# *Adopting*
# Real World Evidence

WITH DALTON

Peter Pekos

## Company Vision

"To make the impossible possible, Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

## Disclaimer

This technical report is intended to provide information to quality and regulatory professionals on the best practices and application of real world data. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

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# RWD vs. RWE

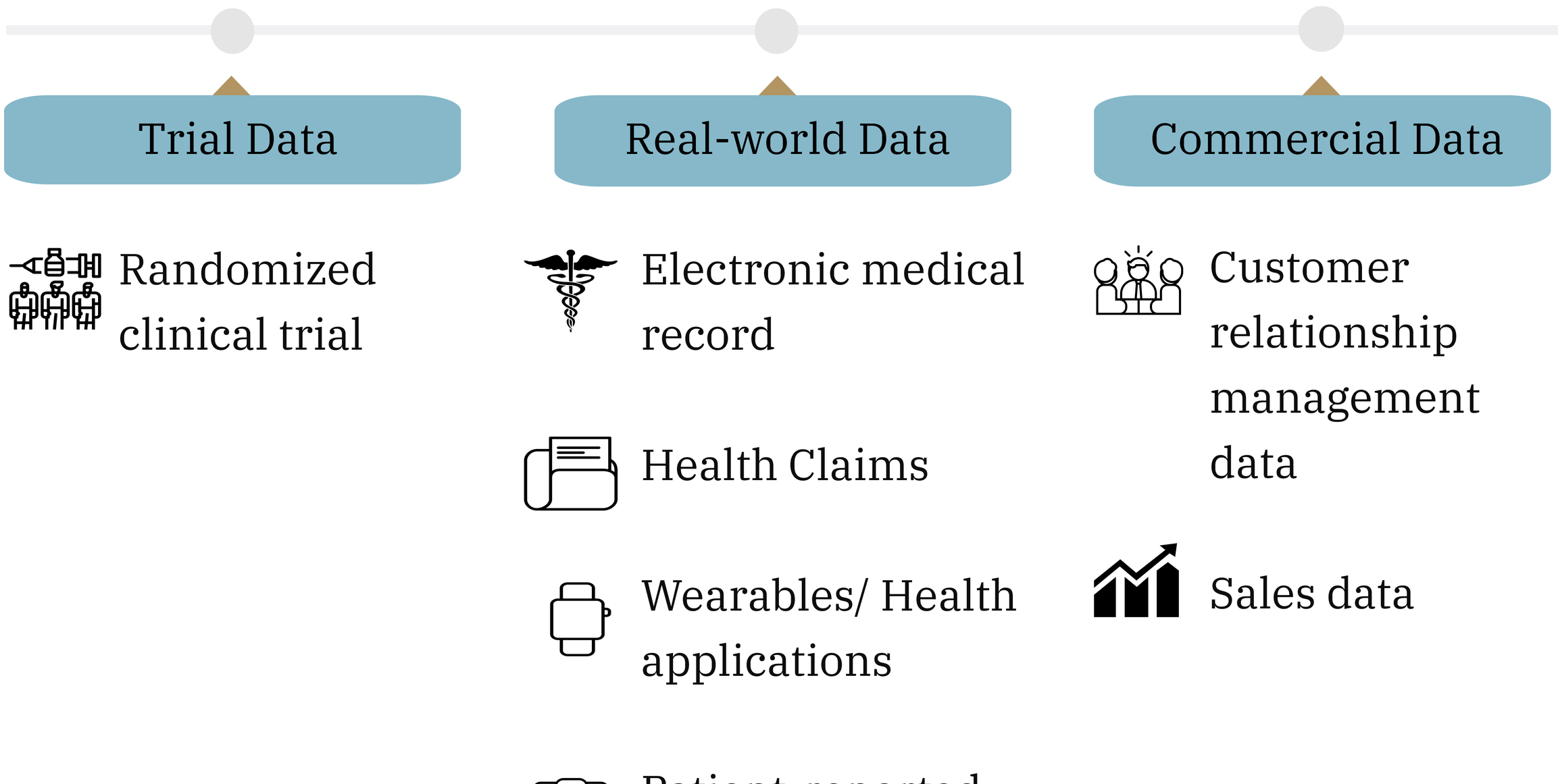
## What is RWD?

