OK I get it: in Rare Diseases, the FDA allows the use of Synthetic Control Arms. But how?

PHUSE SDE Americas Winter

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Who is Fadi

- Engineer by degree
- PhD in London
  - PhIV study, looking for people with hypertension
  - Administering compounds from AZ, Pfizer and a placebo
- Occupation
  - ESSEVEE
  - SAS
  - Big WWILFER
- This presentation reflects the opinions of the presenters and should not be construed or considered to represent regulatory authorities' views or policies.

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To Wwilf

Verb: to wwilf

Definition:

To engage in the act of searching for information or content on a computer or the internet with a specific goal in mind, only to become distracted by unrelated content, subsequently losing focus on the original search objective. This behavior often leads to a cycle of clicking on tangential topics, spending extended periods of time on unrelated content, and ultimately forgetting the initial purpose of the search.

Usage:

- *He wwilfed for hours last night, starting with a simple search and ending up on a completely different topic.*
- *I always wwilf when I try to research something online; there's just so much interesting information out there.*

Origin:

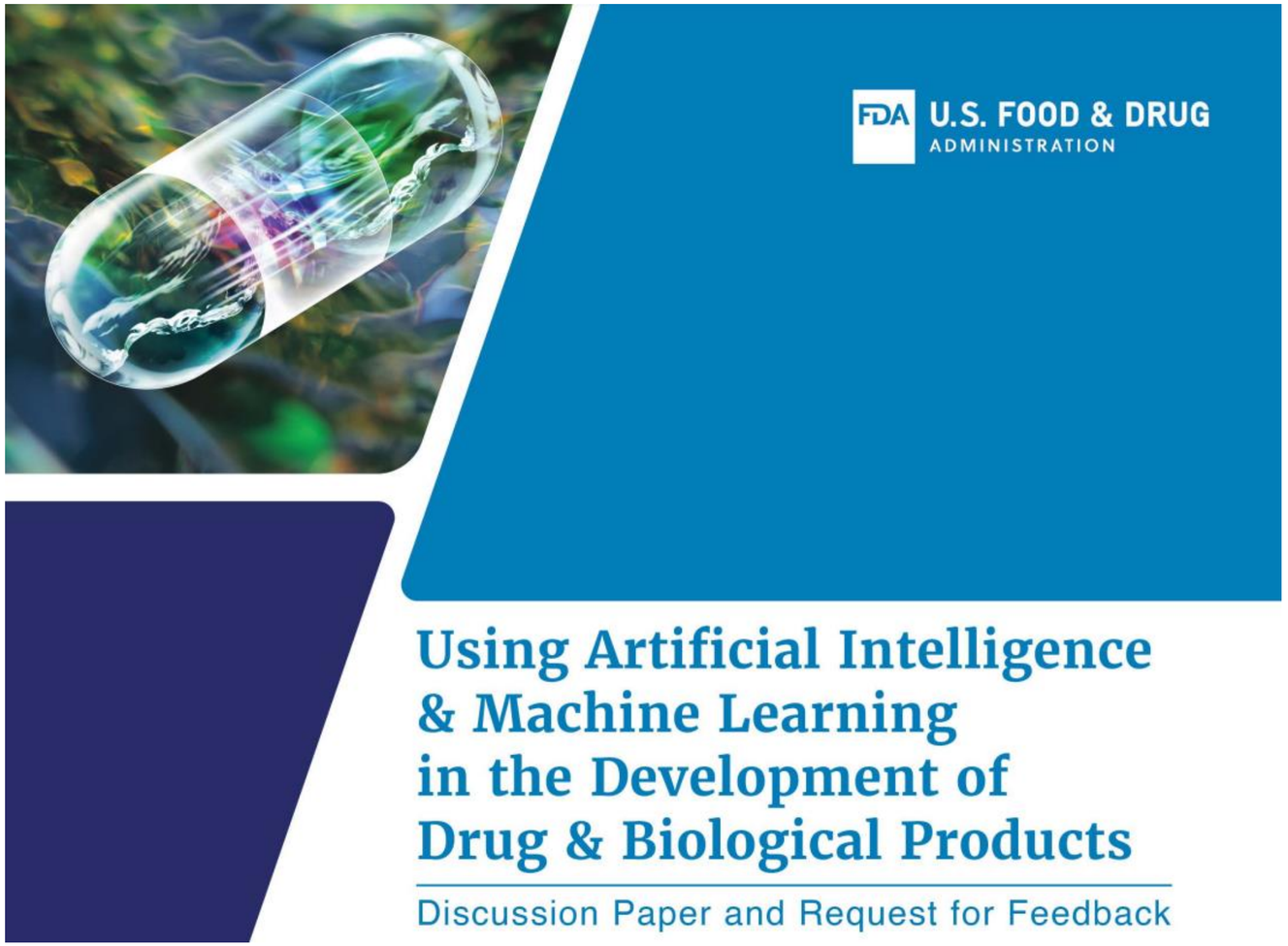
The term "wwilf" is derived from the acronym "WWILF," standing for "What Was I Looking For." It encapsulates the common experience of internet users who find themselves lost in a web of diverse and captivating content, losing sight of their original search intent.

Synonyms:

Procrastisurf, click-trance, internet rabbit hole, digital distraction cycle.

Wwilfing about AI in Medicine

US FDA and EU EMA pave the way



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

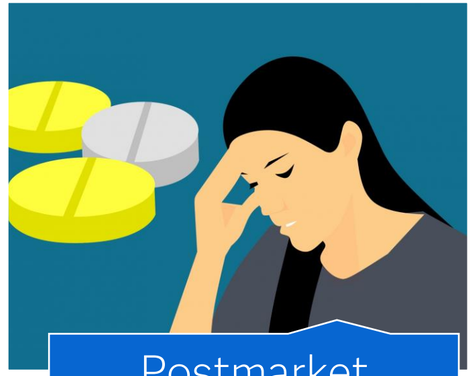
Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

Where does the FDA contemplate AI in Drug Development?

Drug Discovery

Nonclinical

Clinical



Postmarket Surveillance

Manufacturing

Rare Disease & Synthetic Control Arm references

Dose/Dosing Regiment Optimisation

AI/ML can be used to characterize and predict PK profiles after drug administration. It can also be used to study the relationship between drug exposure and response, taking into consideration confounding factors. These kinds of models can be used to optimize the dose/dosing regimen selection for a study (Liu et al., 2021; Lu, Deng, Zhang, Liu, & Guan, 2021). This could potentially include aiding in dose optimization in special populations where there may be limited data (e.g., rare disease studies, pediatric and pregnant populations).

c. Data Analysis

AI/ML has been used to analyze high volumes of diverse and complex RWD extracted from EHRs, medical claims, and disease registries, among other sources. Additionally, the use of AI/ML in predictive modeling and counterfactual simulation to inform clinical trial designs is being actively explored. For example, *in silico* clinical trials utilize computational modeling and simulation to evaluate drug candidates using a virtual cohort of simulated participants with realistic variability of traits representing the desired participant population (Pappalardo, Russo, Tshinanu, & Viceconti, 2019). AI/ML could be employed in these situations to aid in evaluating a vast number of counterfactual simulations and to predict trial outcomes before human trials.

