KPMG

# Real World Data and Evidence in Drug and Device Development

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## Introduction

Real world data (RWD) and the generation from it of real word evidence (RWE) provides a foundation for strong pharmaceutical and medical device development by acting as the critical bridge from clinical effectiveness to commercial viability. Pharmaceutical and medical device companies have long utilised RWE to determine the benefit/risk balance of treatments in routine practice across populations and geographical regions. RWE is also used to inform decision making, to encourage stakeholder data sharing, to respond to requests from external stakeholders, to improve therapies and to gain regulatory approval for new treatments.

**Real world data (RWD) and real world evidence (RWE) can be defined as:**

**RWD** are data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources and can include:[(a)]

- Electronic health record (EHR) data
- Medical Claims data
- Product or disease registry data
- Data obtained from digital health technologies
- Data gathered from other sources that can inform on health status, e.g. questionnaires

**RWE** is the clinical evidence associated with the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated from RWD using many different study designs.[(a)]

## The role of RWD / RWE in decision-making

RWE enables regulators, policy makers, purchasers and healthcare authorities to make ongoing, evidence-based decisions, linked to approval, monitoring and early access to drugs.[(b)] Depending on the characteristics and the quality of the RWD used, the U.S. Food and Drug Administration (FDA) considers RWE as scientifically valid for regulatory decision-making and speeding up approval processes. The Blincyto study (blinatumomab) is an example of RWE optimizing the registration of a product. Blinatumomab was initially approved by the FDA under accelerated approval with a control arm made of historical data from 694 comparable patients extracted from over 2000 patient records in the European Union and the USA. A further study in a randomized controlled trial (RCT) was then required by the FDA to verify the clinical benefit identified from the RWE. Cases of medical device registrations being supported by RWE also serve as examples of the benefit of high-quality RWE for informing or supporting a regulatory decision.[(c)]

The use of advanced analytics to draw insights from RWE datasets continues to improve the utility and potential benefit of this new data source. Globally, modernisation in analytical techniques such as predictive models, machine learning, probabilistic causal models, and unsupervised algorithms are helping to make RWE an increasingly powerful resource for pharmaceutical and medical device companies.[(d)]

## Data quality

The European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) have initiated the “big data steering group workplan”, which aims to establish a certification process for RWD sources.[(e)] It is widely understood that a data quality framework is required to build the trust of patients and healthcare professionals in the decisions reached by regulators when big data underpins those decisions[(f)]. As a result of this framework, companies utilising this approach can make decisions with confidence when selecting data sources.

Note:

(a) https://www.fda.gov/media/120060/download

(b) https://pubmed.ncbi.nlm.nih.gov/36254408/

(c) Real-world evidence and product development: Opportunities, challenges and risk mitigation - PMC (nih.gov)

(d) How pharma companies are applying advanced analytics to real-world evidence generation | McKinsey

(e) https://www.ema.europa.eu/en/documents/work-programme/workplan-2021-2023-hma/ema-joint-big-data-steering-group_en.pdf

(e) PowerPoint Presentation (europa.eu)

# Real World Data and Evidence in Drug and Device Development (cont.)

## Real World Data (RWD)

- Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- Patient-level data not collected in conventional randomized controlled trials
- Examples: electronic health records (EHRs), health insurance claims data, mortality data, consumer data, registries, data collected in observational studies, chart reviews.

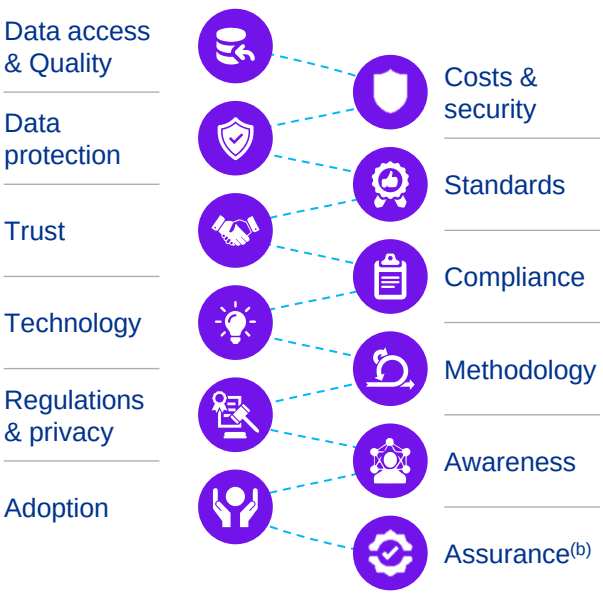
## Real-World Insights (RWI)

