Beyond Trials: The Growing Role of Real-World Evidence in Drug Regulation

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Session overview

- Foundation of Real-World Evidence
- RWE vs randomised controlled trials
- Regulatory use of RWE
- TGA perspective and regulatory evolution
- International guidance and expectations
- Implementing fit-for-purpose RWE

Foundations of Real-World Evidence

Definitions

RWD

- **FDA:** Data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources.

- **EMA** : RWD refers to data relating to patient health status or healthcare delivery collected outside of traditional clinical trials, such as electronic health records (EHRs), claims data, and registry data

- **ICH** (Draft) - RWD are defined as data reflecting usual clinical practice and are related to a person or patient's experience, health status, or care delivery

Common sources of RWD

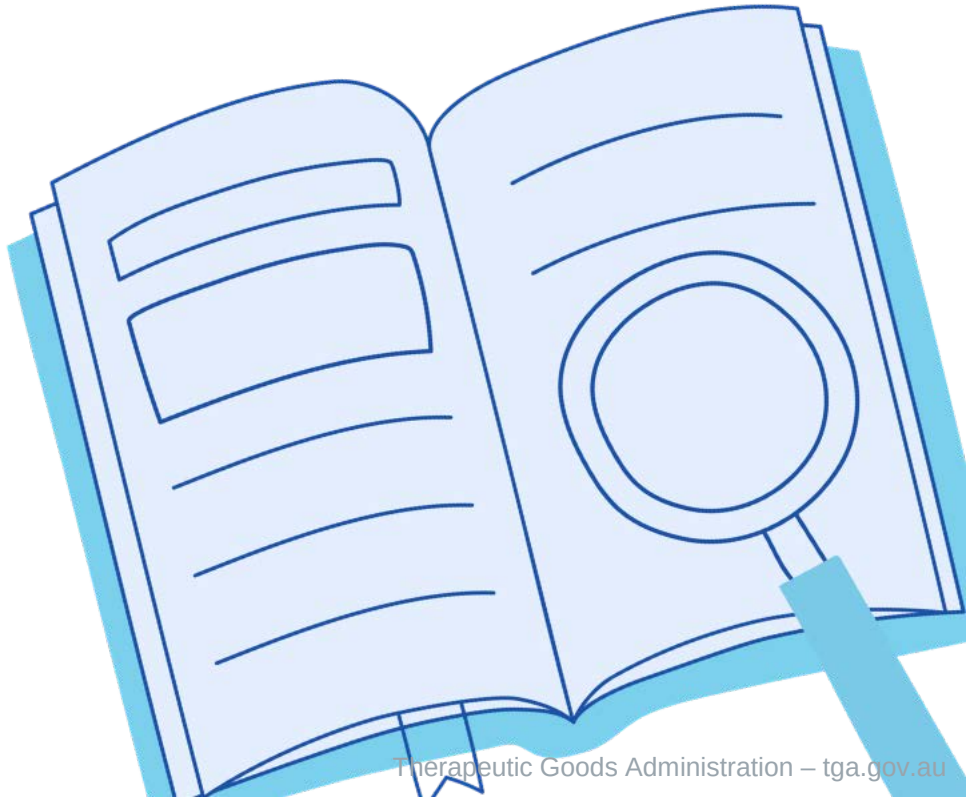
- Electronic health records (EHRs)
- Administrative claims / billing datasets
- Disease and product registries
- Patient-reported outcomes (PROs) / PROMs
- Device- or app-generated data (where relevant to endpoints

Real World Evidence

FDA : Real-world evidence is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

EMA :
Clinical evidence regarding the usage and potential benefits or risks of a medicinal product derived from the analysis of Real-World Data (RWD)

ICH (Draft): Evidence regarding the usage and potential benefits or risks of medicines derived from the analysis of RWD.



Patient Reported Outcome Measures (PROM)

Patient outcomes data, reported directly by patients that can be interpreted as information that captures patients' experiences, perspectives, needs and priorities.*

Non- Interventional Studies/ Observational study

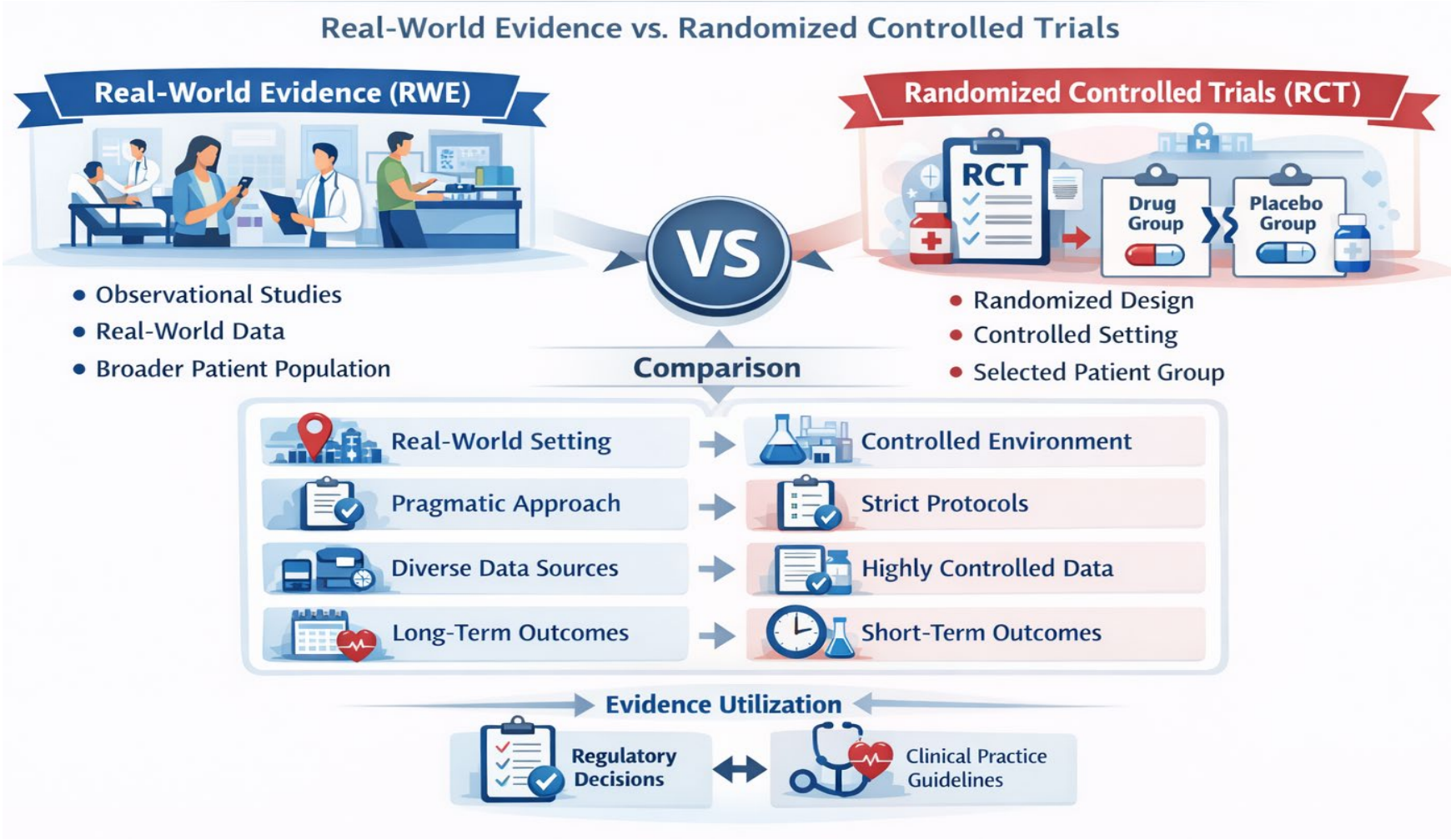
A non-interventional study (observational study) is one in which**:

- Patients receive treatment as part of routine clinical practice
- The investigator does not assign a specific intervention according to a study protocol
- Outcomes are observed and analysed using epidemiological methods rather than controlled interventions.