At an even more personalized level, AI/ML can also be used in the context of digital twins of patients, an emerging method that could potentially be used in clinical research. To create digital twins of patients, AI/ML can be utilized to build *in silico* representations or replicas of an individual that can dynamically reflect molecular and physiological status over time (European Medicines Agency, 2022; Laubenbacher, Sluka, & Glazier, 2021; Schuler et al., 2021). In comparison to a participant in a clinical trial that received an investigational treatment, the digital twin could potentially provide a comprehensive, longitudinal, and computationally generated clinical record that describes what may have happened to that specific participant if they had received a placebo.

Digital Twins

(= Synthetic Control Arms on Steroids)

FDA on AI

List of Publications

Oct 2022 : Distributed Manufacturing and Point-of-Care Manufacturing of Drugs

May 2023 : AI/ML for Drug Development Discussion Paper

May 2023 : Artificial Intelligence in Drug Manufacturing

FDA on RWE

List of Publications

Aug 2017 : Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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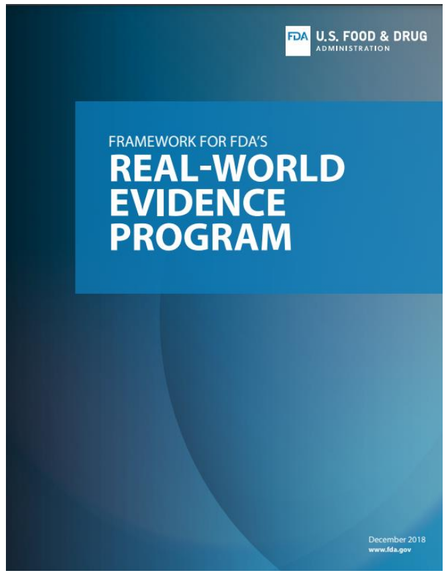
Real World Data (RWD) & Real World Evidence (RWE)

RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
RWE is the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from analysis of RWD.

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices



Framework for FDA's RWE Program

FDA on RWE

List of Publications

Aug 2017 : Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Synthetic Control Arms… remind me?

Real-World Evidence – Where Are We Now?
John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.
New Engl Journal Med 386;18 May 5, 2022

PERSPECTIVE

REAL-WORLD EVIDENCE — WHERE ARE WE NOW?

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

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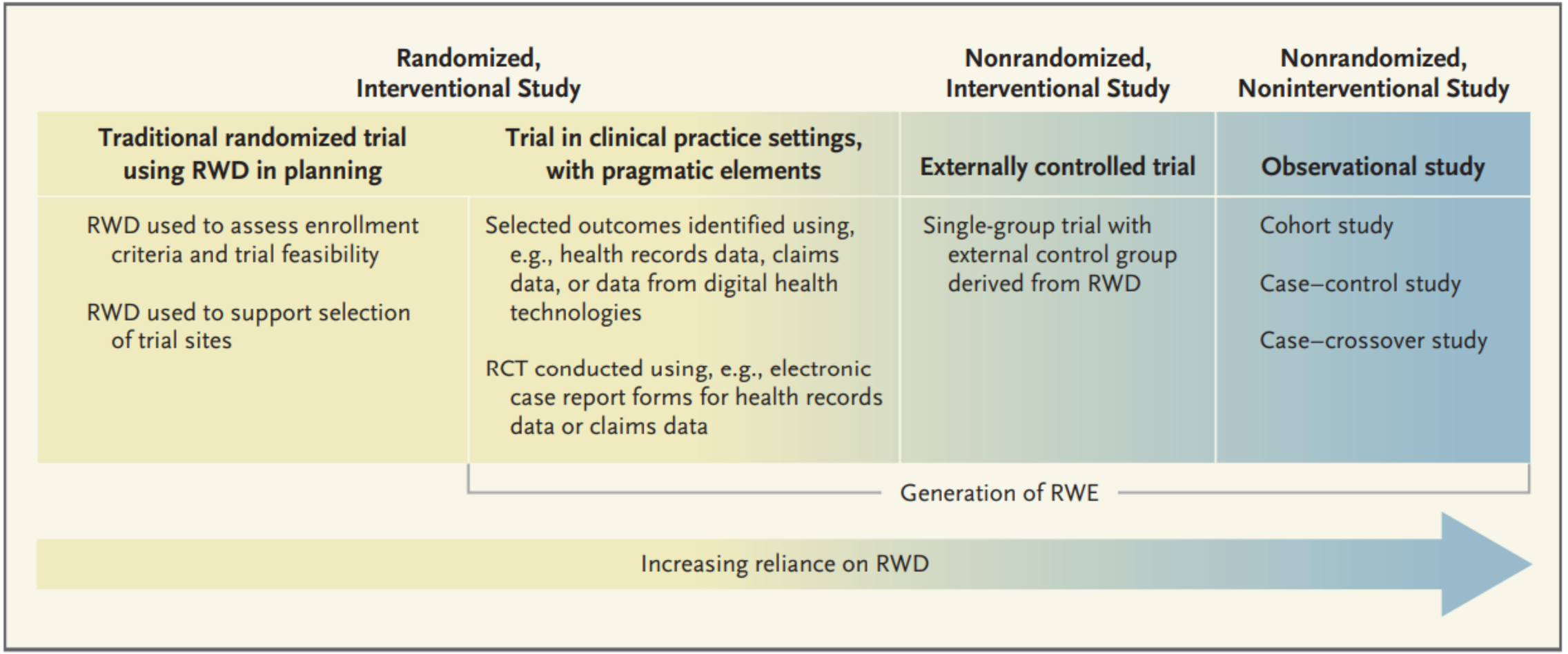

Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

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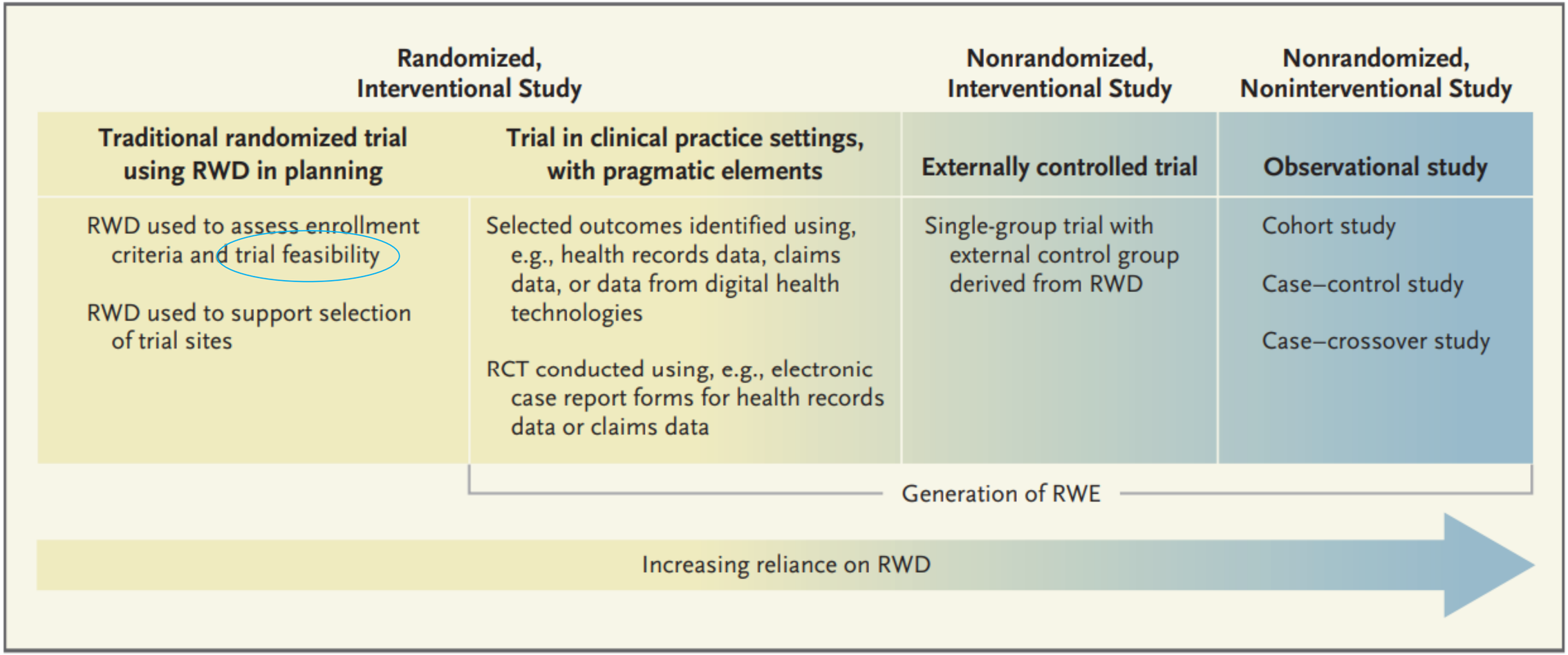

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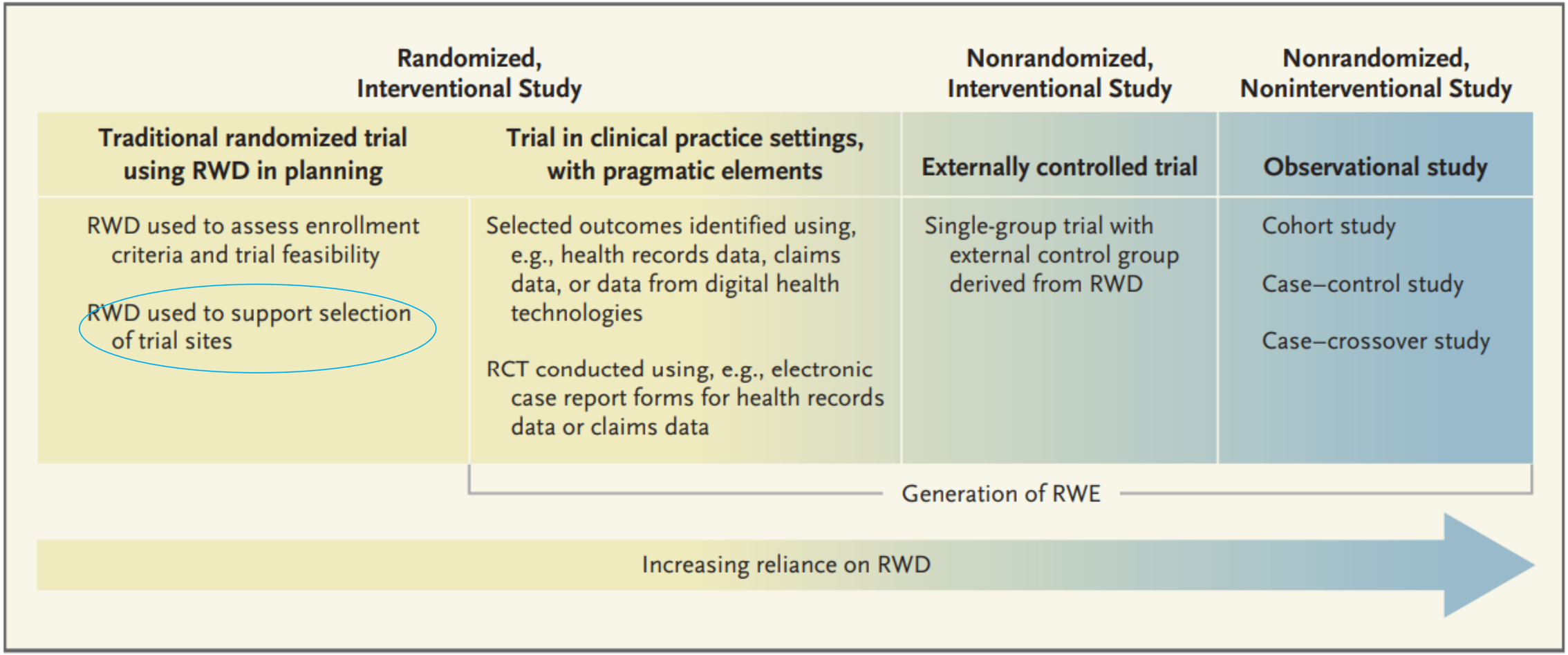