- Insights generated from RWD using appropriate scientific and/or generated commercial analytics

## Real-World Evidence (RWE)

- Evidence obtained from Real World, insights generated from RWD using different study designs or analyses, potentially including but not limited to, randomised trials, and observational studies (prospective and or retrospective.)[(a)]

## Challenges




## How can RWE and RWI be used?

- Decision making,
- Response generation to requests from external stakeholders, and improvement of therapies.
- Market positioning.
- Growing regulatory acceptance.
- Continuous benefit-risk assessment
- Improving demand from payers and physicians.
- Increasing familiarity with digital processes and analytics enabling companies to derive much broader benefits from RWE.[(c)]

Note:
(a) Introduction to real-world evidence studies -PMC (nih.gov)
(b) The Real-World Data Challenges Radar: A Review on the Challenges and Risks regarding the Use of Real-World Data - FullText - Digital Biomarkers 2021, Vol. 5, No. 2 - Karger Publishers
(c) Real world data: an opportunity to supplement existing evidence for th | JMDH (dovepress.com)

# The Value of Real World Data / Evidence

### Reasons to consider using RWE / RWD

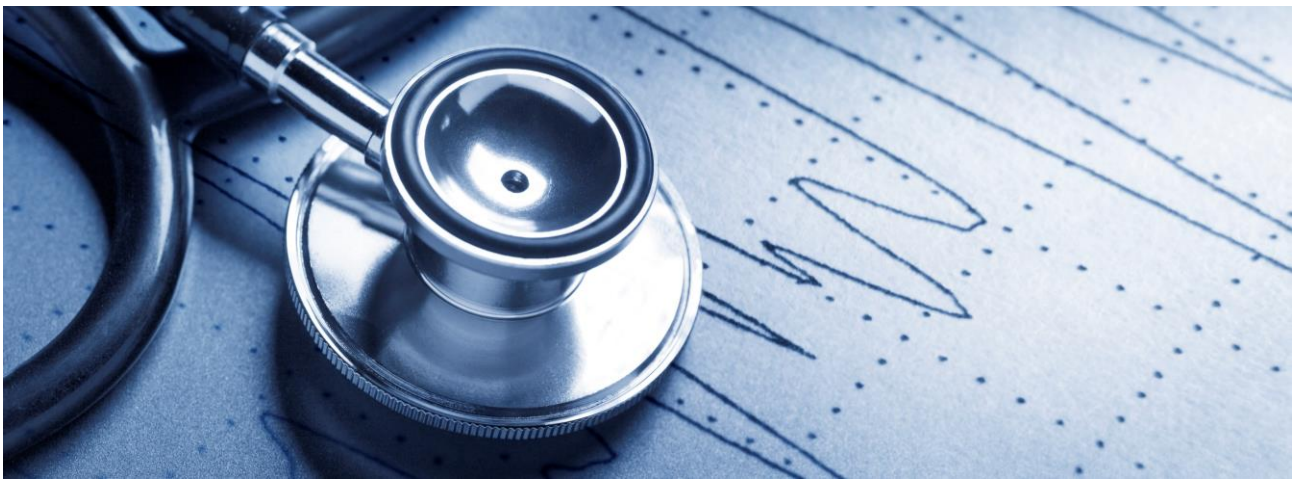
Over recent decades, increasingly complex drug approval processes have necessitated concerted efforts to accelerate and reduce the cost burden of regulatory decision-making. This includes a shift toward a defined, integral role for RWE within regulatory approval processes.

Although data from RCTs remain standard for new drug evaluations, there are situations where a robust clinical trial is not practical, for example due to:

1. low recruitment prospects (e.g., for rare diseases)
2. prohibitive anticipated costs
3. resource needs or ethical prohibition
4. time constraints – the clinical trial process is time consuming, which can delay availability of new effective treatments