*https://www.tga.gov.au/sites/default/files/real-world-evidence-and-patient-reported-outcomes-in-the-regulatory-context.pdf
**https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-evidence-considerations-regarding-non-interventional-studies-drug-and-biological-products

RWE vs Randomised Controlled Trials

Understanding methodological differences and complementary roles



Study Design and Methodological Differences

Randomised Controlled Trials (RCTs)

RCTs use strict protocols and randomisation to minimize bias and allow strong causal inference in controlled environments.

Real-World Evidence (RWE) Studies

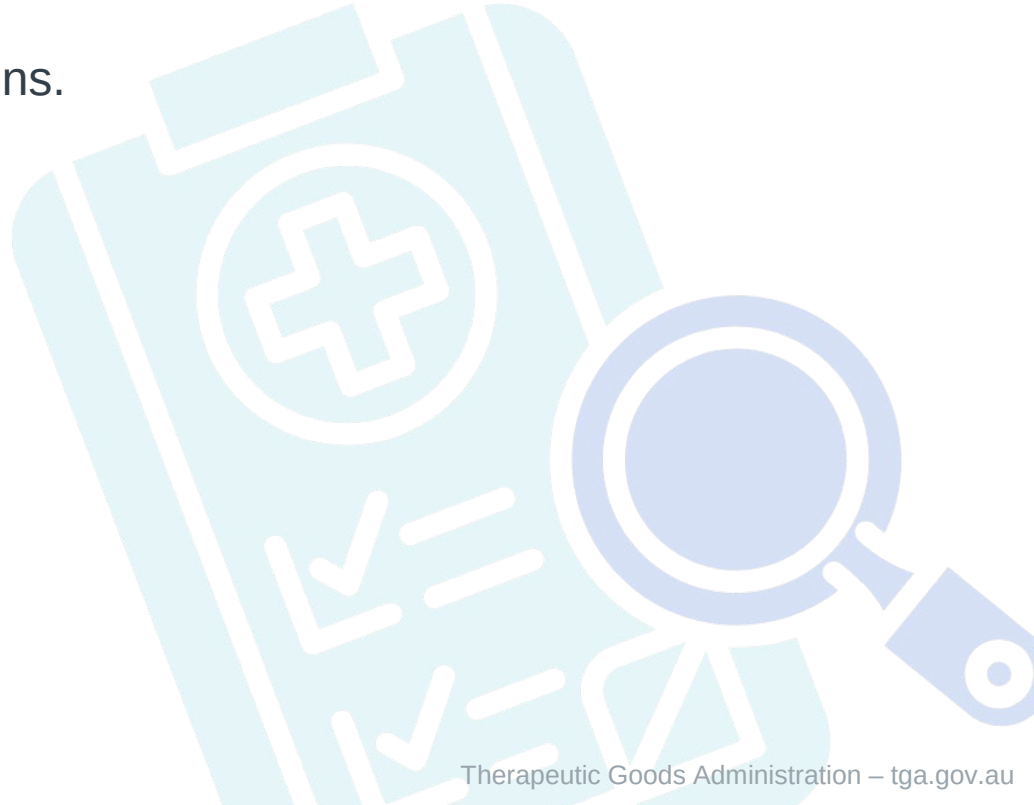
RWE studies use observational designs in routine clinical practice, reflecting diverse and heterogeneous patient populations.

Addressing Bias in RWE

Advanced statistical techniques like propensity score matching reduce bias but residual confounding may still exist.

Validity and Evidence Focus

RCTs prioritize internal validity; RWE studies emphasize external validity requiring robust analytical approaches.



Strengths and Limitations of RCTs and RWE

Strengths of RCTs

RCTs establish cause-and-effect relationships using randomization and control groups, widely accepted as high-level evidence.

Limitations of RCTs

RCTs are costly, time-consuming, and have limited generalizability due to strict criteria and underrepresented populations.

Advantages of RWE

RWE captures real-world patient data, offering insights into diverse populations, long-term outcomes, and cost-effective studies.

Limitations of RWE

RWE may have data quality issues and bias, requiring careful design and validation for reliable decision-

Regulatory Use and Integration

Role of Randomized Controlled Trials

RCTs provide high confidence in benefit-risk assessments through controlled design and internal validity.

Importance of Real-World Evidence

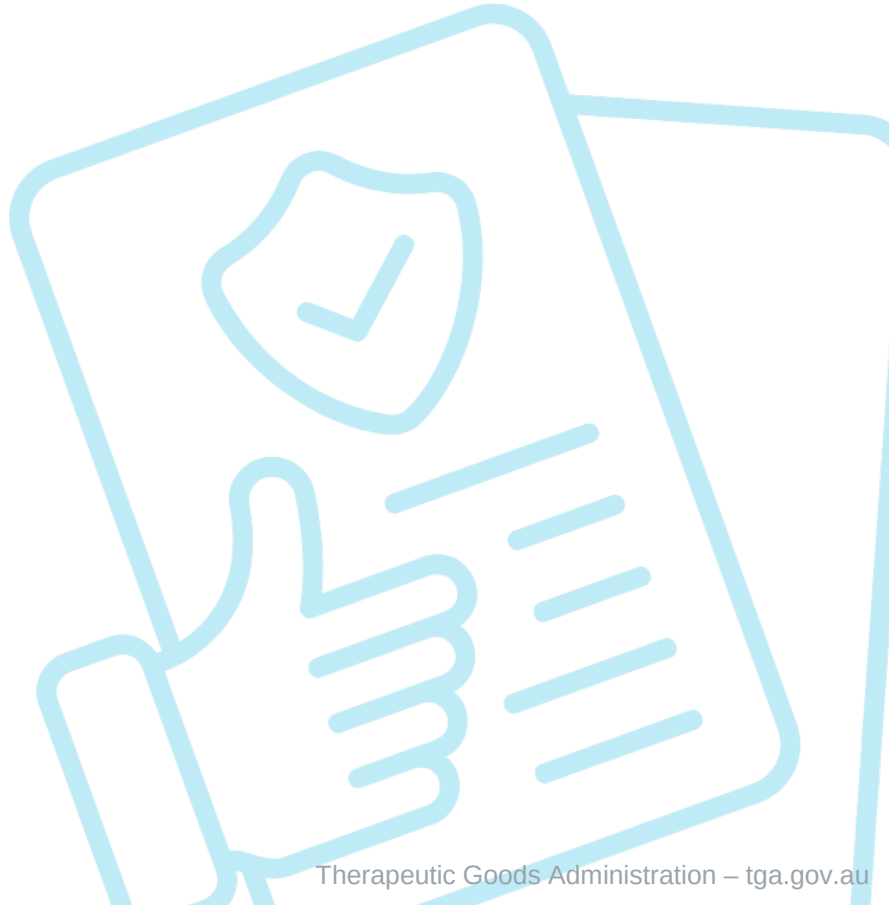
RWE complements RCTs by providing data on treatment effectiveness and safety in routine clinical practice.

Special Regulatory Applications

RWE supports decisions in orphan diseases, rare conditions, and accelerated approval pathways.

Ensuring Data Robustness

Regulatory bodies stress RWE must be fit for purpose—robust, reliable, and relevant for decisions.



In Summary… RCT vs RWE

Complementary Evidence Approaches

RCTs and RWE are complementary, providing rigorous efficacy data and real-world insights respectively.

Strength of RCTs

RCTs minimize bias and establish causality under controlled conditions, key for regulatory approval.