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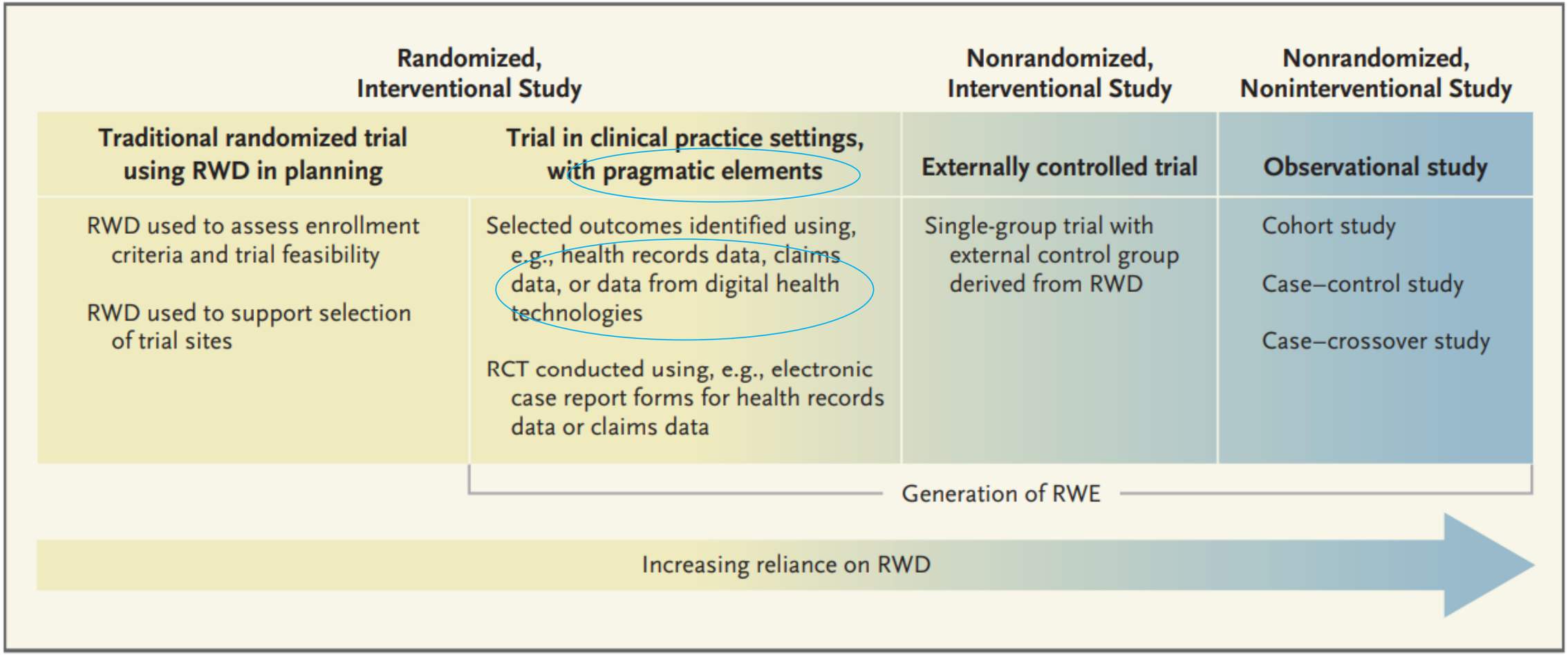

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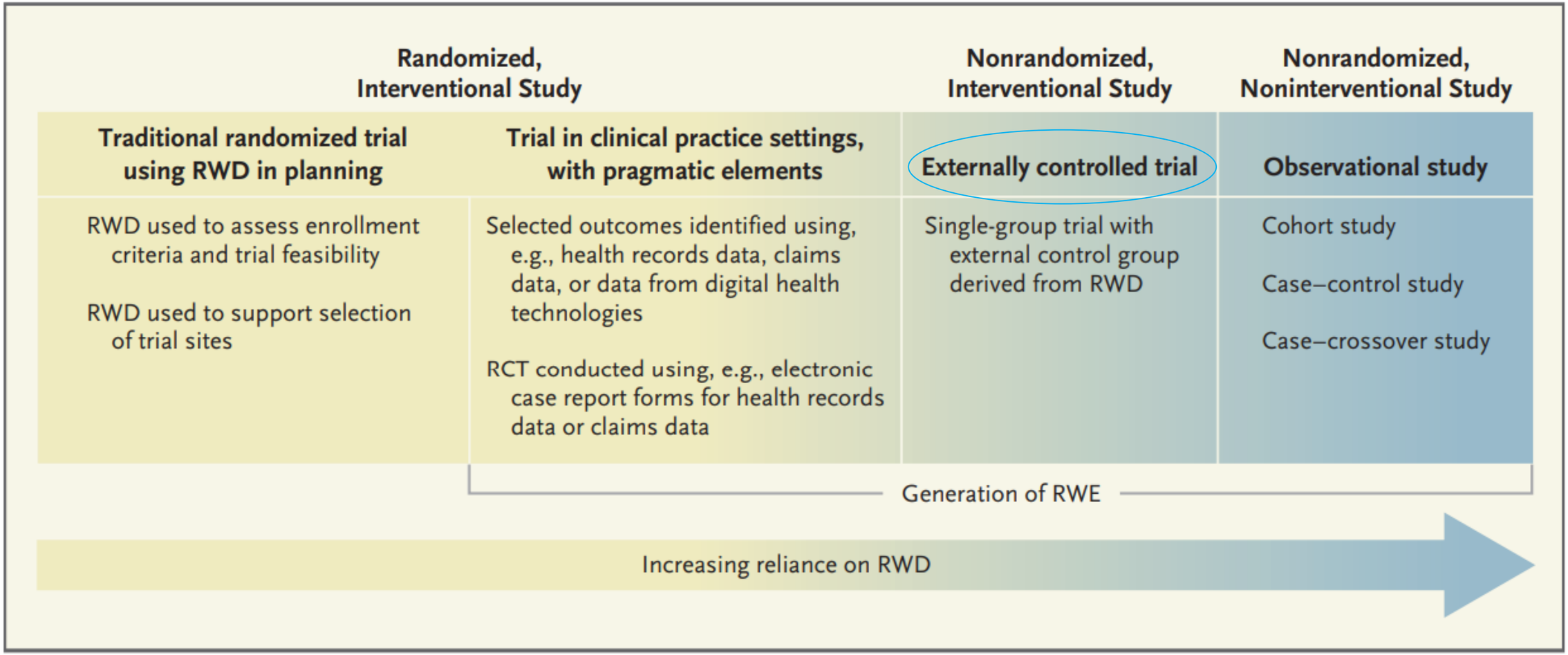

