Utilizing Real World Data for Clinical Evidence Generation.

A guide for Digital Health Technologies

FDA

NICE
National Institute for Health and Care Excellence

This following carousel has been compiled using these 3 resources:

Contains Nonbinding Recommendations

Draft – Not for Implementation

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on December 19, 2023.

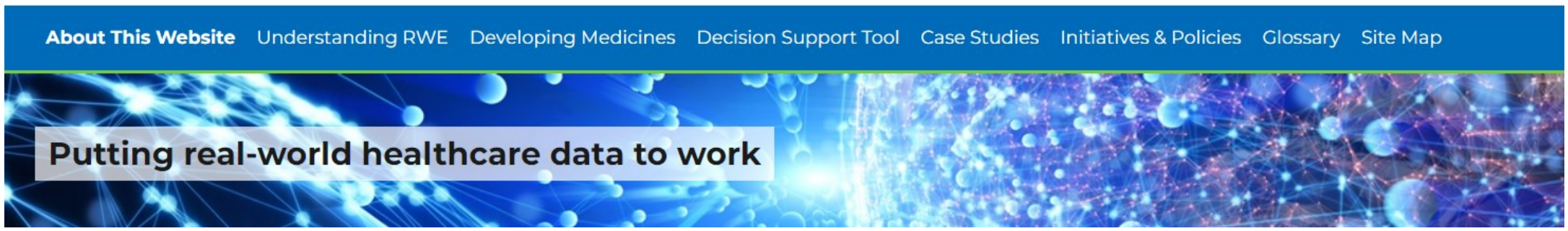
Available here:

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-use-real-world-evidence-support-regulatory-decision-making-medical-devices

This following carousel has been compiled using these 3 resources:

RWE Navigator

Get Real



Available here:

https://rwe-navigator.eu/

Available here:

https://www.nice.org.uk/corporate/ecd9/chapter/overview

INTRODUCTION

The rapid increase in the use of technology, such as **electronic systems, biosensors, mobile and wearable devices in healthcare**, has led to the accumulation of large amounts of RWD.

These data can help enhance the study designing and conduct in order to address **unmet clinical needs**.

Real-world data can improve our understanding of **health and social care delivery**, **patient health and experiences**, and the **effects of interventions on patient** and system outcomes in routine settings.

WHAT IS REAL WORLD DATA?

Broadly, all data collected routinely (that is, not as a part of RCTs) on patient health from different sources, are called RWD.

The US FDA defines RWD as:

"the **data relating to patient health status** and/or the delivery of health care **routinely collected from a variety of sources**, such as electronic health records (EHRs), claims and billing activities, product and disease registries, patient generated data from in-home settings, and data from other sources, such as mobile devices".

WHAT IS REAL WORLD EVIDENCE?

The analysis of RWD generates **real-world evidence** (RWE).

As per the USFDA, RWE is:

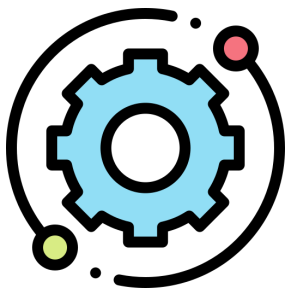
"The **clinical evidence** regarding the usage and potential benefits or risks of a medical product **derived from analysis of RWD**"

RANDOMISED CONTROLLED TRIALS

Randomised controlled trials (RCTs) are currently the preferred source of evidence on the effects of interventions.

However, randomised trials may not be available for several reasons, including:

— **Randomisation is considered unethical or unfeasible** (for instance, for some rare or severe diseases with unmet need)



— **Technical challenges make randomisation impractical**, which is most common for medical devices and interventional procedures

— **Funding is not available for a trial** (for example, when the intervention is already used in routine practice).

BENEFITS OF RWD.

1. RWD fosters **inclusion of target populations that are otherwise underrepresented** in clinical studies.

2. Use of RWD may provide an efficient means of generating the necessary clinical evidence to **support regulatory decisions.**

3. RWD that includes patient experience data may **provide new insights** into the performance of a device.

4. Leveraging RWD may **allow for studies of a longer period of time** than would be practical in a traditional clinical study

5. RWD may include **information from broader clinical experiences** than is usually represented in traditional clinical studies.

LIMITATIONS OF RWD.