Value of Real-World Evidence

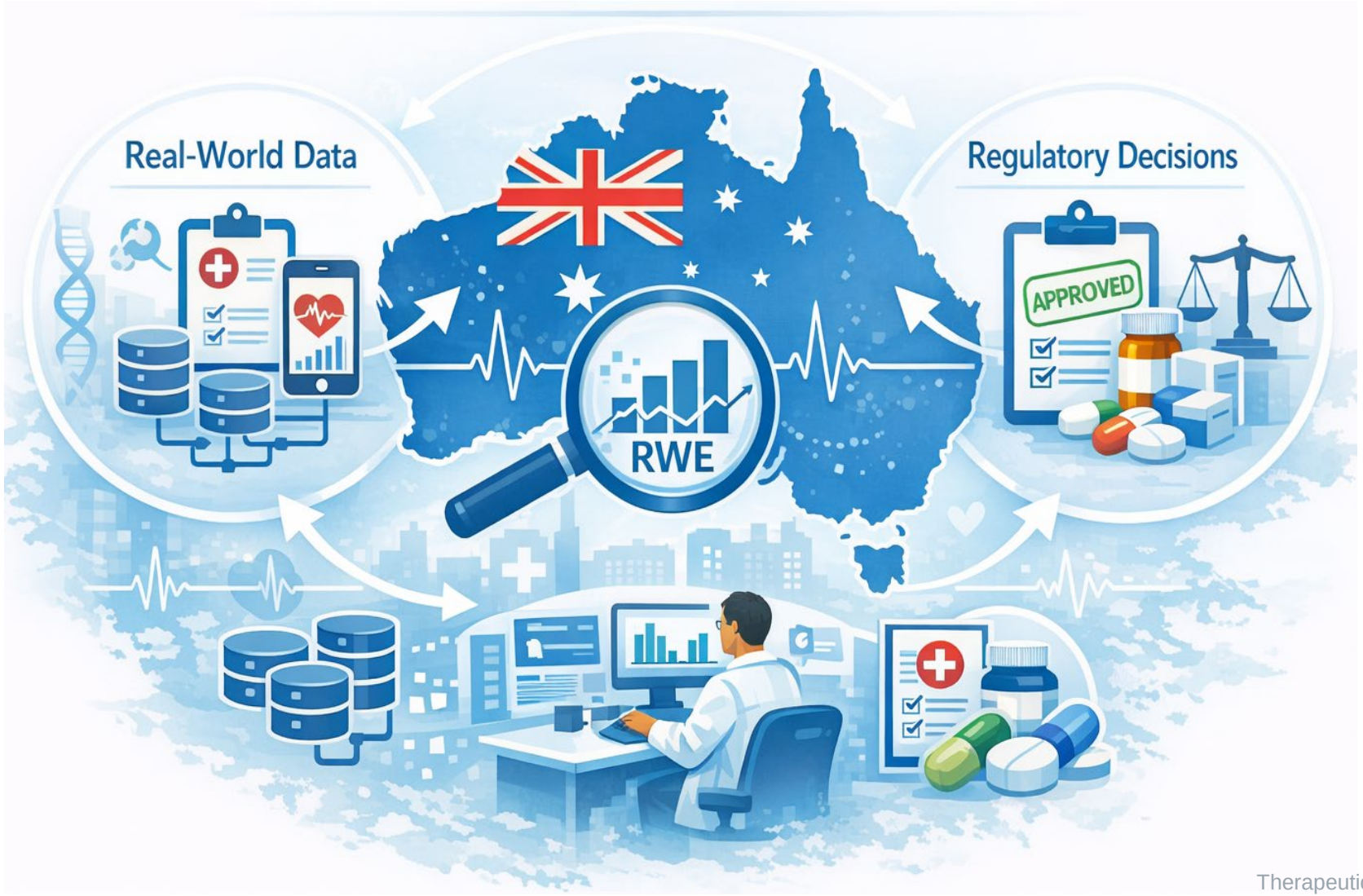
RWE captures real-world variability, assessing treatment effectiveness and safety over time.

Integrated Regulatory Approach

Regulatory agencies can use both RCT and RWE for comprehensive evaluation and better decision-making.

TGA Perspective and Regulatory Evolution

From the 2021 review to current practice



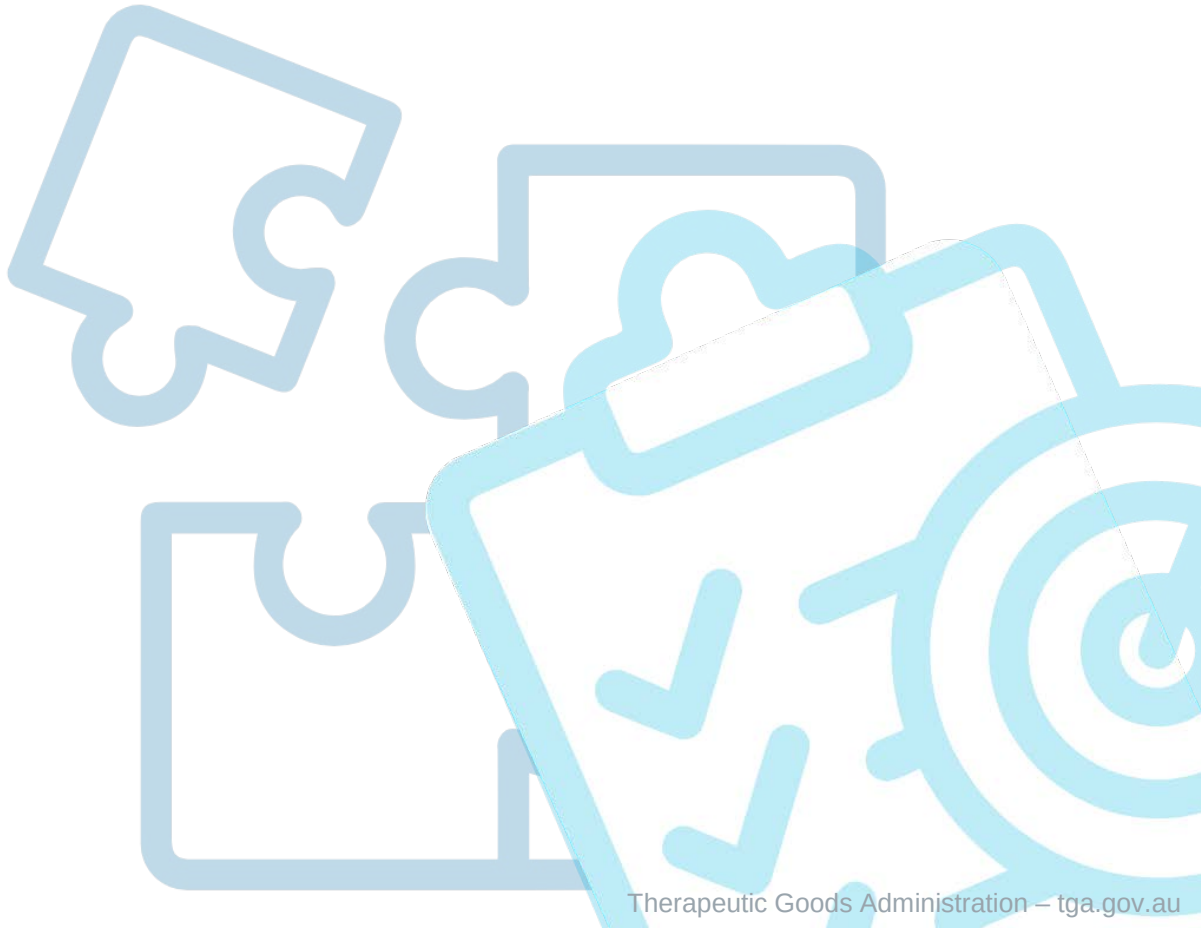
TGA Review in 2021

- Industry and consumers are unclear on how the TGA uses Real World Evidence (RWE)
- Rapid review commissioned by the TGA
- Examined COR regulatory documents on RWE
- Performed 50 targeted stakeholder interviews
- Review found:
  - Ambiguity (internally and externally) surrounding TGA's RWE use, potentially limiting its adoption.
  - Recommended TGA improve communication about how we accept and use RWE.

https://www.tga.gov.au/review-real-world-evidence-and-patient-reported-outcomes

TGA's Plan

- Develop Australian RWE definition
- Collaborate with overseas regulators
- Consult on the development and adoption of guidance documents
- Provide guidance around use of RWE for pre-market evaluations
- Communicate when RWE has been used to make a regulatory decision
- Support RWE use:
  - To complement clinical trials to support access, repurposing, and evidence generation where RCTs are not feasible.
  - Eg in Orphan, rare Oncology, Provisional and Repurposing of medicines



What changed after the 2021 review?

Increased Clarity and Transparency: TGA focused on clear guidance and transparency around the role of RWE and PROs in decision-making.

