observational studies or estimated from epidemiological studies. Routinely collected data or register data may also be relevant for some assessments. Spontaneous adverse event reports are standard methods to identify safety signals. All studies should be critically appraised. Inclusion of data that is likely biased, even if no better evidence is available, may lead to biased conclusions. Comparing data from RCTs and observational studies is useful. Once a relationship between a treatment and a harm is suspected, the best way to assess causality is to conduct a RCT.	
France — HAS	Provide studies according to the evidence hierarchy: meta-analysis of good methodological quality; clinical trial, or observational study designed; and implemented according to current methodological requirements. Resubmissions are the same as initial submissions or extension of indications. Safety: Evidence from PSUR, alerts, pharmacovigilance data, or data from registration authorities.	NR	Submission guidelines[19,49]

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
UK — NICE	All clinical data; in public domain Includes RCTs and other types of interventional or observational clinical research methodology including large simple trials, cohort or case-control studies or registry data, consistent with EMA policy. Safety: Evidence from comparative RCTs and regulatory summaries is preferred, but non-comparative data may sometimes be relevant (e.g., post-marketing surveillance).	Preference given to head-to-head RCTs, but if these data are not available or are insufficient, then NRS or non-controlled studies may be needed to supplement RCT data. In addition, trials that compare the drug with a non-relevant comparator may be needed to conduct an ITC. RCT is the most appropriate study design for relative treatment effects; inferences are more circumspect if relative treatment effects drawn from studies without randomization or control than those from RCTs. Potential biases of NRS or non-comparative studies should be identified before data analysis and ideally should be quantified and adjusted for. The evidence base for determining cost-effectiveness may be weaker for drugs to treat very rare disorders.	Single Technology Appraisal User guide;[17] Guide to methods of technology appraisal[50]
Scotland — SMC	RCTs, meta-analyses, and other studies for the drug relative to active comparators used in routine clinical practice. Placebo-controlled or uncontrolled studies may be supplied to supplement active-controlled RCTs or if no active-controlled trials are available. Resubmissions require new clinical evidence or a new analysis of existing data (not specified). Data from regulatory authorities may also be used for evaluation of safety.	Active-controlled RCTs are most relevant; if not available then placebo-controlled studies or uncontrolled studies may be used to provide evidence of the benefits of the drug.	Guidance to manufacturers[18] Procedure for reassessment[51]

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
Germany — IQWiG	RCTs are the gold standard for benefit assessments of drugs; other study designs may be accepted only in exceptional cases (if it's impossible to implement an RCT or in cases where dramatic effects are observed, such as diseases with certain mortality without intervention). Evaluation of safety is based on data from controlled intervention studies used to assess efficacy. Additional data, if appropriate, may be supplied by observational studies, pharmacovigilance, and regulatory data.	Conclusions for benefit assessments are usually inferred only from the results of direct comparative studies. RCTs are required to demonstrate causality; other study designs mostly cannot answer required questions with sufficient certainty due to potential biases. The use of non-randomized data for benefit assessment requires particular justification or specific preconditions and special demands on quality. The same principles regarding evidence standards exist for orphan diseases. The Institute states that those with rare diseases have the right to most reliable data possible. However in extremely rare diseases the demand for parallel comparative studies may be inappropriate and historical controls may be acceptable.	General Methods 4.2[20]
Netherlands — ZIN	Most recently published research data. Meta-analyses, systematic reviews, observational studies, and reports on clinical studies, provided they were published in peer-reviewed journals. Resubmissions must include new published data (not specified). **Safety:** Assessment based on all evidence from RCTs, observational research, and voluntary reports for which causality has been established.	Gold standard is randomized, double-blind comparative research. The best evidence for determining relative efficacy is research that directly compares the drug with the standard or usual treatment. Comparison with placebo is less valuable unless no treatment is available or the new drug is being added to existing therapy. If direct comparison is not possible, indirect comparison will be made, although the evidential value is lower.	Assessment procedures for reimbursement[21]
Sweden — TLV	Pivotal phase II and phase III studies.[22] RCTs, systematic reviews, comparative studies.[15]	Best evidence directly compares studies with the most relevant alternative. If no direct comparative studies, it is possible to use indirect comparative studies, e.g., systematic reviews. Same rules apply to orphan drugs.	Guide for companies;[22] Oyebode et al.[15]
Finland — PPB	RCTs, (EPAR, published articles), also all other published relevant studies (including epidemiological studies), review articles, meta-analyses. **Safety:** PSUR, EPAR.	Preference for RCTs.	Application instructions[23]