Trust in real-world evidence studies

- Real-world data is often complex and requires substantial preparation before it can be analysed.
- Concerns about the **integrity and trustworthiness of the resulting evidence** (for example, resulting from data dredging or cherry-picking) need to be addressed.

Data quality and relevance

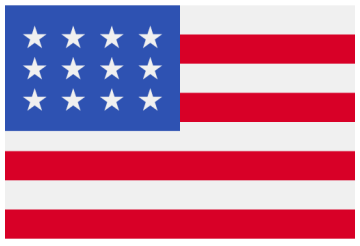
- Some types of data are often, though not always, **absent from real-world data sources.**
- Other variables may be collected at an insufficiently granular level.

Risk of Bias

- Real-world data are at risk of a variety of bias including: **Selection bias, information bias, confounding and reverse causation bias**.

RWD & REGULATIONS.

There is an increase in interest in RWD for medicines and medical devices in major regulatory bodies.

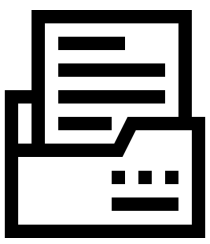


FDA has released a draft guidance on the use of Real World Evidence to Support Regulatory Decision-Making for Medical Devices.

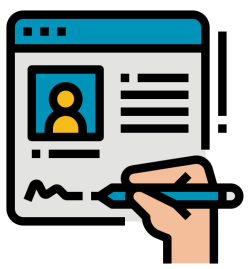
In Europe, the **EMA has launched the vision statement for 2025 to facilitate using RWE** for regulatory decision making and to improve and monitor medicines.

In the UK, the **NICE launched an RWE framework in June 2022** for optimising RWD to fill the knowledge gaps, thus making innovative care accessible to patients

SOURCES OF RWD (1)

Electronic health records 	**Computerised individual patient records.** These are typically used to inform the clinical management of patients. These sometimes integrate data from other information systems including laboratory, genomic, and imaging systems.	**The Clinical Practice Research Datalink (CPRD) GOLD** contains demographic and clinical information on patients enrolled in participating general practices across the UK.
Administrative Data 	**Data collected for administrative purposes** by health and social care services.	**The Hospital Episode Statistics (HES) Admitted Patient Care dataset** contains information on diagnoses and procedures done for all patients admitted to NHS hospitals or NHS-funded treatments in private hospitals.

SOURCES OF RWD (2)

Claims Data 	**A type of administrative data on healthcare service** use often collected from insurance -based systems.	**Centres for Medicare & Medicaid Services data** contains data on individuals in receipt of Medicare services derived from reimbursement information or payment of bills.
Patient registries 	**Registries are organised systems that collect uniform data (clinical and other)** to identify specified outcomes for a population defined by a particular disease, condition or exposure. Registries can serve several purposes including research, clinical care or policy. Registries can include interventional studies.	**The Systemic Anti-Cancer Therapy (SACT) dataset** contains information on all patients treated with anticancer therapies from NHS England providers. This data is widely used within NICE to provide information on drugs approved for use within the Cancer Drugs Fund.

SOURCES OF RWD (3)

Patient Generated Health Data 	**Data generated directly by patients or their carers** including from wearable medical or personal devices, mobile apps, social media, and other internet based tools. Data can be collected <u>actively</u> (for example, by people entering data on a form) or <u>passively</u> (for example, a smart watch that measures people's activity level).
Chart reviews 	**Data extracted retrospectively from a review of patient health records** (including paper or electronic records). Chart reviews are widely used in <u>natural history studies</u>. They may allow the extraction of data not reported in routine data sources.

SOURCES OF RWD (4)

Audit and service evaluations 	Clinical audits are done to understand how **current standards of care measure against best practice or a set standard**, and subsequently inform quality improvement. Data can be collected prospectively or retrospectively. Service evaluations are done to define and judge current care.
Health surveys, interviews and focus groups. 	**Health surveys involve systematic collection of data about health and disease** in a human population through surveys. They have various purposes including understanding trends in health in a population or understanding patients' experiences of care. Interviews and focus groups are done to collect qualitative data such as patient perception and experiences.

FIT FOR PURPOSE RWD.

Regulatory bodies such as the FDA recognizes that **RWD used to generate RWE, may have limitations**.

Researchers should understand the **strengths and limitations** of generating evidence from RWD to address a specific study question.