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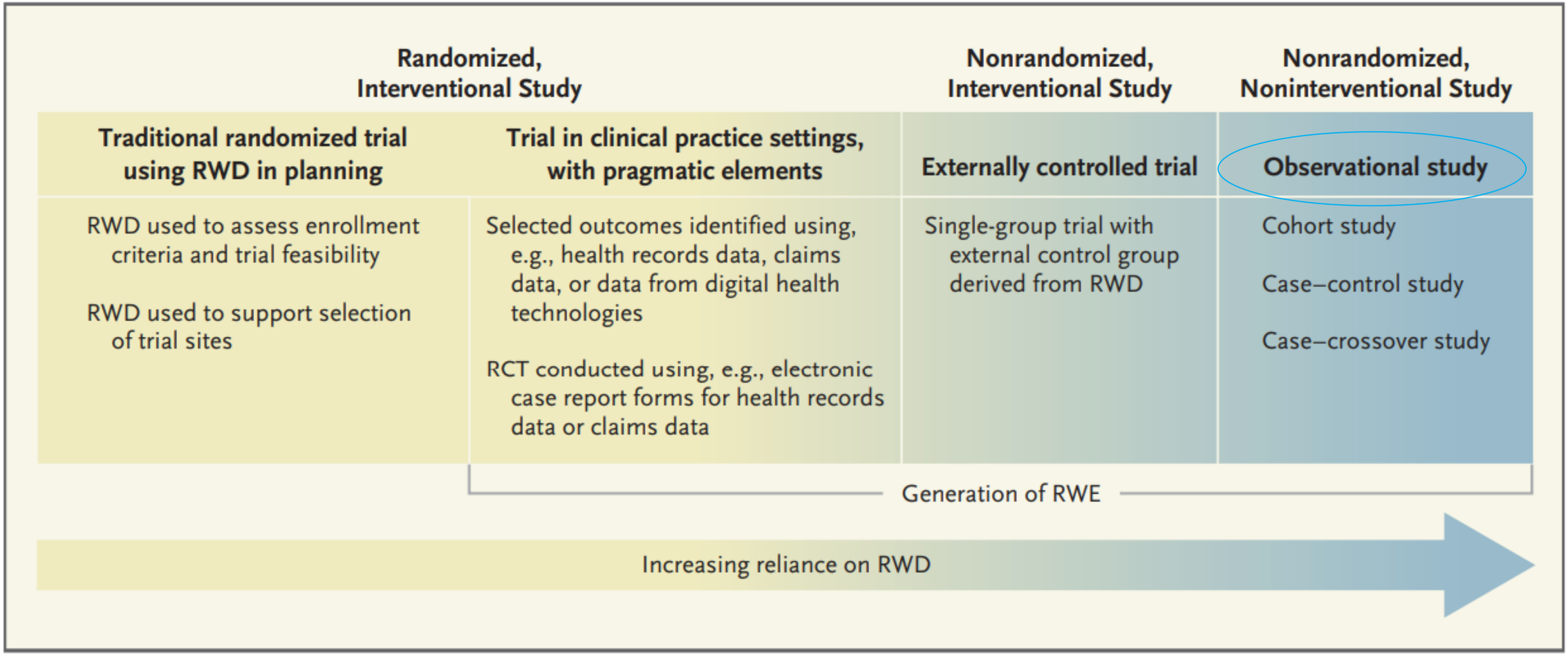

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FDA approves new use of transplant drug based on real-world evidence

Observational study - 2021

FDA approved a new use for Prograf (tacrolimus) ***based on a non-interventional (observational) study providing real-world evidence (RWE) of effectiveness****. FDA approved Prograf for use in combination with other immunosuppressant drugs to prevent organ rejection in adult and pediatric patients receiving lung transplantation*

Pfizer Uses EHR Data to Support Expanded Indication for Male Breast Cancer

Observational study - 2019

*"**The approval is based on RWD** from electronic health records and post-marketing reports of Ibrance™ in male patients sourced from three databases: IQVIA Insurance database, Flatiron Health Breast Cancer database and the Pfizer global safety database"*

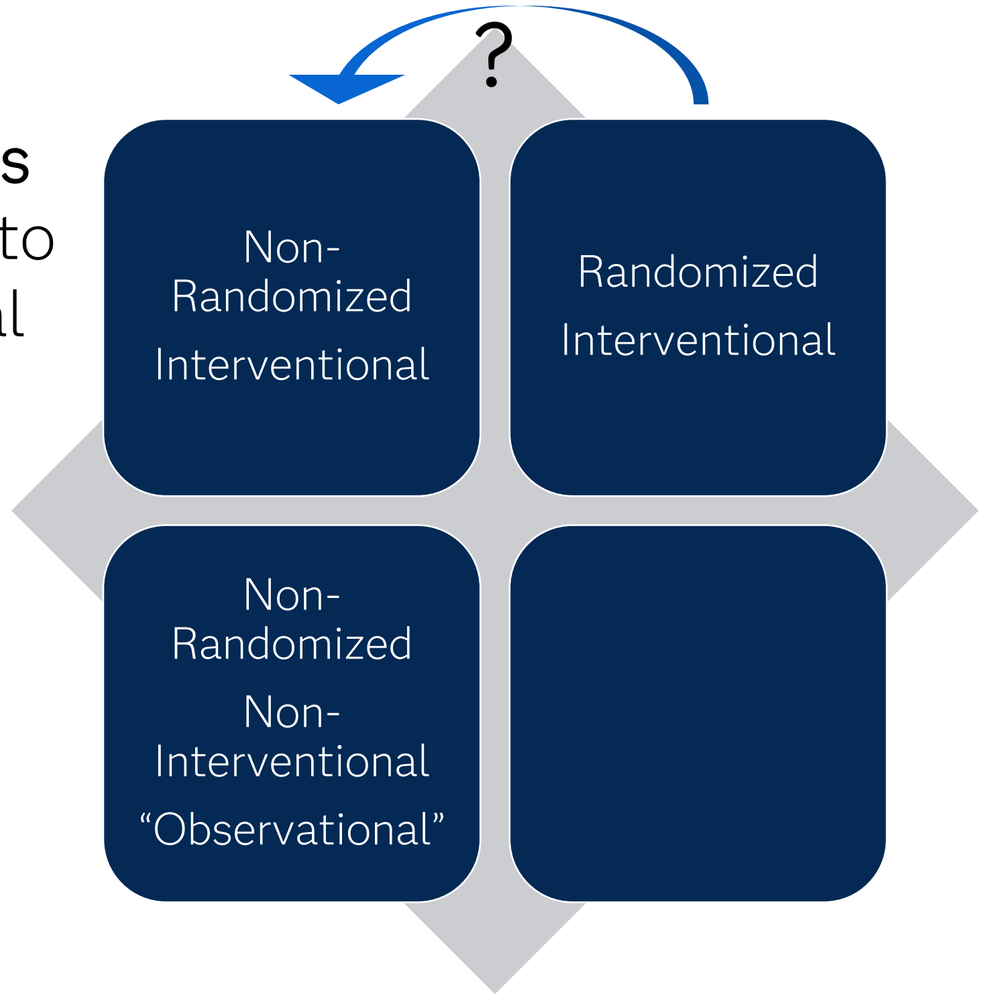
https://www.raps.org/news-and-articles/news-articles/2019/4/pfizer-uses-ehr-data-to-support-expanded-indicatio

In summary

Non-Randomized needs Synthetic Control Arms

Externally controlled trials
Outcomes are compared to a group of people external to the trial who had not received the same treatment.

