



Australian Government

Department of Health

Therapeutic Goods Administration

# Real world evidence and patient reported outcomes in the regulatory context

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**TGA** Health Safety  
Regulation

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## Overview

Timely access to new medicines and medical devices is important for patients and health professionals. In making regulatory decisions, the TGA requires evidence that demonstrates that products are safe to use and fit-for-purpose. Appropriate use of real-world evidence (RWE) and patient reported outcomes (PROs) can improve the quality of information used in making regulatory decisions and ensure that such decisions are as relevant as possible for the type of product and their intended patients.

In May 2021 the TGA commissioned a rapid review including around 50 targeted stakeholder interviews on their understanding, and our use, of RWE and PROs. The reviews also examined regulatory documents describing how RWE and PROs are used by some comparable overseas medicine and medical device regulators.

It found that while the TGA currently accepts RWE and PROs for regulatory purposes, the use of such evidence and communication of how it is used in decision making could be improved. Real world evidence already underpins TGA's post-market safety work on medicines, vaccines, and medical devices but there is a less well-developed understanding both internally and externally of how it can be used in pre-market approval of products. Specifically, feedback from those consulted highlighted a need for TGA to better define RWE and PROs, explain how it utilises such evidence and develop or adopt guidance documents on RWE and PROs to assist sponsors making a regulatory submission. The evidence generation process for medicines and medical devices differ so separate guidance for medicines and medical devices will be required.

## TGA response

The TGA already accepts the inclusion of RWE and PROs in submissions and assesses them during the review process. However, we acknowledge that this has been insufficiently communicated to some sponsors, healthcare professionals and patient groups. In addition, the critical use of RWE for emerging technologies, such as gene, cell and tissue therapies and software based medical devices is a critical and necessary component to understanding and enhancing the performance of such products.

During 2021-22 we will establish a central point of information on the TGA website to:

- communicate the use of RWE and PROs for pre-market evaluation of products and how we define it,
- consult on the development or adoption of separate draft guidance documents for medicines and medical devices, and
- communicate when RWE and PROs have been utilised in reaching a regulatory decision.

We will also confirm how the utilisation of RWE and PROs already underpin post-market safety monitoring.

## Summary of review findings

Patients are central to the development of clinical evidence on products during clinical trials, compassionate use programs and off label use, although it can be difficult to obtain high quality data in the latter two situations. Patients may often have differing perspectives on the impact of medicines or medical devices on their quality of life or other outcomes than those established as formal endpoints in clinical trials. Patients have an understandable deep interest in the impact of the information they communicate on the assessment of risks and benefits of new therapeutic goods.

Apart from providing definitions of RWE and PROs, and development or adoption of guidance for evidence generation or use, the TGA can also provide advice to potential applicants and designers of RWE and PROs programs intended for regulatory use. For example, the TGA currently works closely with the designers and managers of many of the medical device clinical quality registries that record and report outcomes, to ensure that the data quality is suitable for regulatory purposes.

## Definitions

The TGA should consider adopting a broad definition of both RWE and PROs in the regulatory context based on those of the US FDA and Health Canada:

*RWE: “clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of Real World Data, usually collected outside of the clinical trial (for therapeutics) or investigational testing (for medical devices) setting”.*

*PROs: “patient outcomes data, reported directly by patients that can be interpreted as information that captures patients’ experiences, perspectives, needs and priorities”*

These definitions should form part of the clear communication about how RWE and PROs can be submitted to the TGA as part of applications for medicines and medical devices or for post-market requirements such as Risk Management Plans for high risk medicines. These data can also be used to support ongoing validation of changes to specific medical devices, such as software based devices, as part of the lifecycle approach to improving performance.

## Sources of data

In assessing medicines and medical devices for safety, quality, and efficacy (medicines) or whether they meet their intended purpose (medical devices) the TGA requires rigorous sources of evidence. It is also critical that the evidence be free from bias, and in this context well-designed clinical trials will remain the main means of evidence generation in most cases. However, we recognise that in some cases, trial designs such as Randomised Controlled Trials (RCTs) are not feasible because of the impossibility of blinding, or of ethical issues. RCTs can be costly and time-consuming and constraints on patient eligibility for enrolment can mean that the efficacy or suitability of some therapies has not been adequately explored in certain subpopulations.