**Real-world data (RWD)** is the healthcare data collected from sources that are routinely used to contain or track patient health status and healthcare delivery, such as:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Personal devices and health applications

## What is RWE?

**Real-world evidence (RWE),** generated by different study designs or analyses, is the clinical evidence derived from real-world data, which are observational data outside the context of randomized controlled trials, generated during routine clinical practice. RWE demonstrates the use and possible advantages, or risks, of a medical product approval based on the analysis of RWD.



# Introduction

The application of real-world data and real-world evidence as a tool for healthcare decision-making continues to evolve in the pharmaceutical industry. Although RWE has been around for many years, recent advances in digital and advanced analytics have increased the acceptance of RWE among physicians, payers, and regulators as its multipurpose evidence infrastructure have the potential to significantly improve patient outcomes, patient care, reduce costs, and boost efficiencies in health care systems. Companies are in fact encouraged to move away from sole reliance on randomized clinical trials and towards integrating high-quality, real-time data during the research and development of new medications, devices, and technology. For instance, AstraZeneca evaluated the real-world effectiveness of their diabetic medicine Farxiga to competitors using real-world data (AstraZeneca, 2018). In limited instances, regulatory agencies have even accepted RWE to support drug product approvals, primarily for oncology and rare diseases. Pfizer's use of electronic medical record (EMR) data in seeking approval for Ibrance to treat male breast cancer is one example (Pfizer, 2022). However, there are still quite a few barriers that impede its widespread implementation.

## When Would RWE Be Needed?

Although randomized controlled trials (RCT) are the gold standard for establishing the efficacy and safety of medical products and treatments, there are instances whereby an RCT would be impossible, impractical, or unethical to conduct. In such cases, using RWE as a tool would be beneficial. RWE also serves to complement evidence during pre-authorization phase and post-authorization phases.

(Malamis & Howley, 2022)

# Current and Future Uses of RWE

### *Current*

- Comparative effectiveness
- Patient characteristics
- Biomarker stratification
- Treatment patterns
- Healthcare resource consumption
- Complementing pre-authorization evidence (i.e., contextualising uncontrolled trial results)
- Providing evidence in the post-authorization phase (i.e., safety and efficacy studies)

### *Emerging*

- Guiding patient perspective
- Genomics/ precision medicine therapies
- External comparators

### *Future*

- Integrated evidence generation infrastructure: RCT, observational, secondary data
- Continuous real-time insight / evidence generation for product launch – aligned with payor / regulatory requirements (i.e., post-authorisation safety study / post-authorisation efficacy study)
- Continuous real-time treatment pattern monitoring

## Used during R&D to

- Compare trial data with real-world evidence (RWE) to strengthen dossier
- Demonstrate the economic value of treatment to the payer
- Enable outcome-based pricing
- Achieve label expansion by removing the necessity for a new randomised controlled trial

## Used to improve market access by

- Determining unmet needs
- Improving site selection and accelerate recruitment
- Accelerating time to market
- Refining formularies by determining optimal dosing based on patient response
- Recognizing safety and efficacy profiles

## Used to enhance sales by

- Targeting underdiagnosed patients
- Identifying patients likely to switch or discontinue
- Shaping product positioning
- Gaining insight into healthcare-provider decision-making
- Providing recommendations at the point of care based on predictions of outcomes

## Used during post authorization to

- Increase pharmacovigilance by monitoring real-world usage for safety and adverse occurrences and quickly generate detailed views of advantages and challenges
- Identify subpopulations for which effect outperforms trials

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(Rudrapatna & Butte, 2020)

# Advantages and Challenges of RWE

## Pros

- ✓ Real-time information on treatment efficacy in the real world
- ✓ Integrated research across clinical trial, primary, and secondary data
- ✓ Quicker product launch