If the RWD source appears relevant and reliable, then additional assessment of the study-specific derived datasets may help **demonstrate the RWD are fit-for-purpose** to address the study question.

The **following 7 criteria** may be used to determine whether the RWD sources and the proposed design and analysis can generate evidence **that is sufficiently robust to be used for the given study question and regulatory purpose**.

CRITERIA 1 - COMPLETE AND GOOD

The data should be accurate, as complete as possible, and of adequate data quality to credibly address the question at hand.

Conducting a clinical investigation in accordance with **Good Clinical Practice (GCP)** provides assurance that the data and results from the clinical investigation are credible and accurate and that the rights, safety, and well-being of subjects are protected.

CRITERIA 2 - DATA AVAILABILITY.

The RWD should **contain sufficient detail to capture the information needed** to evaluate the question being addressed in the target population.

CRITERIA 3 - DATA LINKAGES

Researchers should assess whether and **how data from different sources can be obtained and integrated** given the potential for differences in target population characteristics, clinical practices, and coding across data sources.

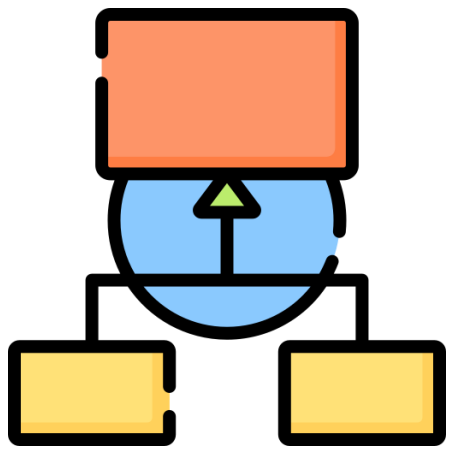
Any linkages performed within and across RWD sources **should use a predefined linkage methodology** that is:

- **Scientifically valid**,
- **Protects the privacy** of individuals whose data will be used,
- Supports **interoperability**,
- Accounts for differences in **coding and reporting across sources**.

CRITERIA 4 – TIMELINES

As with traditional clinical studies, the time between data collection and release for research should be reasonable and the RWD considered for the study should **reflect the current clinical environment.**

(e.g., RWD from before a major change in clinical practice may not be timely).



CRITERIA 5 - GENERALIZABILITY OF DATA

Once a study question is defined, the specific study sample meeting inclusion and exclusion criteria should be :

(1) **representative of the population** in the RWD source eligible for use of the device within the specified indication and

(2) **generalizable to the target population** with the condition of interest.

CRITERIA 6 - DATA COLLECTION

To ensure the reliability of the RWD source, data should be **collected and processed in a consistent and methodical manner**. This should cover:

- Which **types of data** were collected.
- How these were **coded or recorded**.
- **How data was collected**.
- Changes to data collection **over time**.
- **Quality assurance processes** for data collection that were in place.
- **Transformations performed on the data** such as conversion to a common data model or other data standards.

CRITERIA 7
DATA CHARACTERISTICS

The **sample size should be large enough** to produce robust estimates.

The **follow up should be long enough** for the outcomes of interest to have occurred or accrued (for outcomes such as healthcare costs).

The amount of data available before the start of follow up may also be important to **provide information on confounders** and identify new users of an intervention.

DATA SUITABILITY ASSESSMENT TOOL (DATA-SAT).

NICE has also developed the **data suitability assessment tool** to help the consistent and structured presentation of real world data suitability at the point of assessment.

NICE real-world evidence framework

Corporate document [ECD9] Published: 23 June 2022

Corporate document | Tools and resources

Tools and resources

Case studies

- MedTech case study 1 – myCOPD
- MedTech case study 2 – Sleepio
- Drug case study 3 – Mobocertinib

Implementation support

- DataSAT assessment template Word 22 KB 23 June 2022
- Methods to address bias reporting template Word 20 KB 23 June 2022
- Real-world evidence framework user profiles Word 479 KB 23 June 2022