RWE and PROs can contribute valuable additional perspectives, especially on measures that are difficult to assess in clinical trials. Their use can potentially broaden access for certain populations that would not otherwise be eligible in RCTs, or for which suitably powered RCTs may be difficult to conduct. The fast-paced changes in emerging technologies and access to worldwide data stores (e.g. from mobile software apps) should also be considered as useful sources of RWE.

Given that the dossier is submitted by the applicant, to an extent the use of RWE or PROs is not for the regulator to determine. However, pre-submission meetings that include discussion on RWE and PROs may help to clarify what is available and appropriate to use.

## Existing TGA and international regulatory guidance documents

With medicines, RWE is typically regarded as supplementary or supportive to many regulatory applications. However, its potential may be increased in situations such as in rare diseases with small patient numbers where large RCTs may not be feasible (or the data available). RWE and PROs may potentially be useful in other situations, such as a potential extension of indications where the medicine's new indication has been used in hospital or compassionate programs, or for assessment of old medicines for repurposing where appropriate clinical data has been systematically collected and analysed. However, it will be critical in these cases that the quality of the RWE or PRO data is sufficient for regulatory purposes.

With medical devices, clinical success of many medical devices is dependent on the surgeon's skills, and the performance of implantable devices can change over time. The TGA has developed "Clinical Evidence Guidelines for medical devices". These guidelines are intended to provide guidance to manufacturers of medical devices on what constitutes clinical evidence and the process of clinical data generation and clinical evaluation to produce such evidence (see [www.tga.gov.au/resource/clinical-evidence-guidelines-medical-devices](http://www.tga.gov.au/resource/clinical-evidence-guidelines-medical-devices)).

TGA's Clinical Evidence Guidelines are currently being updated and recognise that while it is usual to conduct formal clinical trials for medical devices, in particular implantable and other medium to high risk devices for the purposes of regulatory submission, these trials are typically smaller than medicines trials and blinding and/or randomisation may not be feasible. Other sources of clinical experience data may come from sources such as electronic health records, insurance claims and registries. Increasingly patient-generated data including from home-use settings and data gathered from mobile devices will become increasingly important. The introduction of a medical device Unique Device Identifier, for example will also significantly increase the ability to monitor specific medical devices and patient outcomes globally. How these types of new data sources and identifiers and their use for RWE and PROs will need to be more clearly set out.

The TGA will focus on the adoption of regulatory specific guidance to clarify data requirements and encourage the appropriate inclusion of RWE and PROs in submissions. As a small market for medicines and medical devices in the global context, we recognise the importance of not imposing bespoke Australian requirements on those making local regulatory submissions. For many years, following stakeholder consultation, the TGA has adopted regulatory guidance for medicines submissions developed by the European Medicines Agency, but also from the US FDA and other comparable regulators. Guidance will be communicated on both the generation (by those making regulatory submissions to the TGA) and utilisation (by the TGA in reviewing submissions) of RWE and PROs. A list of currently available guidance which could be considered for adoption is provided at Appendix 1. For medical devices, guidance published by the International Medical Device Regulators Forum, including on clinical evidence, software based medical devices and use of registry data may also be adopted as appropriate to the Australian context and settings.

The TGA will continue to assess international sources (including the medical and scientific literature and regulatory guidance) for generation of RWE and PROs to maximise alignment with other regulator practices. Regulatory science in this area continues to develop and the TGA will continue to monitor ongoing research in the area and as appropriate, further adapt guidance documents.