In these circumstances, innovative approaches are needed to assess the benefits and risks of a medication. One such approach is to use RWD to help highlight unmet medical needs and demonstrate the effectiveness, tolerability and patterns of care of a given pharmacological agent in real-life settings and populations.[(a)]

| Current routine use of RWE / RWD | Future outlook for RWE / RWD |
|---|---|
| • The use of RWD/RWE in regulatory decision-making is not new. For many years RWD/RWE have been required in the post-approval setting of medicines to further evaluate safety and benefit-risk in the context of pharmacovigilance activities.<br>• Although these post-approval commitments are not applied to all medicines that are authorised through 'traditional' clinical trial programmes, it may be that regulators will place a greater emphasis on such commitments if an authorisation is based wholly or partly on RWD sources. | • Recently published guidance indicates that the use of observational studies, alongside RCTs using RWD, is well-within the scope of FDA and EMA thinking to support regulatory decision making across the entire product life cycle. This includes early product development, approvals, extensions to indications, as well as safety.<br>• Most regulatory guidance on observational studies has so far focused on safety endpoints. There is however, a growing need to develop guidance and methods specific to pharmacoepidemiology studies, to assess benefit and effectiveness outcomes. |



Note: (a) Evolving use of real-world evidence in the regulatory process: a focus on immuno-oncology treatment and outcomes | Future Oncology (futuremedicine.com)

# Case Studies

## Case Study 1 - RWE Used to Support the Registration of an Osteoporosis Product in China

**Background:**

- In June 2020, the National Medical Products Administration in China approved Prolia, the fist monoclonal antibody for the treatment of postmenopausal osteoporosis (PMO) in women at high risk of fractures.[(a)] The approval was supported by a novel market authorisation approval (MAA), including data from the global clinical trial programme, together with results from a real-world study.
- The real-world study was developed to evaluate two key regulatory points:
    1. The effectiveness of Prolia for the reduction of clinical osteoporotic fractures among Chinese women with PCO
    2. The safety of Prolia among Chinese women with PMO in Taiwan and Hong Kong

**What data were used?**

- A population-level, claims database from Taiwan and a population-level, clinical database from Hong Kong were used as data sources.
- Both databases included demographic and clinical information on diagnosis and procedures for large proportions of the populations. Together, they provided information for over 40,000 Prolia patients.

**1) The effectiveness of Prolia for the reduction of clinical osteoporotic fractures among Chinese women with PMO;** and

**Results:**

- Risk reductions assessed in the real-world study of ethnic Chinese women on Prolia were compared with results from the phase 3 multiregional clinical trials study (FREEDOM).
- The relative reduction in risk for clinical vertebral fracture, hip fracture and nonvertebral fractures for the treatment cohort versus the non-treatment cohort observed in the real-world study were similar to the reductions in fracture risk demonstrated by FREEDOM.

**2) The safety of Prolia among Chinese women with PMO in Taiwan and Hong Kong**

**Results:**

- The magnitude of three important risks associated with Prolia (osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and hypocalcemia) in a large longitudinal sample of patients in the Taiwan and Hong Kong databases were assessed.
- While there are differences in patient populations, clinical practices, and healthcare systems, the overall rates of ONJ, AFF, and hypocalcemia observed in Chinese patients were relatively low and similar to rates found in Western observational data sources (within the range of ± 1 per 1000).

**Conclusion:**

This case illustrates how RWE can be used effectively in providing evidence to confirm the benefits and risks associated with a new pharmaceutical product, and enable label expansion to new patient populations.

Note: (a) A Novel Case Study of the Use of Real-World Evidence to Support the Registration of an Osteoporosis Product in China - PubMed (nih.gov)

# Case Studies

## Case Study 2 - RWE and GlaxoSmithKline's (GSK) Salford Lung Study

**Background:**

- GSK's Salford Lung Study is considered a pioneering example and the first of its kind globally, demonstrating a major advance in the way that clinical trials are conducted.
- The study was a large, multi-million pound real-world trial conducted with a pre-license medicine across a patient population within a single geographical setting [a].
- GSK worked with a variety of NHS organisations to recruit patients in Salford, Greater Manchester (UK) to provide RWE in the trial assessing safety and effectiveness of Relvar Ellipta (fluticasone furoate 'FF'/vilanterol 'VI' or 'FF/VI') for treatment of chronic obstructive pulmonary disease (COPD) and asthma [b].

**What data were used and how?**

- Researchers decided to consider not only whether the treatment worked, but also whether the treatment worked in the real world, taking into consideration factors such as variations and errors in taking medication, and interaction with other medication.
- The study included few exclusion criteria. This enabled participation of much more representative populations of COPD and asthma patients. The study also facilitated a much more natural, 'real' setting for patients, where participants continued to interact with their nurse or general practitioner as normal, and collected medication from their usual pharmacy.