Education

- Framework summary PowerPoint 997 KB 12 January 2024

Available here:

https://www.nice.org.uk/corporate/ecd9/resources

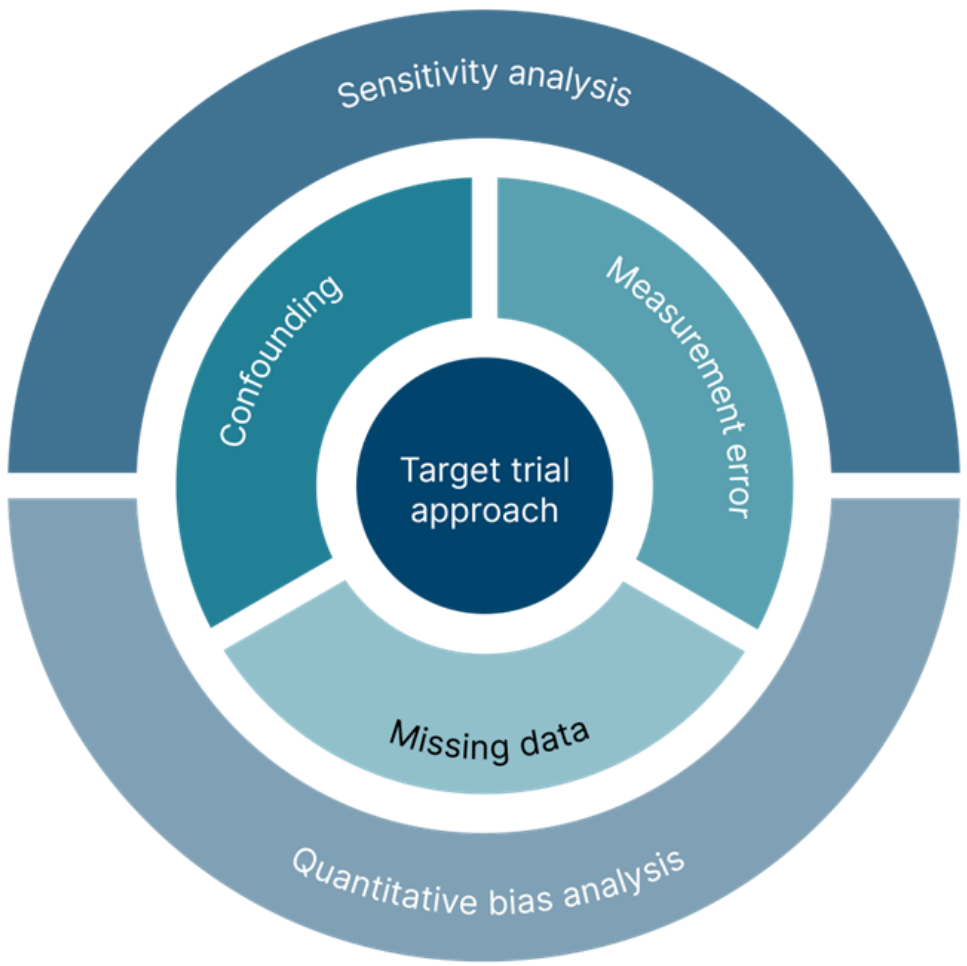
GENERATING RWE WITH RWD.

As with all clinical evidence generation, choosing the appropriate design for studies using RWD depends on the study question, device, outcome, key covariates, and the specific study objectives or hypotheses.

These study designs may include:

- **Single-arm studies with comparisons** to external controls, in whole or part;
- **Objective performance criteria** or performance goals;
- **Non-interventional studies** (observational studies) (comparative cohort studies, case-control studies, self-controlled studies, and descriptive studies);
- **Randomized controlled trials** using RWD to supplement one or more study arms.

NICE - APPROACH TO RWE.



- Design studies to emulate the preferred randomised controlled trial – use a “target trial approach”.
- Identify potential confounders and address these considering observed and unobserved confounding.
- Consider the impact of bias from informative censoring, missing data, and measurement error – address appropriately where required.
- Use sensitivity and bias analyses to assess the robustness of study findings.

EXAMPLES OF GOOD RWE STUDIES:

Available here:

https://www.fda.gov/media/174819/download

REPORTING RWE STUDIES.

The International Council of Harmonization (ICH) has introduced a **"structured template for planning and reporting on RWE study implementation" (STaRT-RWE)** for safety and effectiveness reporting in RWE studies.