## Cons

- Lack of medical-level precision
- Inconsistent quality of real-world data sources (most prevalent in the United States and Europe)
- Lack of RWE analytics standards
- Privacy issues about sharing personal information
- Collaborating with multiple parties that have access to the data as evidence platforms are not in the public domain
- Correlating biomarkers with results
- Removing confounders
- Meeting regulatory criteria

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# RWE News

June
**2020**

Health Canada and CADTH (Canadian Agency for Drugs and Technologies in Health) recently announced their intention to collaborate on the optimization of systematically incorporating RWE into both regulatory and reimbursement decision-making in Canada due to the rising number of challenges around drugs for rare indications and rapidly rising costs. If adopted, this will have a significant influence on how pharmaceuticals are authorised and paid for in Canada.

Feb
**2022**

Europe initiates DARWIN EU® – a network of real-world healthcare data sources from throughout Europe as part of the European Medicines Agencies Network Strategy to 2025. In February 2022, EMA hosted a multi-stakeholder information webinar to describe the founding of DARWIN EU, highlight prospects for collaboration, and answer questions. By the end of 2022, the research database will launch four investigations with the assistance of ten research partners to collect real-world evidence (RWE). For more information, click here.

June
**2022**

The US Food and Drug Administration (FDA) has released four draft guidance outlining how it will apply real-world data (RWD) in regulatory decision-making. More guideline publications, including specifics on research designs that use RWD for external control arms, are in the works. For more information, click here.

June
**2022**

EMA, FDA, and HC co-chaired an ICMRA workshop to share their experience on RWE achievements and challenges in pharmaceutical regulation, and to identify potential opportunities for future international regulatory collaboration. The four areas of opportunities identified for regulatory collaboration include:

- Harmonization of RWD and RWE terminologies
- Convergence on RWD and RWE guidance and best practice
- Readiness to address current and growing public health concerns
- Transparency

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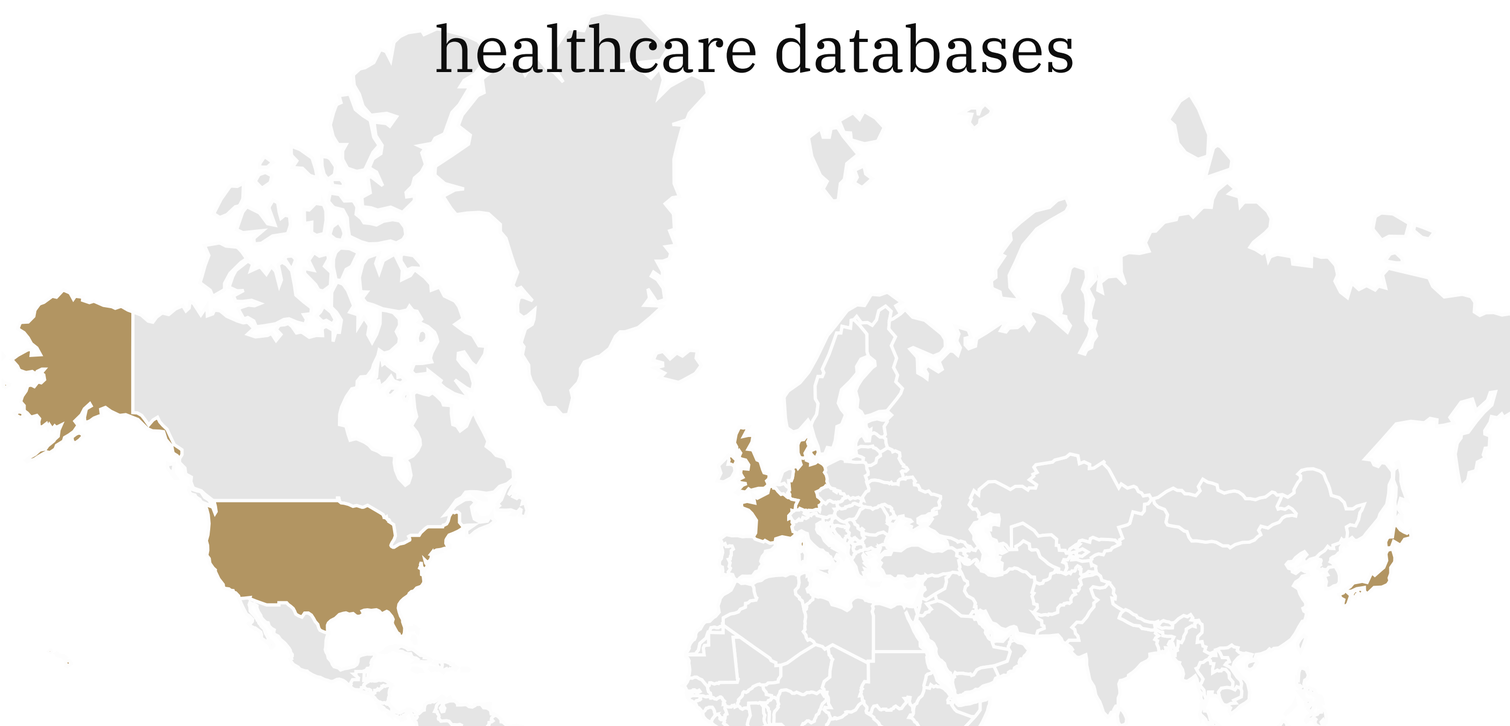
# Examples of Real-World Databases