Can be
- Historical
- Concurrent



Ask for a “Type C” meeting with the FDA

PRIOR TO RECRUTEMENT

- Goal
  - Assess appropriateness of a non-randomized study
  - Assess the proposed data sources
  - Assess design flaws
- We’re OK for rare diseases, right?
  - “Case-By-Case assessment”
  - Informed by issues including
    - Heterogeneity of the diseases
    - Preliminary evidence of the drug being investigated
    - The statistical approach
    - Whether superiority or non-inferiority

“In many situations, however, the **likelihood of credibly demonstrating the effectiveness** of a drug of interest with an external control **is low**, and sponsors should choose a more suitable approach **regardless of the prevalence of diseases.**” 😳

Recap

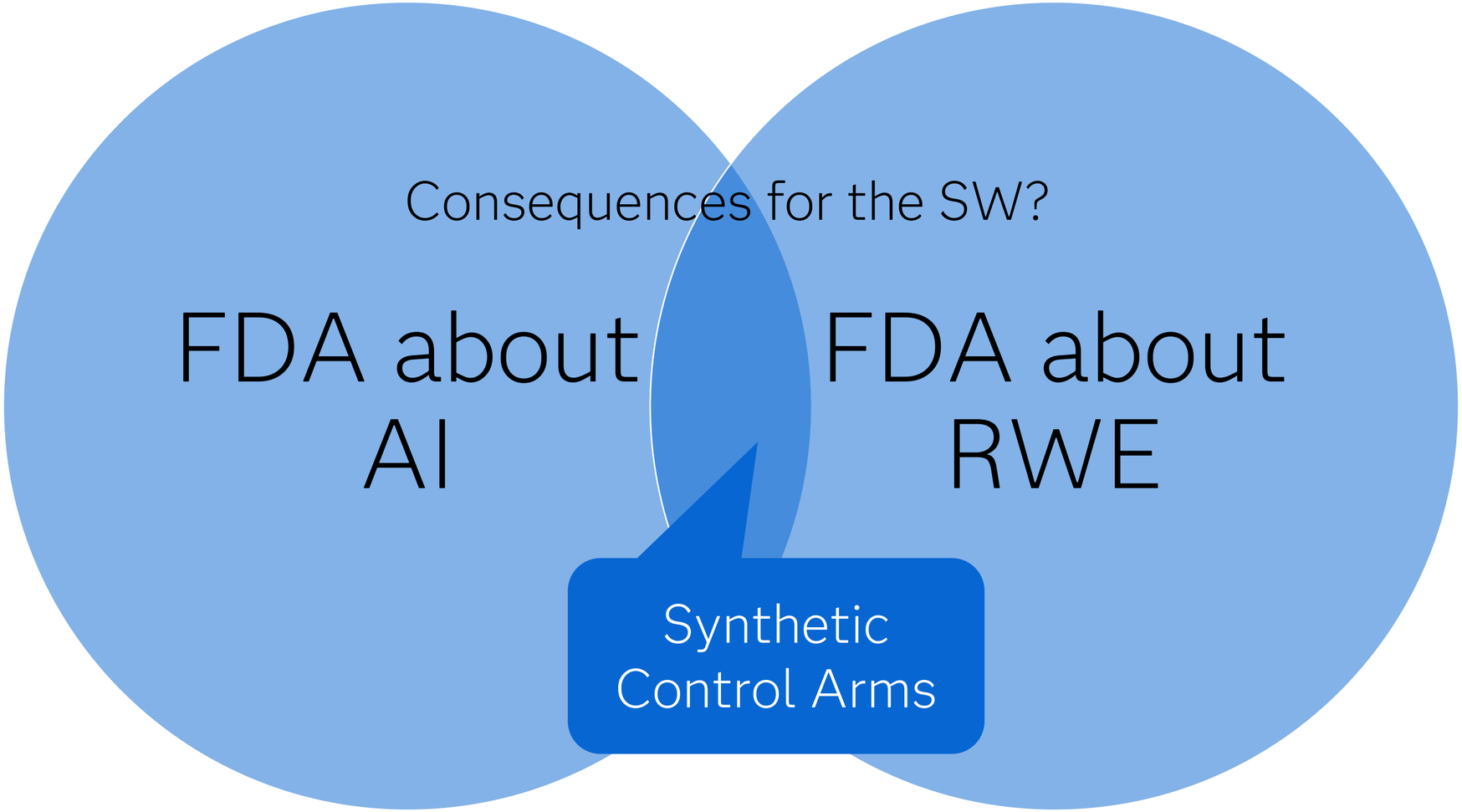


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Figure 1: Magic Quadrant for Data Quality Solutions

Source: Gartner (November 2022)

Table. Summary of Considerations for Assessing Comparability of Data[29]

Focus of Comparison	Considerations for Data Comparability
Time periods	Various aspects of clinical care may change over time, such as the standard of care for the condition of interest, types of treatments, supportive care regimens, and criteria for determining disease response or progression. Such temporal differences are difficult to address using statistical analyses alone. It is important to consider whether and how different time frames in the treatment arm and the external control arm impact the interpretability of study findings.
Geographic region	Standards of care and other factors (e.g., access to care) that affect health-related outcomes can vary across geographic regions and health care systems. A balance of participants or patients across geographic regions and health care systems in an externally controlled trial, when possible, can help reduce the impact of confounding based on such differences.
Diagnosis	The criteria used to establish a diagnosis may differ based on practice variation or may have changed in the interval between when the treatment arm of the trial was conducted and when the data for the external control arm were collected. Sponsors should consider the diagnostic standards used and whether relevant clinical tests to establish a diagnosis were conducted and reported equally across the compared arms.
Prognosis	Based on demographic and clinical characteristics—and if sufficient knowledge of relevant prognostic factors is available—prognostic indicators for the participants or patients in each arm of the trial should be evaluated and shown to be of sufficient similarity to permit an unbiased assessment of the treatment-outcome association.
Treatments	Attributes of the treatment of interest—including drug formulation, dose, route of administration, timing, frequency, and duration as well as specific rules for dose modifications, interruptions, discontinuations, and adherence—will have been prespecified or measured in the treatment arm. In contrast, specific aspects of a comparator treatment (as applicable) in the external control arm may not have been


CYBER

FDA on RWE

List of Publications

Non-Randomized Interventional

Non-Interventional "Observational"

Aug 2017 : Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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Design Considerations