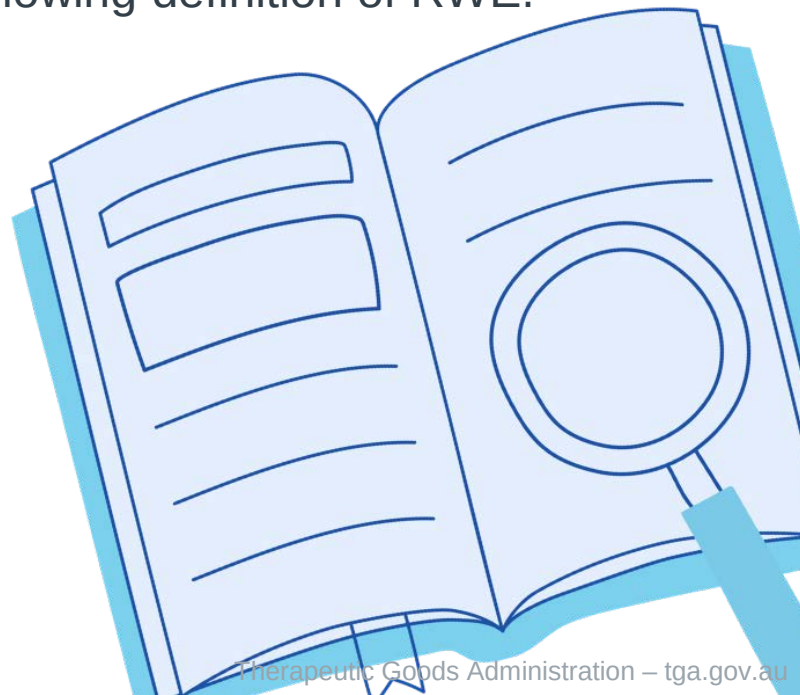
- **Formal Definition of RWE:** Adoption of a formal RWE definition anchors consistent language for evidence beyond traditional trials.
- The TGA undertook a targeted consultation with stakeholders from industry and consumer groups on the adoption of FDA's definition of RWE.
- **Updated Pre-submission Planning Form:** PPF revisions - sponsors to declare use of RWE, RWD, and PROs in submissions upfront.
- **Improved Transparency in Reports:** AusPARs to describe how RWE and PROs influence regulatory decisions, enhancing stakeholder insight.
- **Continuing engagement with comparable overseas regulators on use of real-world evidence (RWE) and real-world data (RWD)**
- The TGA notes the growing usage of RWE internationally and will continue to actively monitor and engage with comparable overseas regulators on developments in this area.

Formal Definition of RWE

- Adoption of a formal RWE definition anchors consistent language for evidence beyond traditional trials.
- The TGA undertook a targeted consultation with key stakeholders from industry and consumer groups on the adoption of FDA's definition of RWE.
- The stakeholders responded to the survey by 28 November 2022, providing valuable feedback on options.
- Based on the outcome of this consultation, the TGA has adopted the following definition of RWE.

Definition:

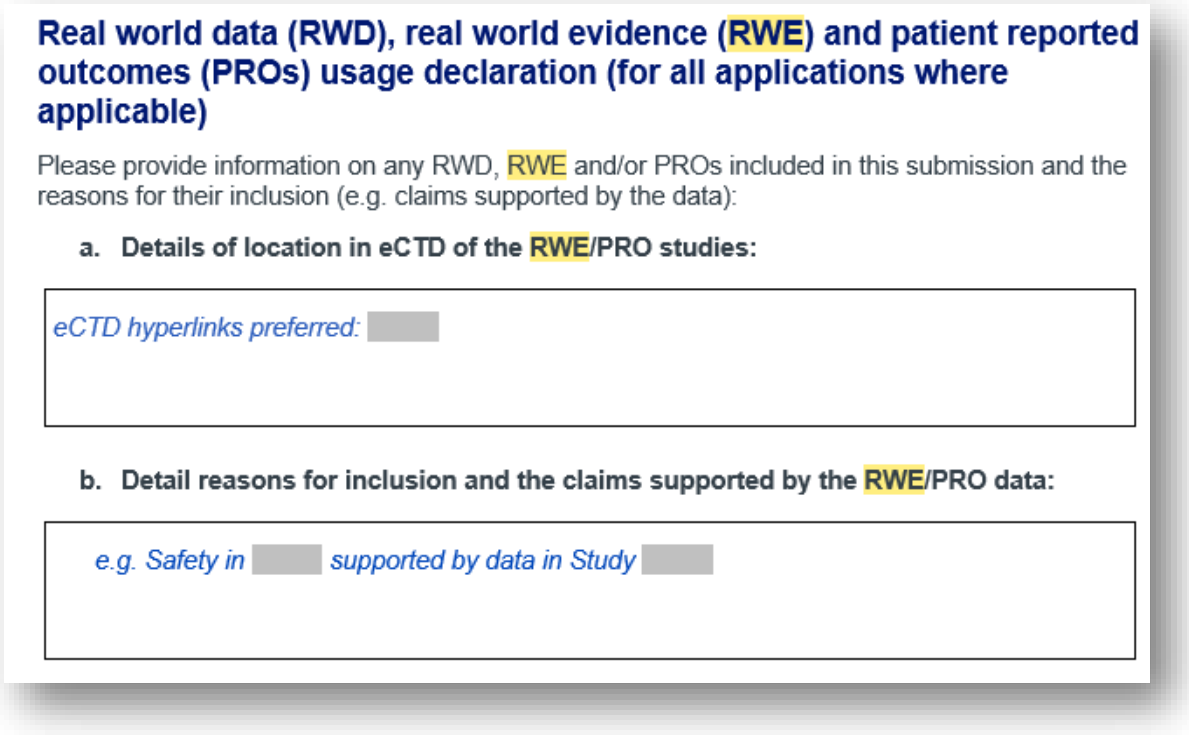
Data regarding the usage, or the potential benefits or risks, of a therapeutic good derived from sources other than traditional clinical trials.



Amendments to the Pre-submission Planning Form (PPF)

Updated Pre-submission Planning Form

- PPF revisions require sponsors to declare use of RWE, RWD, and PROs in submissions upfront.
- The TGA has amended the Pre-submission Planning Form (PPF) to include a RWE usage declaration for sponsors of prescription medicines applications.
- Sponsors are encouraged to provide information on any RWE, RWD and/or PRO included in their submission and reasons for including this data e.g., the claims these data are supporting.



Real world data (RWD), real world evidence (RWE) and patient reported outcomes (PROs) usage declaration (for all applications where applicable)

Please provide information on any RWD, RWE and/or PROs included in this submission and the reasons for their inclusion (e.g. claims supported by the data):

a. **Details of location in eCTD of the RWE/PRO studies:**

eCTD hyperlinks preferred:

b. **Detail reasons for inclusion and the claims supported by the RWE/PRO data:**

e.g. Safety in *supported by data in Study*

https://www.tga.gov.au/news/news-articles/real-world-evidence-and-patient-reported-outcomes#amendments-to-the-presubmission-planning-form-ppf-for-medicines

Improved Transparency in Reports

AusPARs now describe how RWE and PROs influence regulatory decisions, enhancing stakeholder insight

- Enhances transparency of TGA regulatory decision-making
- Describes how non-trial evidence contributes to evaluation.

Exkivity (mobocertinib)AusPAR

Study TAK-788-5002

Study TAK-788-5002 was considered as a supportive study for this submission.

Due to the rarity of ex20ins mutation positive NSCLC and the lack of a specific standard of care for these patients, an analysis of real world data was submitted as historical benchmark data to support interpretation of the pivotal evidence.

Study TAK-788-5002 was a retrospective, observational cohort study of patients with NSCLC harbouring *EGFR* ex20ins mutations. This study used longitudinal data (data cut off 29 February 2020) from the Flatiron Health Research Database: a de-identified database of United States electronic health records.