Where possible the guidance will also explain how the TGA would utilise such evidence in its evaluation, including its use in decision-making and including relevant patient populations for a medicine or medical device. Separate guidance for medical devices and medicines will be required, because the generation of such evidence is often quite different to warrant such, even though some technologies may increasingly require reference to both. This also is consistent

with approaches used by other regulators. Rather than draft new guidance documents, we propose to consult during 2021/22 on the potential adoption of selected guidance documents from comparable overseas regulators (see [www.tga.gov.au/ws-sg-index](http://www.tga.gov.au/ws-sg-index)).

## Data quality

RWE in a regulatory submission is particularly useful when both the natural history of the disease and target patient populations reported on are well defined; when there are significant numbers of patients reporting PROs and the reported effect size is clinically significant in the setting of a lack of therapeutic alternatives. Similarly, with medical devices, use of data from well-established registries that have a significant number of patients and device types collected over a period contributes to the value and significance of performance reported.

However, RWE and PROs are no different from clinical trial data in that evidence quality is critical. The hypothesis to be supported by RWE and/or PROs needs to be evaluated by protocol and analytical plan that characterises consistent data collection and identifies and addresses any potential biases. Endpoints in RWE still need to be captured accurately, and basic processes of management of data quality and Good Clinical Practice followed in assembling the data. Finally, in a regulatory submission it will be important to refer to the totality of evidence to avoid overreliance on a single source.

## The TGA's approach

The TGA will more extensively communicate the current status of use of RWE and PROs, to overcome the perception that they are not currently part of the regulatory landscape. While resources do not permit TGA to fund or undertake research on RWE we will monitor work by comparable regulators and regulatory science coalitions on the use of RWE/ PROs to remain abreast of their evolving status.

Further during 2021/22 the TGA will undertake the following:

- Require applicants to identify why and where RWE and PROs have been included in the application and its purpose for inclusion, as is the case in the USA.
- Include in medicine Decision Summaries and Australian Public Assessment Reports (AusPAR) a statement outlining whether RWE and PROs were included in the submission and, if applicable, how the evidence was used in the TGA's decision making.
- Provide greater clarity of how RWE and PROs can be used to support applications, especially for software-based medical devices including apps. As part of the *Action Plan for Medical Devices*, released in 2019 and currently being implemented, to "*Provide more information to patients about the devices they use*" which includes a commitment to "publish more information about decisions made and the medical device products regulated by the TGA" could also include information about RWE and PROs. While the sheer numbers being included on the ARTG each year preclude the development of a public decision document on each medical device, it may be more feasible (and more relevant for patients) for high risk (i.e. Class III and AIMD) devices.
- Encourage the adoption of medical device unique device identifiers in the broader healthcare system and specifically, in medical device registries, to support a stronger foundation for the collection of RWE and PROs.
- Review whether there are specific implications for the use of RWE and PROs in particular pathways such as orphan or provisional pathways for medicines or for repurposing of medicines.

- Consider how to best implement this work in context of international collaborations and how improvements could be incorporated into the assessment of products for Australian patients.

## Appendix 1: Current frameworks and guidance documents on the use of RWE and/or PROs

Few regulators have issued final comprehensive guidance on real world evidence or patient reported outcomes for therapeutics, but several drafts and frameworks exist. Selected guidance will be consulted on for potential adoption or adaptation by the TGA.

### European Medicines Agency

<p><b>Draft Guidance: Guideline on Registry-Based Studies (Sep 2020)</b></p>	<p><a href="https://www.ema.europa.eu/en/guideline-registry-based-studies-0">https://www.ema.europa.eu/en/guideline-registry-based-studies-0</a></p>	<p>Focuses on studies based on disease or condition registries to examine the use, safety and effectiveness of medicines prescribed to or used by patients included in the registry. It also outlines regulatory considerations related to the establishment and management of patient registries, to enable their use in registry-based studies.</p>
<p><b>Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations (Nov 2018)</b></p>	<p><a href="https://www.segcib.org/ema-consultation-discussion-paper-use-of-patient-disease-registries-for-regulatory-purposes-methodological-and-operational-considerations/">https://www.segcib.org/ema-consultation-discussion-paper-use-of-patient-disease-registries-for-regulatory-purposes-methodological-and-operational-considerations/</a></p>	<p>Discusses methodological and operational aspects of the use of patient disease registries and registry studies for regulatory purposes.</p>