SAP = Statistical Analysis Plan | Estimand Framework

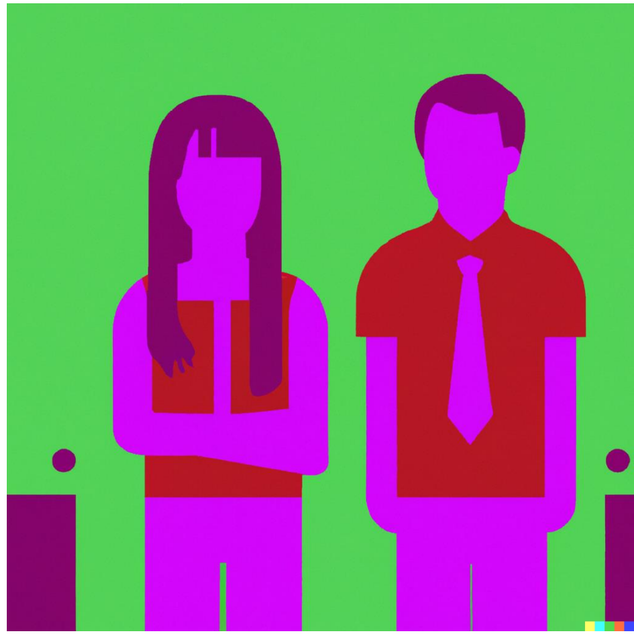
- Define Control Arm up front
- Prespecify
  - Data sources
  - Baseline eligibility (inclusion and exclusion) criteria
  - Appropriate exposure definitions and windows
  - Well-defined and clinically meaningful endpoints
  - Cogent analytic plans
  - Approaches to minimize missing data
  - Approaches to minimize sources of bias

The **estimand framework**—involving a precise description of the treatment effect reflecting the clinical question posed by the study objective—can be used to help design an externally controlled trial. An estimand is comprised conceptually of the **study population, treatment of interest and comparator, outcome of interest, handling of intercurrent events, and summary measures.**

- Characteristics of Study Populations – do you know the "confounding factors" such as age, sex, race, socioeconomic status, geographic region?
- Attributes of Treatment – is a positive effect really due to the treatment, or due to adherence, dose, timing of initiation, or duration of treatment
- Designation of Index Date (Time Zero) – avoiding "bias due to immortal time"
- Assessment of Outcomes – "usually not recorded with the same rigor during routine clinical care compared to approaches used in clinical trials"

Basically…



DALL·E History Collections

Edit the detailed description

a pop art interpretation of two different groups of people

Study Monitoring

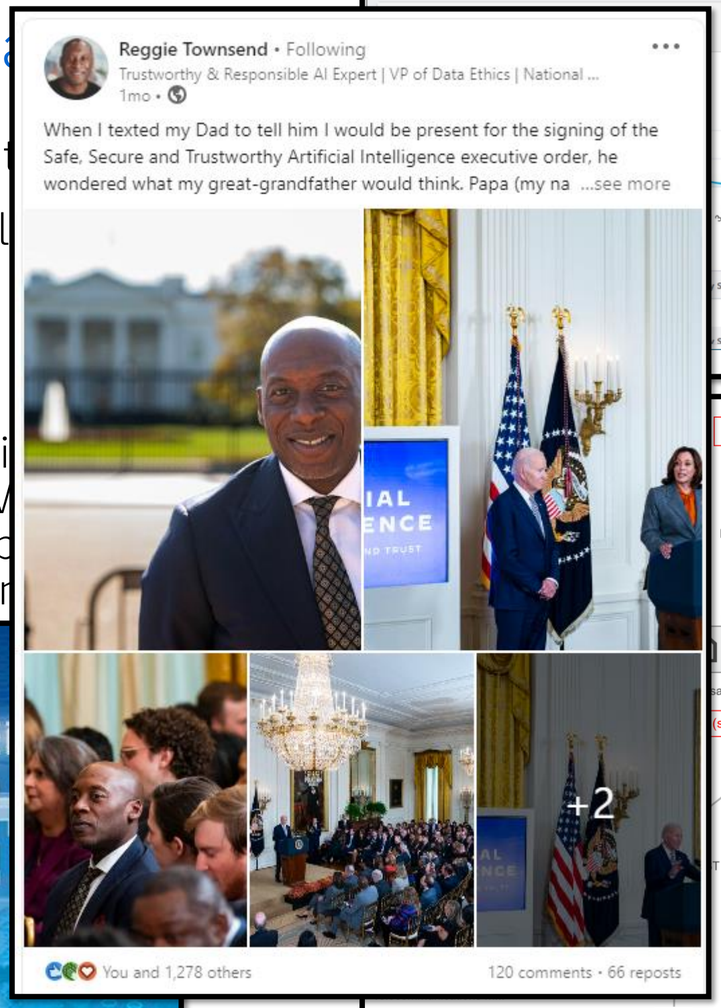
Traceability Traceability Tra

(1) the study is conducted according t

(2) data submitted to FDA are reliabl

(3) data are appropriately protected

"For non-interventional studies, moni
begin at the data extraction from RW
focus on the protection of human sub
applicable, and on maintaining data ir