Adoption of international guidelines

Following a rigorous consultation process, the TGA has adopted the following international scientific guidelines to offer guidance to the industry on the use of RWE and RWD in regulatory submissions:

International scientific guideline: Guideline on registry-based studies EMA/426390/2021

International scientific guideline: Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man. The use of patient-reported outcome (PRO) measures in oncology studies EMA/CHMP/292464/2014

Submitting documents using RWD and RWE to FDA for drugs and biologics – Guidance for Industry FDA 2022

Rare Diseases: Natural History Studies for Drug Development – Draft Guidance for Industry FDA2019

Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products – Draft Guidance for Industry FDA 2021

Data Standards for Drug and Biological Product Submissions Containing Real-World Data – Draft Guidance for Industry FDA 2023

Use of Electronic Health Record Data in Clinical Investigations – Guidance for Industry FDA 2024

International Guidance and Expectations

FDA, EMA, and global regulatory alignment

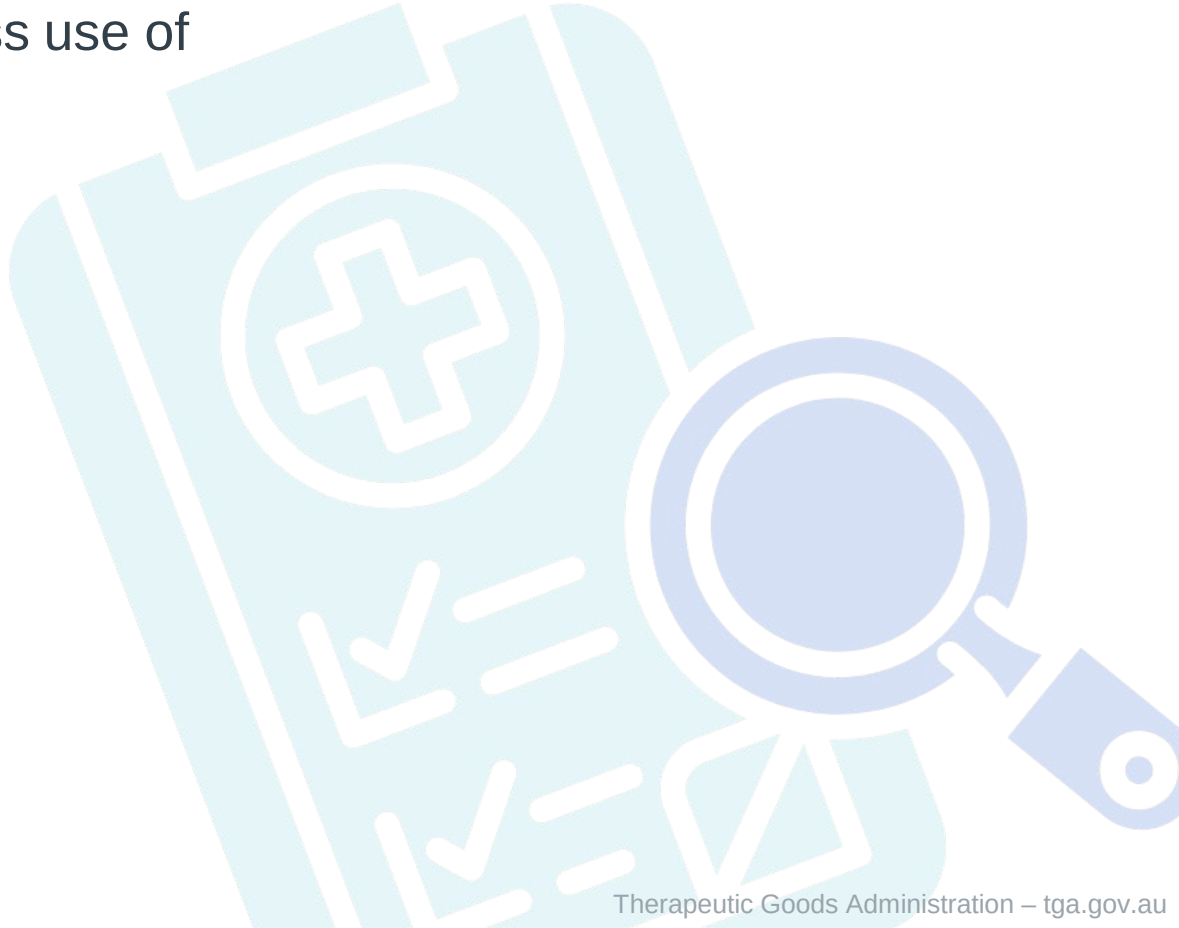
FDA RWE guidance for industry: Draft , 2021

- Types of Clinical Studies Using RWD
- Regulatory Status: IND vs Non-IND Studies
- Use of Non-Interventional Studies in Regulatory Decisions
- Transparency and Pre-specification Expectations
- Data Sources, Access, and Reproducibility
- Study Monitoring, Safety Reporting, and Responsibilities

https://www.fda.gov/media/154714/download

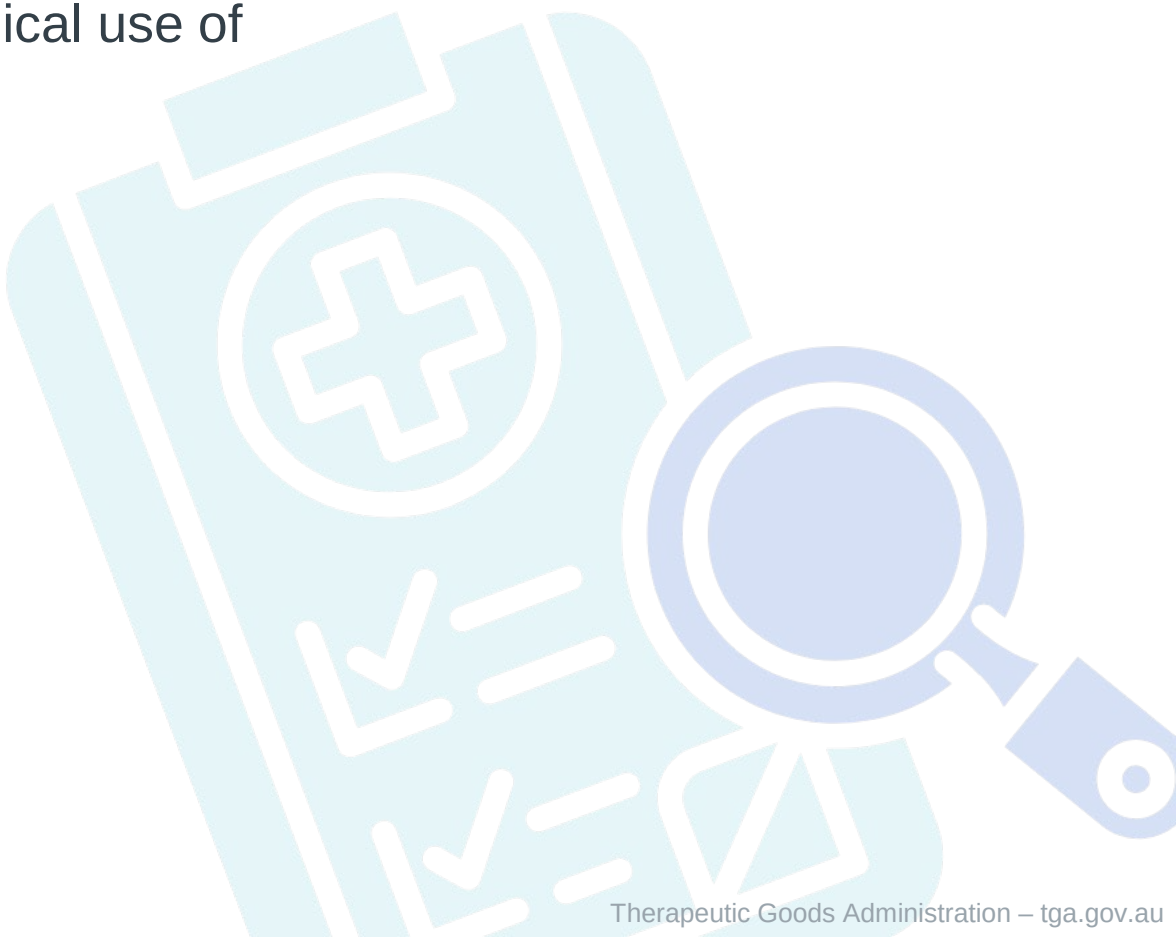
Types of Clinical Studies Using RWD

- FDA considers both interventional and non-interventional study designs when RWD are used.
- Interventional studies assign interventions by protocol (e.g. RCTs, pragmatic trials).
- Non-interventional (observational) studies assess use of marketed medicines in routine practice.
- Common observational designs include cohort and case-control studies.