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
Norway	RCTs, observational studies.	NR	Oyebode et al.[15]
Australia PBAC	Best available clinical evidence to support effectiveness and safety **Safety:** PSUR, development safety update report, pharmacovigilance studies, NRS, studies in other indications (excluding case series, case reports, or studies of short duration).	Strongly prefers evidence based on direct randomized trials; if not available then RCTs that allow for conduct of ITC; if not available then NRS. This approach is based on as assumed hierarchy of evidence from RCTs to NRS, with ITC preferred over NRS although it is not always true that ITCs are less prone to bias than well-conducted NRS. NRS are at a high risk of bias and submission should include an assessment of the internal validity of NRS. NRS may provide useful information in the following situations: • when it is unethical to conduct randomised trials (i.e., when the treatment effect is extraordinarily large in observational studies) • when randomised trials are not feasible (i.e., rare disease) • when rare adverse events cannot be feasibly captured within the duration of a randomised trial (provide NRS data in addition to RCT data) • when eligibility criteria for the trial are very restrictive, meaning that the applicability of the treatment effect to the target population is unknown (provide NRS data in addition to RCT data).	Guideline for submission[27]
	RWE may be accepted for rare diseases, priority reviews, significant unmet clinical need, ethical considerations preventing RCT conduct, innovative or breakthrough drugs, or potentially large budget impact.[a] No restrictions placed on study designs or sources accepted. Safety data beyond the trial evidence is required (e.g., periodic safety reports, drug exposure data, and post-marketing adverse event reports).	RWE may be used to supplement RCT evidence on effectiveness or safety, in order to address any uncertainties from the RCT data. In the absence of RCT evidence for ethical reasons, orphan diseases, unmet need, or lifesaving scenarios, RWE could be considered. In cases of conflicting RCT and RWE, RWE would likely be used to address applicability and outstanding uncertainties from RCTs.	

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	Additional evidence is required to inform specific questions pertaining to the new drug and these may be informed by RWD (e.g., expert opinions from surveys on the impact of the treatment on current practice; to address applicability issues with clinical trial data; to support a claim of improved adherence; to assess prevalence or diagnostic test accuracy for drugs where efficacy shown in biomarker defined populations.) Other RWD may include inputs to economic models, patterns of health care resource use, or to identify appropriate comparators Resubmissions are the same as initial drug submissions.	"Evaluation of RWE (as the sole source of data) to determine and quantify the comparative effects of a medicine may require a prudent approach and is unlikely to represent conclusive evidence in this context." Other uses of RWD may be to provide data on treatment adherence or to validate surrogate outcomes. They may also be used to identify relevant comparators, assess treatment utilization, or use of other health resources.	Survey
New Zealand PHARMAC	Key clinical data including published RCTs and meta-analyses. Other sources include observational studies, unpublished trial data, expert opinion, and case reports. Safety: observational longitudinal clinical studies, RCTs, case reports on expected or unexpected adverse drug reactions, and post-marketing surveillance data.	Greater weight is assigned to well-designed RCTs over other data sources. Head-to-head comparative RCTs are of particular interest.	Guidelines for Funding Applications[28]
	All study designs and sources. Other: prescription and outcome data from New Zealand and Australian administrative data set Resubmissions are the same as initial drug submissions.	RWE may be used to establish or supplement evidence on effectiveness or safety, provide data on treatment adherence or to validate surrogate outcomes. RWE may bring significant added value in populations not well studied in RCTs, drugs with potentially large budget impact, or when data on long-term outcomes is required (e.g., vaccination programs). May also be useful to provide adherence and usage rates in clinical practice or when RCTs are not feasible such as for public health interventions.	Survey

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
Regulatory Agencies			
Health Canada	All relevant data are accepted (with no limits on study designs or sources); however, the weight of RWE in a regulatory decision will vary according to the circumstance. Resubmissions are the same as initial drug submissions.	The TPD is in the early stages of exploring the possibility of enhanced use of RWE to further support pre-market regulatory decisions. RWE may be used to establish or supplement evidence on effectiveness or safety, provide data on treatment adherence, or to validate surrogate outcomes. RWE may bring significant added value in rare conditions, priority reviews, populations not well studied in RCTs or those with significant unmet clinical need, innovative or breakthrough drugs, or to provide superior external validity relative to the population of interest. "RWE can lend support to RCT data by providing greater external validity, information on subpopulations, off-label use, and misuse. It is also useful for situations where an RCT is not feasible (e.g., as for ultra-rare diseases) or not ethical (e.g., in pregnant women)." "A sufficiently large, well-conducted RCT remains the gold standard for providing the cleanest, unbiased source of efficacy and safety data in order to formulate a benefit-risk assessment. Comparably, RWE is likely to be far more confounded and more varied in source and therefore in expertise required to evaluate it. Solutions could include establishing further guidance that defines appropriate use of RWE and resources to evaluate it (training)."	Survey

CDR = CADTH Common Drug Review; EMA = European Medicines Agency; EPAR = European public assessment report; EUnetHTA = European Network for Health Technology Assessment; HAS = Haute Autorité de Santé; HTA = health technology assessment; INESSS = Institut national d'excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NR = not reported; NRS = non-randomized study; PBAC = Pharmaceutical Benefits Advisory Committee; pCODR = CADTH pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency ; PPB = Pharmaceuticals Pricing Board; PSUR = Periodic Safety Update Report; RCT = randomized controlled trial; RWD = real-world data; RWE = real-world evidence; SMC = Scottish Medicines Consortium; TGA = Therapeutic Goods Administration; TLV = Dental and Pharmaceutical Benefits Agency; TPD = Therapeutic Products Directorate; ZIN = Zorginstituut Nederland.

[a] RWE may be provided as part of the Managed Entry Program; however, this is not a requirement of an initial drug submission.