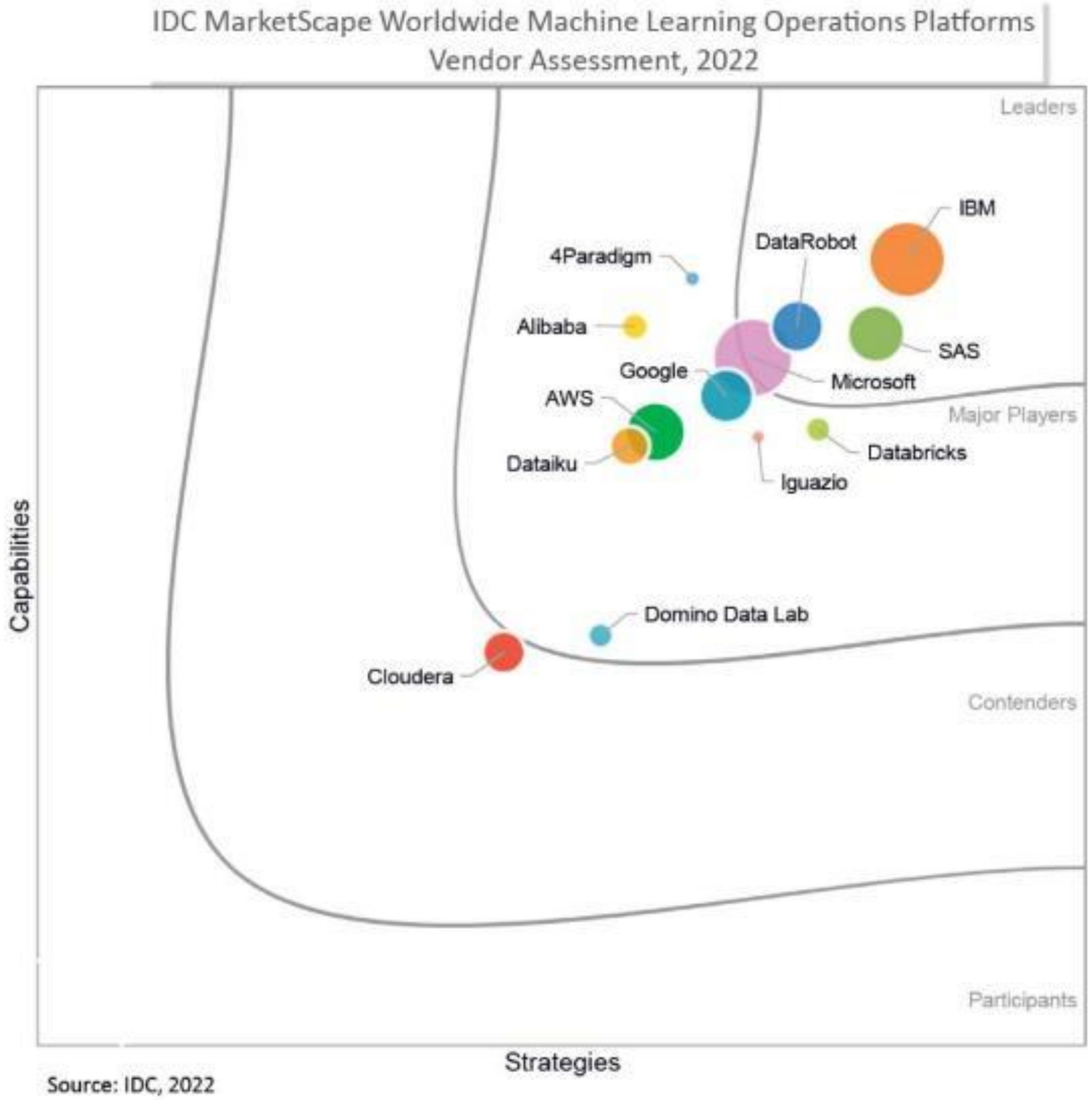
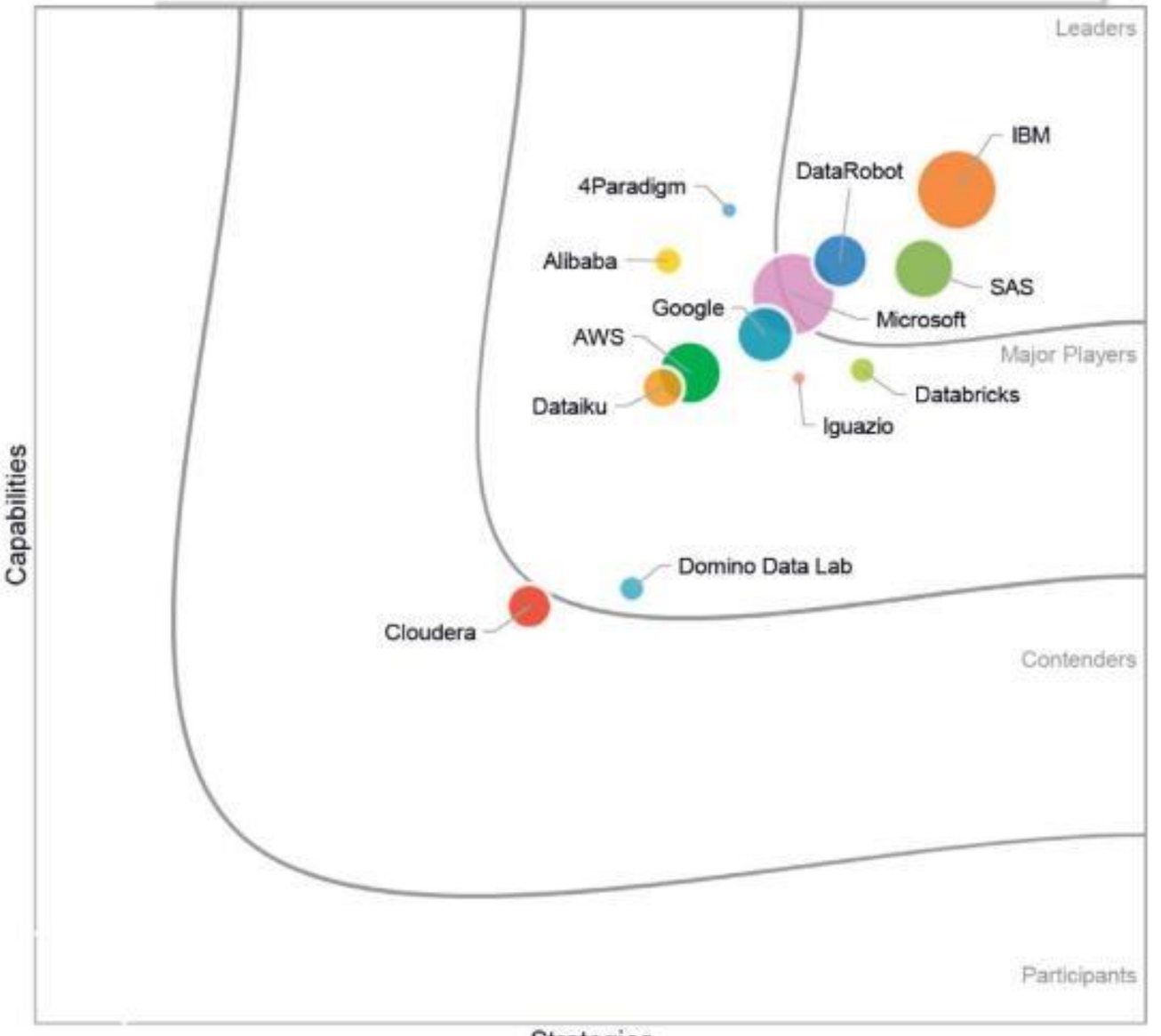


Figure 1: Magic Quadrant for Data Quality Solutions

IDC MarketScape Worldwide Machine Learning Operations Platforms Vendor Assessment, 2022



Source: IDC, 2022

Key Considerations for the Use of RWE in Submission

Data

Whether the RWD are fit for use

[Framework for FDA's RWE Program]

Methods

Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

Process

Whether the study conduct meets FDA regulatory requirements

Reliability

Relevance

Transparency & Reproducibility

p13

The framework will include consideration of the following:

1. Whether the RWD are fit for use

2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

OK I get it: in Rare Diseases, the FDA allows the use of Synthetic Control Arms. But how?

PHUSE SDE Americas Winter

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