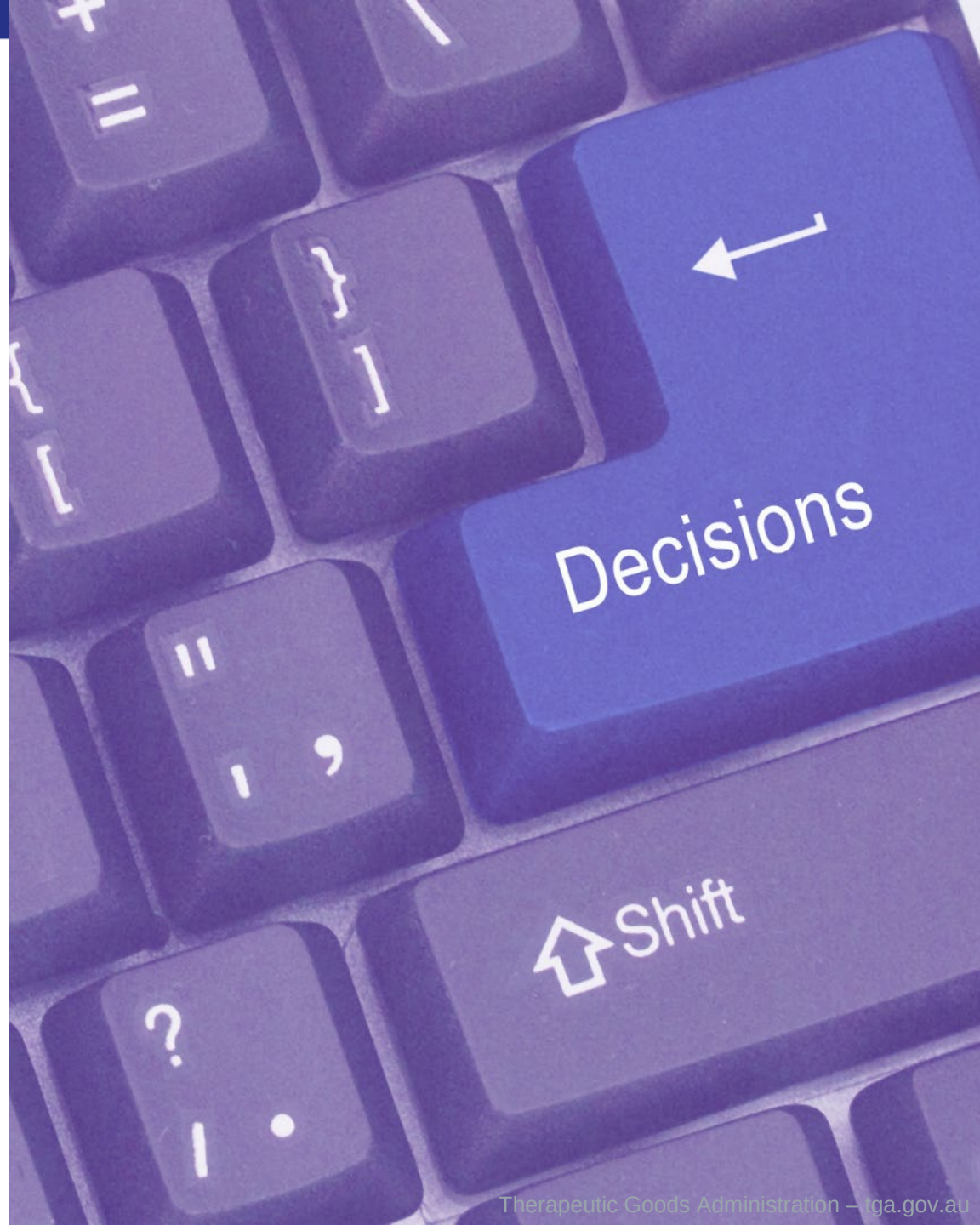
Regulatory Status: IND vs Non-IND Studies

- Interventional studies generally meet the definition of a clinical investigation.
- Such studies are typically subject to Investigational new drug (IND) requirements.
- Non-interventional studies analyse routine clinical use of marketed drugs.
- Observational studies do not require an IND when there is no protocol-directed treatment assignment.



Use of Non-Interventional Studies in Regulatory Decisions

- All evidence must meet applicable legal standards for safety and effectiveness.
- Observational studies may support new indications or post-approval requirements.
- Some studies include additional activities such as questionnaires or laboratory tests.
- Human subject protection requirements still apply even when an IND is not required.



Transparency and Pre-specification Expectations

- FDA encourages early engagement when observational studies may support submissions.
- Study protocols and statistical analysis plans should be finalized before analyses.
- Protocols and SAPs should be date-stamped and changes documented.
- FDA must be confident that studies were not designed or analysed to favors a conclusion.

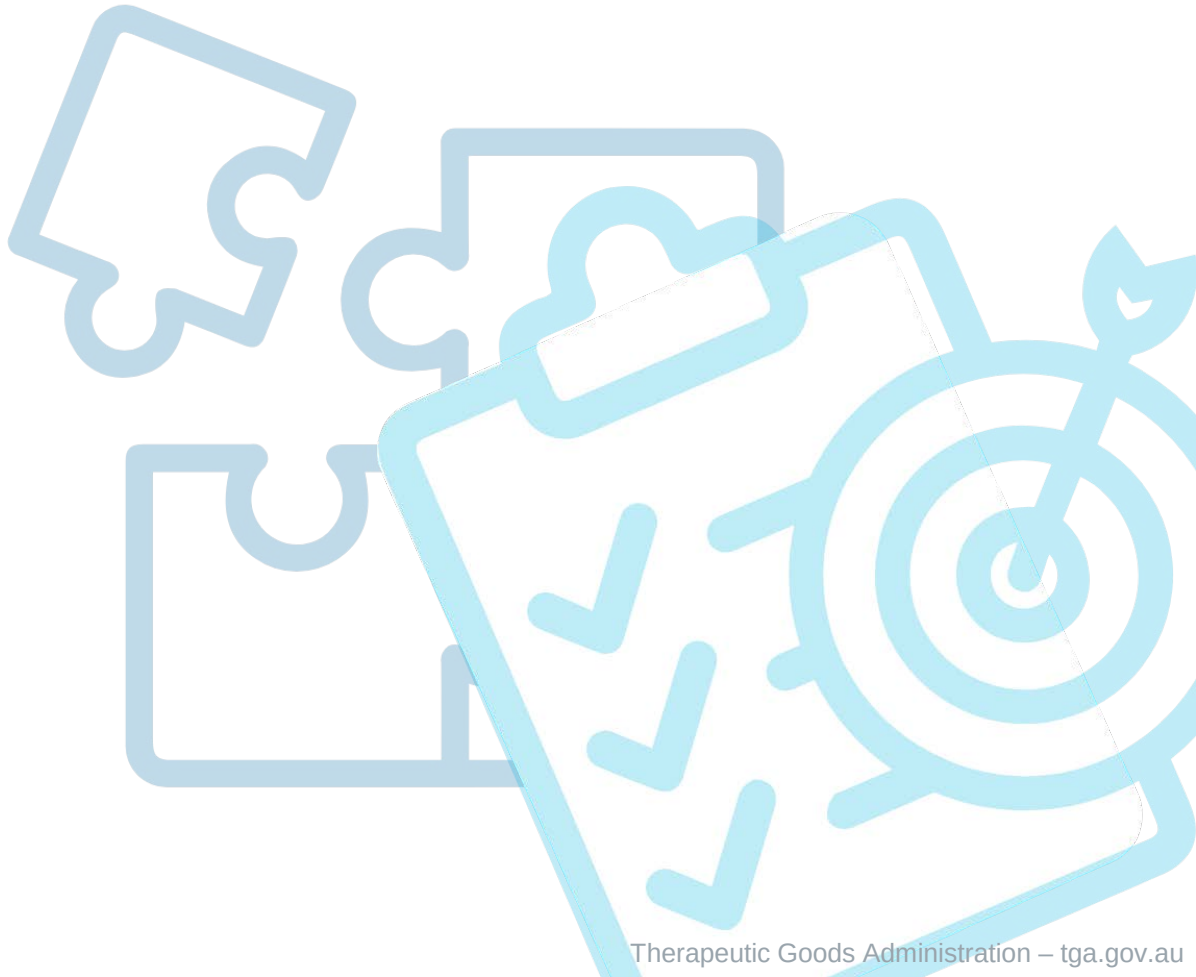
Note: TGA offers pre-submissions advice
(not the trial planning)

Data Sources, Access, and Reproducibility

- Sponsors should ensure FDA access to patient-level data when required.
- Third-party data agreements must allow verification and inspection.
- Datasets and analytic code should be well-documented and reproducible.
- All data sources evaluated during study design should be described and justified.