**Results:**

- Results indicated that patients on the drug improved their health compared to those on standard care, without a greater risk of serious adverse events, although with no significant difference in the rate of patient visits to primary or secondary care.

**Conclusion:**

- Overall, the study illustrates the value of RWD/RWE for healthcare funders. In particular, the case demonstrates how use of RWD/RWE can accelerate progress towards a more data-led, integrated model of care – a strategy which has been identified as vital for the long-term viability of the NHS.

Note:
(a) GSK seeks real-world Relovair evidence with Salford Lung Study - PharmaTimes
(b) Case study: Delivering real world research - The Salford Lung Study | NIHR

# Focusing on Real World Data / Evidence with KPMG

## What has changed in terms of recent guidance?

### UK

The UK Medicines and Healthcare products Regulatory Agency's (MHRA) new guidance on using real-world data to support clinical trials opens the door to quicker access to medicines for patients. This new guidance follows consultation with key stakeholder groups including the pharmaceutical industry, academic researchers, trade associations, patient organisations/charities, healthcare providers and regulatory organisations. When used in this innovative way, RWD has the potential to increase speed and reduce costs associated with developing medicines through clinical development programmes. In addition, this approach can also improve patient access to medicines.[(a)] The MHRA now encourages companies wishing to use RWD in their development programmes to actively engage with them to seek scientific advice.

### EU

The EMA have published a number of articles recently on the topic of RWE, for example highlighting a vision for use of RWE in EU medicines regulation and the contribution of RWE in EMA's regulatory decision making. The EMA have also selected the first set of partners to collaborate with DARWIN EU, the Data Analysis and Real-World Interrogation Network[(b)]. The data available to partners will be used for studies to generate RWE to support scientific evaluations and regulatory decision making.

### USA

New FDA guidance published in September 2022 focuses on submissions that intend to utilise RWD and RWE to support a regulatory decision on a product's effectiveness and/or safety. Relevant submission types may include initial investigational new drug applications (IND), meeting requests, study protocols, and final study reports submitted for INDS, biologic licence application (BLAs), or new drug applications (NDAs).

Guidance on RWE / RWD published by MHRA and FDA are not identical, and it is important that organisations are aware of the differences.

## RWE and Company Strategy

RWE can support and improve upon a range of processes: from determining which cohort of patients can benefit most from an intervention, informing regulatory approvals and complementing data from randomized controlled trials, to supporting reimbursement efforts and expanding indications for use.

## How KPMG can support companies?

KPMG has expertise in a range of therapeutic areas and can provide advice through the entire medicine and device regulatory cycle. As the use of RWE becomes more fundamental to the regulatory process, KPMG has expertise in the use of this evidence to support clients in product registration, launch and maintenance of licenses. Our subject matter experts bring together real-world datasets to support regulatory strategy and compliance, clinical development and market access. Our end-to-end services are rooted in deep understanding of clinical operations and regulatory requirements, accelerating medical device and medicines speed to market whilst reducing costs but without compromising safety.

Note:
(a) https://www.gov.uk/government/news/mhras-new-guidance-on-using-real-world-data-to-support-clinical-trials-could-get-medicines-to-patients-sooner
(b) DARWIN EU® welcomes first data partners | European Medicines Agency (europa.eu)

# Our Expertise

## Adrian Griffiths

Healthcare and Life Science Lead

E: adrian.griffiths@kpmg.co.uk

## Anusha Foy

Partner, Head of Life Science Biotech

Life Science Regulatory Solutions Practice

E: anusha.foy@kpmg.co.uk

## Fiona Thomas

Chief Medical Officer

Life Science

E: fiona.thomas1@kpmg.co.uk

## Phil Bryan

Pharmacovigilance Vaccines Expert Advisor

## Tanya Chambers

Senior Manager

Life Science Regulatory Solutions Practice

E: tanya.chambers@kpmg.co.uk

## Liam Johnstone

Associate Manager

Life Science Regulatory Solutions Practice

E: liam.johnstone@kpmg.co.uk

## Sneha Gajbhiye

Consultant

Life Science Regulatory Solutions Practice

E: sneha.dilipgajbhiye@kpmg.co.uk

## Jane Collins

Associate Manager

Life Science Regulatory Solutions Practice

E: jane.collins@kpmg.co.uk

KPMG

kpmg.com/uk



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