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.	

Group	Evidence accepted or required for drug submission	Use or appraisal of RWE	Source
	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.