Study Monitoring, Safety Reporting, and Responsibilities

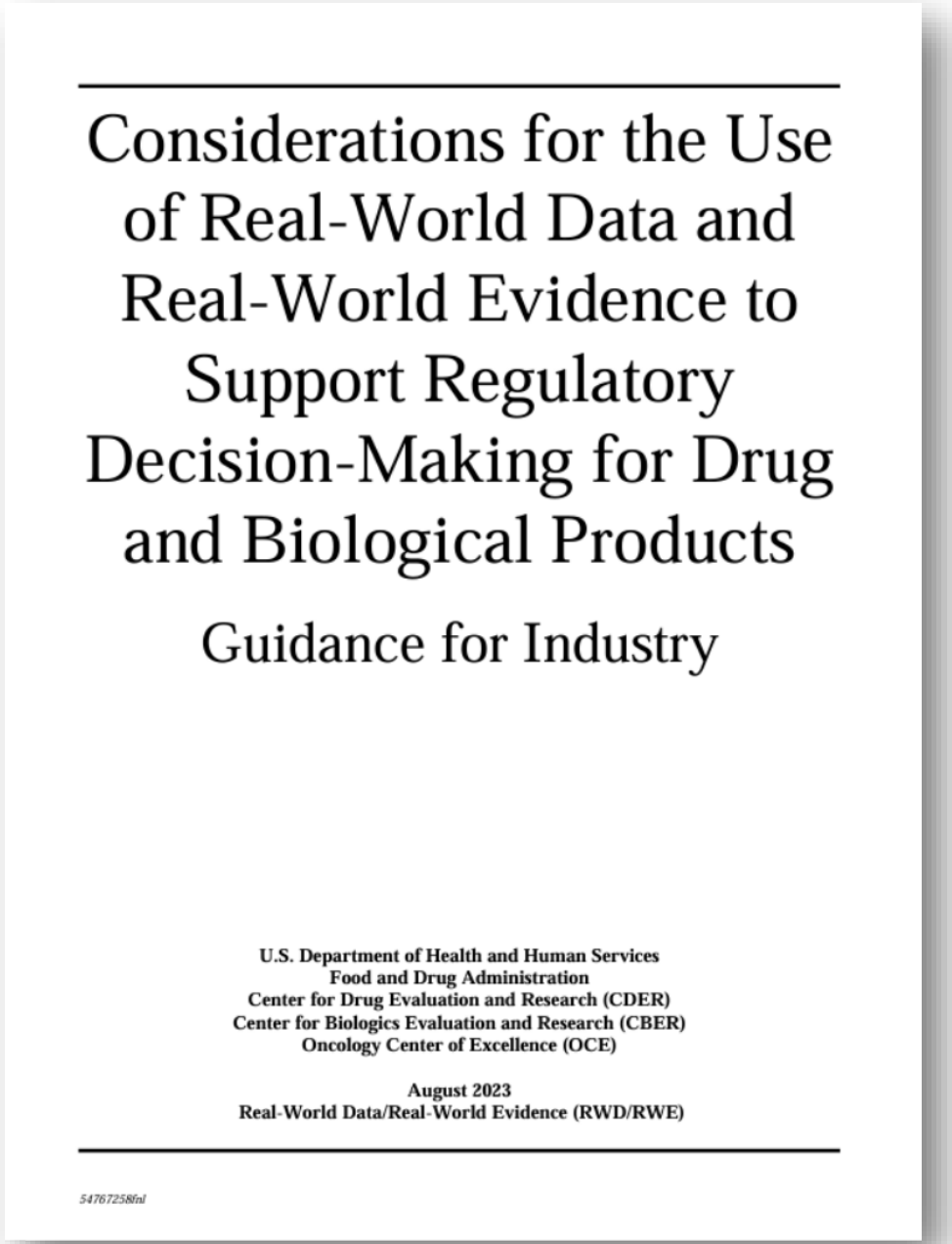
- Study monitoring should focus on reliability and integrity of RWD.
- Risk-based quality management approaches are encouraged.
- Observational studies remain subject to post-marketing safety reporting.
- Sponsors retain full responsibility for design, conduct, and oversight of studies.



FDA Final Guidance 2023

- TGA currently reviewing

https://www.fda.gov/media/171667/download



Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

54767258fnl

Evolution of FDA RWE Guidance: 2021 Draft vs 2023 Final

Regulatory status

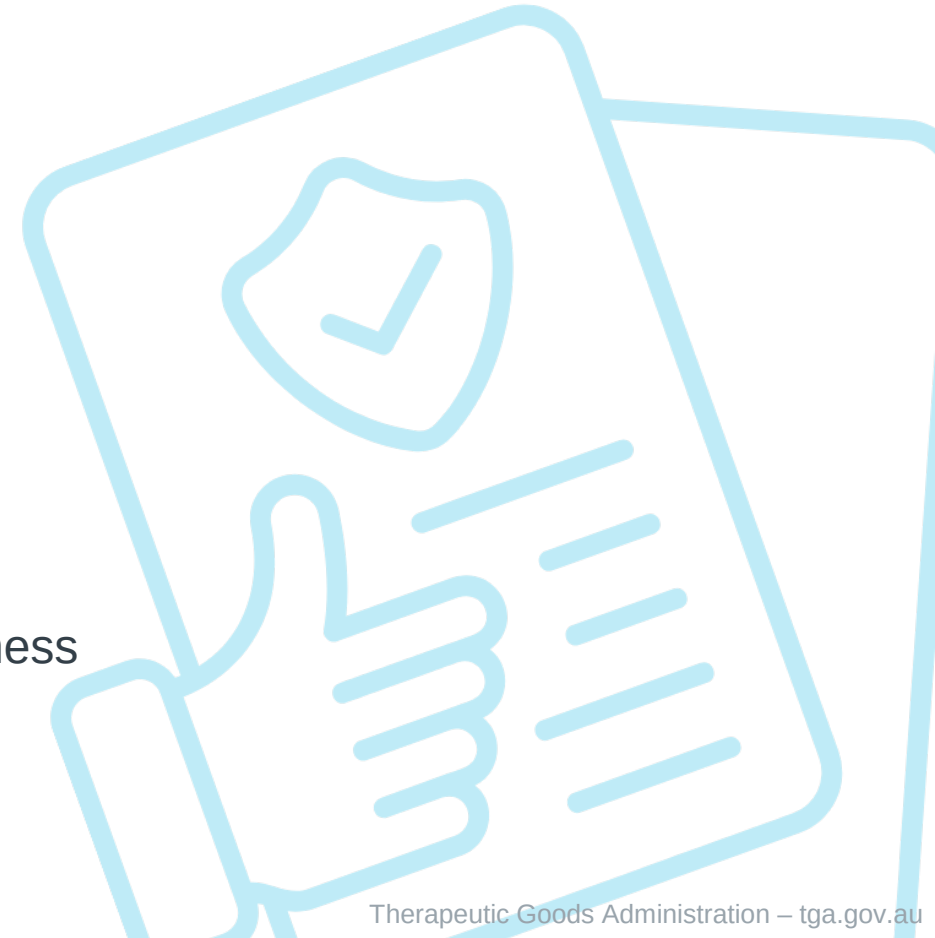
- 2021 guidance issued as Draft – not for implementation and intended for public comment
- 2023 guidance issued as Final Guidance for Industry, representing FDA's current thinking

Purpose and scope

- 2021 guidance focused on explaining principles and regulatory context for RWD/RWE use
- 2023 guidance explicitly supports regulatory decision-making, including new indications and post approval requirements

Regulatory tone

- 2021 draft reflects an exploratory phase of FDA experience with RWE
- 2023 guidance reflects greater confidence and operational readiness



Practical Differences in Sponsor Expectations

- **Transparency and pre-specification:** 2023 guidance strengthens expectations for documented pre-specification, version control, and audit trails.
- **Data access and reproducibility:** 2023 guidance more explicitly requires patient-level datasets, well-annotated code, and reproducible analyses.
- **Oversight and accountability:** Risk-based quality management is more clearly embedded across the full RWD lifecycle. Sponsors retain end-to-end responsibility, including compliance with 21 CFR Part 11, even when third parties are used.