**United States FDA**

Draft guidance: Submitting Documents Using RWD and RWE to FDA (May 2019)	<a href="https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance">https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance</a>	Guidance to encourage applicants who are using RWD/RWE as part of a regulatory submission to provide information on their use of RWE in a simple, uniform format.
Draft guidance: Rare diseases: Natural history Studies for Drug Development (Mar 2019)	<a href="http://www.fda.gov/media/122425/download">http://www.fda.gov/media/122425/download</a> <a href="https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development">https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development</a>	Guidance describes the broad potential uses of a natural history study in all phases of drug development for rare diseases, the strengths and weaknesses of various types of natural history studies, data elements and research plans, and a practical framework for the conduct of a natural history study. This guidance also discusses some considerations for aligning the study design with study objectives and for enhancing the interpretability of study results; patient confidentiality and data protection issues in natural history studies; and potential interactions with FDA related to these studies.
Framework for FDA's RWE Program (Dec 2018)	<a href="https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence">https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence</a>	The Framework clarifies definitions and establishes a 3-part approach for the RWE Program for evaluating RWE: 1) Whether the RWD are "fit for use", 2) Whether the study methodologies used to generate RWE can provide "adequate scientific evidence" to address the regulatory question, and 3) Whether study meets FDA requirements for study conduct.
Final Guidance: Use of RWE to Support Regulatory Decision- Making for Medical Devices (Aug 2017)	<a href="https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices">https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices</a>	Clarifies how FDA evaluates real-world data to determine whether they are sufficient for generating the types of real-world evidence that can be used in regulatory decision-making for medical devices.
Draft guidance: Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry (Apr 2019)	<a href="http://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance">http://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance</a>	This guidance is intended to encourage sponsors and applicants who are using real-world data (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format.

<p>Guidance:</p> <p>Use of Electronic Health Record Data in Clinical Investigations (Jul 2018)</p>	<p><a href="http://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry">http://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry</a></p>	<p>This guidance is intended to assist sponsors, clinical investigators, contract research organisations, institutional review boards, and other interested parties on the use of electronic health record data in FDA-regulated clinical investigations.</p>
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## Health Canada

<p>Framework: Optimizing the Use of RWE to Inform Regulatory Decision-Making (Apr 2019)</p>	<p><a href="http://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html">www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html</a></p>	<p>Notice to invite industry submissions using high quality RWE. Health Canada encourage submissions: that aim to expand evidence-based indications for populations-often excluded from clinical trials (ex: children, seniors, and pregnant women); for drugs/diseases where clinical trials are unfeasible such as may be the case with rare diseases; and/or where clinical trials are unethical, as may be the case during emergencies where dosages from animal studies may need to be extrapolated to treat humans potentially exposed to chemical or biological threats.</p>
<p>Framework: Elements of RWD/E Quality Throughout the Prescription Drug Product Life Cycle (March 2019)</p>	<p><a href="http://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html">www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html</a></p>	<p>Provides overarching principles to guide the generation of real world evidence that would be consistent with regulatory standard. Includes an overview of elements that should be addressed in protocol development and characterizes some of the data quality concerns within submissions containing RWE.</p>
<p>Framework: A strategy to optimize the use of real-world evidence across the medical device life cycle in Canada (Mar 2020)</p>	<p><a href="http://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/real-world-evidence-medical-device-strategy.html">www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/real-world-evidence-medical-device-strategy.html</a></p>	<p>This document in collaboration with Pan-Canadian Health Technology Assessment Collaborative sets out a strategy to improve the accessibility, affordability and appropriate use of medical devices through the optimisation of RWE. A framework will define points across the medical device life cycle where RWE can be useful, and direct guidance document development for devices on RWE use to support regulatory decisions and HTA recommendations</p>

## Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	TGA	24/11/2021

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