| Country | Organization/ Agency | Basis of database |
|---|---|---|
| Japan | MHLW (Ministry of Health, Labour, and Welfare) | National claims database |
| US | CMS (Centers for Medicare & Medicaid Services) | Medicaid/Medicare claims database |
| France | SNDS (French administrative health care database) | National claims database |
| UK | CPRD (Clinical Practice Research Datalink) | Electronic medical record (EMR) data from 10% general practitioners |
| | HES (Hospital Episode Statistics) | English hospital database |
| Germany | WIdO (Wissenschaftliches Institut der AOK) | Regional public sickness funds claims database |
| Denmark | SDS (The Danish Health Data Authority) | National cross-linked healthcare databases |



## Other Examples of Real-World Databases

- **I-O Optimise4:** a BMS-sponsored evidence platform in thoracic oncology.
- **Phedra (now "HONEUR"):** a Janssen-sponsored evidence platform in haematological oncology.

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# FDA & EMA Resources

## FDA

1. Guidance: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
2. Guidance: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
3. Guidance: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products
4. Guidance: Data Standards for Drug and Biological Product Submissions Containing Real-World Data
5. Guidance: Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
6. Guidance: Use of Electronic Health Records in Clinical Investigations
7. Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
8. Publication 2020: Randomized, observational, interventional, and real-world- What's in a name?
9. Publication 2022: Real-World Evidence- Where Are We Now?
10. Guidance: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

## EMA

1. Guidance: Guideline on registry-based studies

*Note that EMA standards are still to be issued in comparison to the US FDA which have provided specific guidance on RWD standards.*

# Dalton's *Services*

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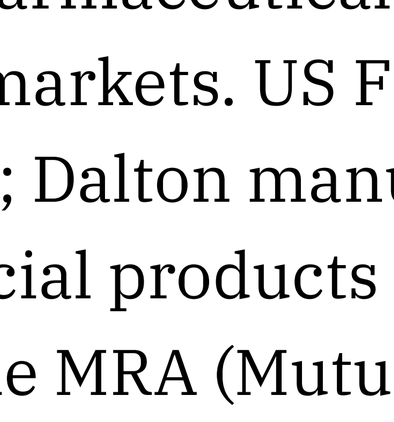
At Dalton we can help with drug innovation through our cGMP APIs. Our skilled scientists can support your drug discovery process through API synthesis for all stages of pre-clinical and clinical trials as well as small scale commercial manufacturing. We provide integrated process development, API manufacturing and finished dose manufacturing at a single location with the expertise required for developing a process that is robust, transferable, and scalable to meet your requirements.

Our API development services include:

- Lead identification
- Synthetic route development
- Feasibility studies & tech transfer
- Process optimization & scale-up
- Scale-up troubleshooting
- Engineering batches
- cGMP API manufacturing



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