Examples: RWE to Support Efficacy & Comparative Context

Use of RWE as external or historical controls

Exkivity (mobocertinib)

- Rare NSCLC population (EGFR exon 20 insertion)
- RWE used as historical benchmark comparator
- Source: retrospective EHR-based cohort study

Zolgensma (onasemnogene abeparvovec)

- Gene therapy for spinal muscular atrophy (SMA)
- RWE from observational cohorts used as natural history controls
- Enabled interpretation of treatment benefit in absence of randomized comparator

Evrysdi (risdiplam)

- Treatment for SMA
- RWE used to construct historical control group
- Supported efficacy in rare disease context with established natural history

RWE for Safety & Real-World Understanding

Use of RWE for safety data and long-term evidence

Ruzurgi (amifampridine)

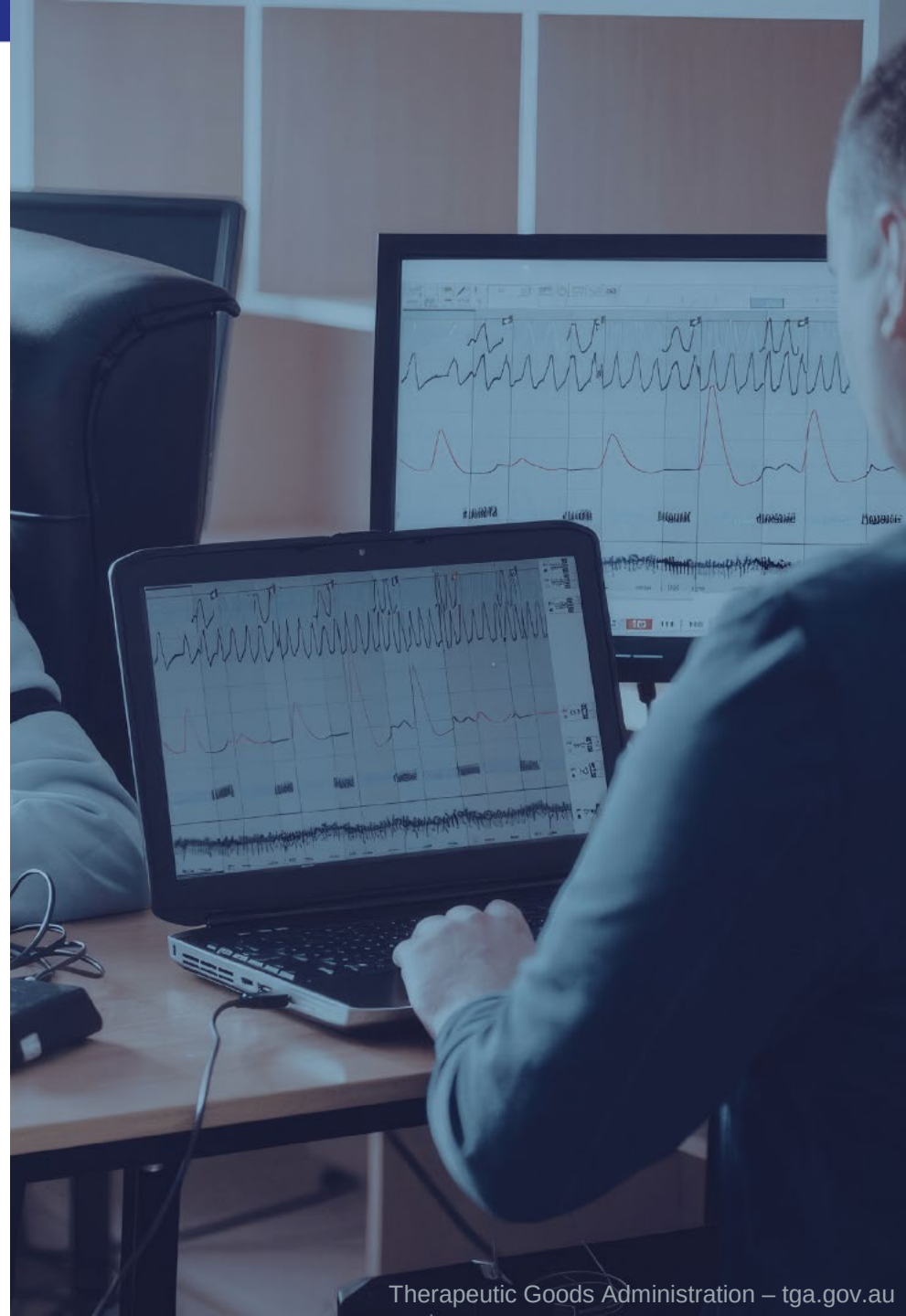
- Indicated for Lambert–Eaton myasthenic syndrome (LEMS)
- RWE source: compassionate use programme follow-up
- Provided long-term safety insights beyond clinical trials

Implementing Fit-for-Purpose RWE

Practical frameworks, risks, and sponsor considerations

Fit-for-purpose assessment: a practical framework

- Data considerations: relevance (population, key variables) and reliability (quality, provenance, missingness).
- Methods considerations: credible design/analysis; bias mitigation; sensitivity analyses.
- Regulatory context: what decision is being made (indication, label, safety, benefit–risk).
- Clinical context: whether the clinical question can be reliably addressed using RWE (equipoise, effect size, prior evidence).



Key risks and how to manage them

- Bias and confounding (selection, channelling, unmeasured confounding).
- Outcome misclassification and incomplete follow-up.
- Missing data and variable assessment timing in routine care.
- Mitigation: prespecified protocol/SAP, appropriate comparators, propensity scores/adjustment, sensitivity analyses, validation of endpoints.

Transparency & reproducibility expectations

- Clear protocol and analysis plan (ideally prespecified).
- Document data provenance, linkage, transformations, and limitations.
- Explain endpoint definitions and validation (algorithms, chart review, adjudication where needed).
- Report uncertainty and residual bias; be explicit about what RWE can and cannot conclude.

Practical checklist

- Decision question: what is being claimed and what decision hinges on RWE?
- Data fitness: population, capture of exposure/outcomes, completeness, provenance, linkage quality.
- Design & comparators: target trial emulation logic, external controls justification, time-zero alignment.
- Bias control: confounding strategy, sensitivity analyses, negative/positive controls (where feasible).
- Results & uncertainty: effect estimates, CI, missingness impact, generalisability.
- Traceability: protocol/SAP, code lists, endpoint validation, audit trail.

TGA Vision!

Global Regulatory Alignment

TGA aligns its regulatory approach with comparable overseas regulators to harmonize data requirements and reduce duplication globally.

Adoption of International Guidelines

TGA adopts guidelines on registry-based studies and PRO measures supporting robust data governance and consistent endpoint reporting.

Transparency and Lifecycle Regulation

TGA includes RWE and PRO usage in evaluation reports, enhancing transparency of regulatory decisions for prescription medicines.

Forward-Looking Engagement

TGA commits to ongoing monitoring and collaboration with global regulators, urging sponsors to align with evolving international standards.

Key Messages

- RWE can add value across the lifecycle when it is fit-for-purpose and transparently presented.
- The regulatory question drives the evidentiary bar and acceptable uncertainty.
- Ongoing priorities: capability building, consistent assessment, and alignment with international best practice.

Questions?

www.tga.gov.au

Australian Government

Department of Health, Disability and Ageing

Therapeutic Goods Administration