Journal Article

BMJ. 2021; 372: m4856.
Published online 2021 Jan 12. doi: 10.1136/bmj.m4856
PMCID: PMC8489282
PMID: 33436424

STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies

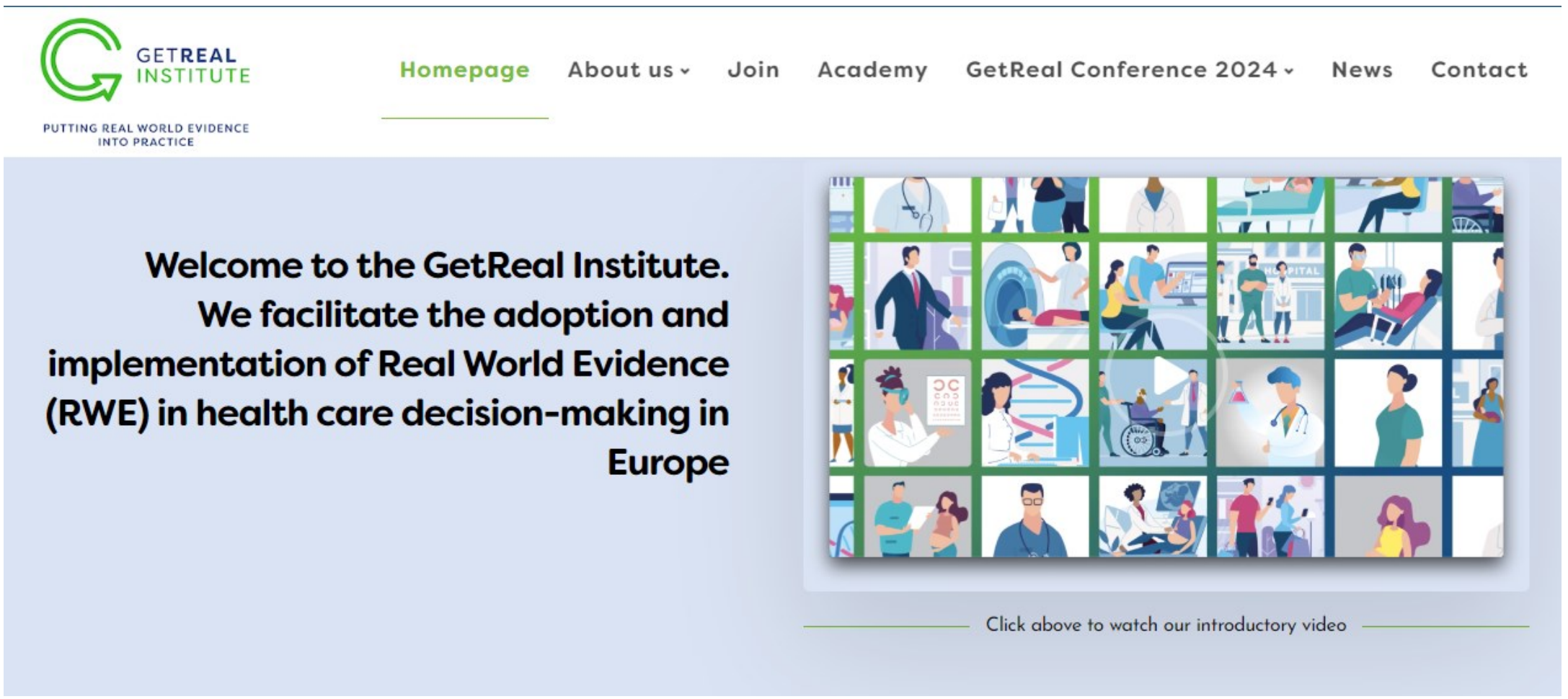
Shirley V Wang, assistant professor,[1] Simone Pinheiro, director,[2] Wei Hua, director,[2] Peter Arlett, head of data analytics and methods,[3,4] Yoshiaki Uyama, office director,[5] Jesse A Berlin, vice president,[6] Dorothee B Bartels, global head of real world evidence and digital sciences,[7] Kristijan H Kahler, executive director,[9] Lily G Bessette, project coordinator,[1] and Sebastian Schneeweiss, division chief and professor[1]

Available here:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8489282/

TO LEARN MORE:

Check out the Get Real Institute for more helpful resources, online courses and educational material!



Available here:

https://www.getreal-institute.org/

Hope you found this helpful!

This is a series we are making to help HealthTech Innovators access better resources.

Just our small way of helping!