U.S. FOOD & DRUG ADMINISTRATION

FDA Real-World Evidence
Embedded RCTs

Jacqueline Corrigan-Curay
April 23, 2020

Disclaimer

- **This talk reflects the views of the author and should not be construed to represent FDA's views or policies.**
- **The speaker has no relevant financial conflicts.**

Expectations in Law for Real-World Evidence: The 21st Century Cures Act

- **FDA shall establish a program *to evaluate the potential use* of real world evidence (RWE) to support:**
  - **Approval of new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Program will be based on a framework that will be issued by December 2018:**
  - **Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address**
- **Draft Guidance to be issued by 2021**
- **PDUFA commitments aligned with 21st Century Cures Act**

FDA Definitions

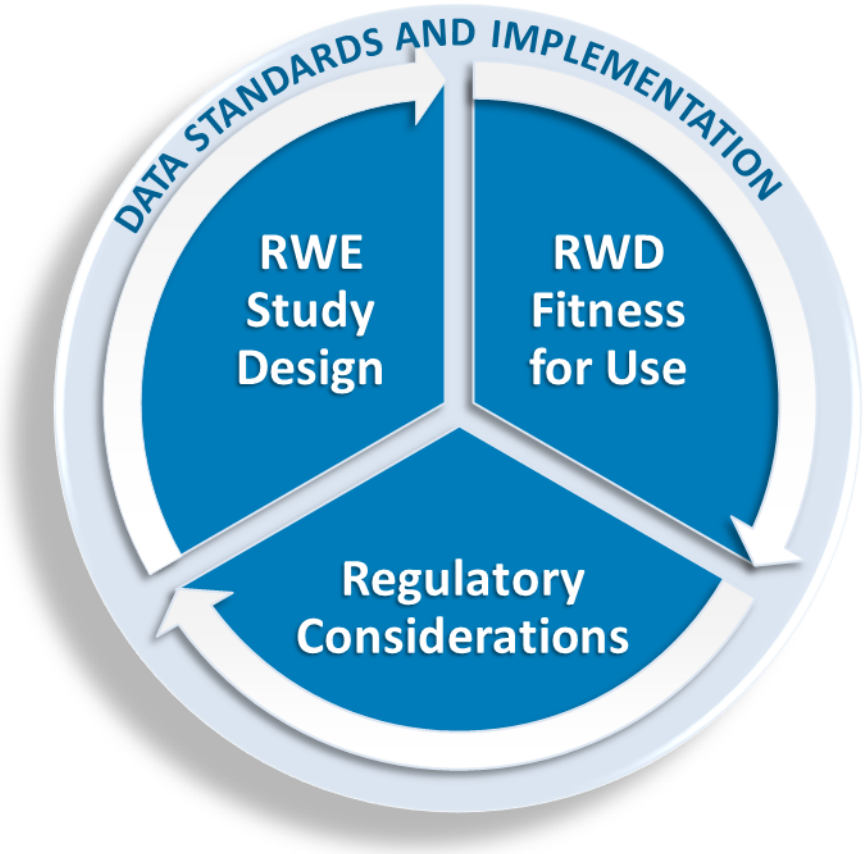
Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- electronic health records (EHRs)
- claims and billing data
- data from 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

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



Considerations

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

Substantial Evidence of Effectiveness

Substantial evidence means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

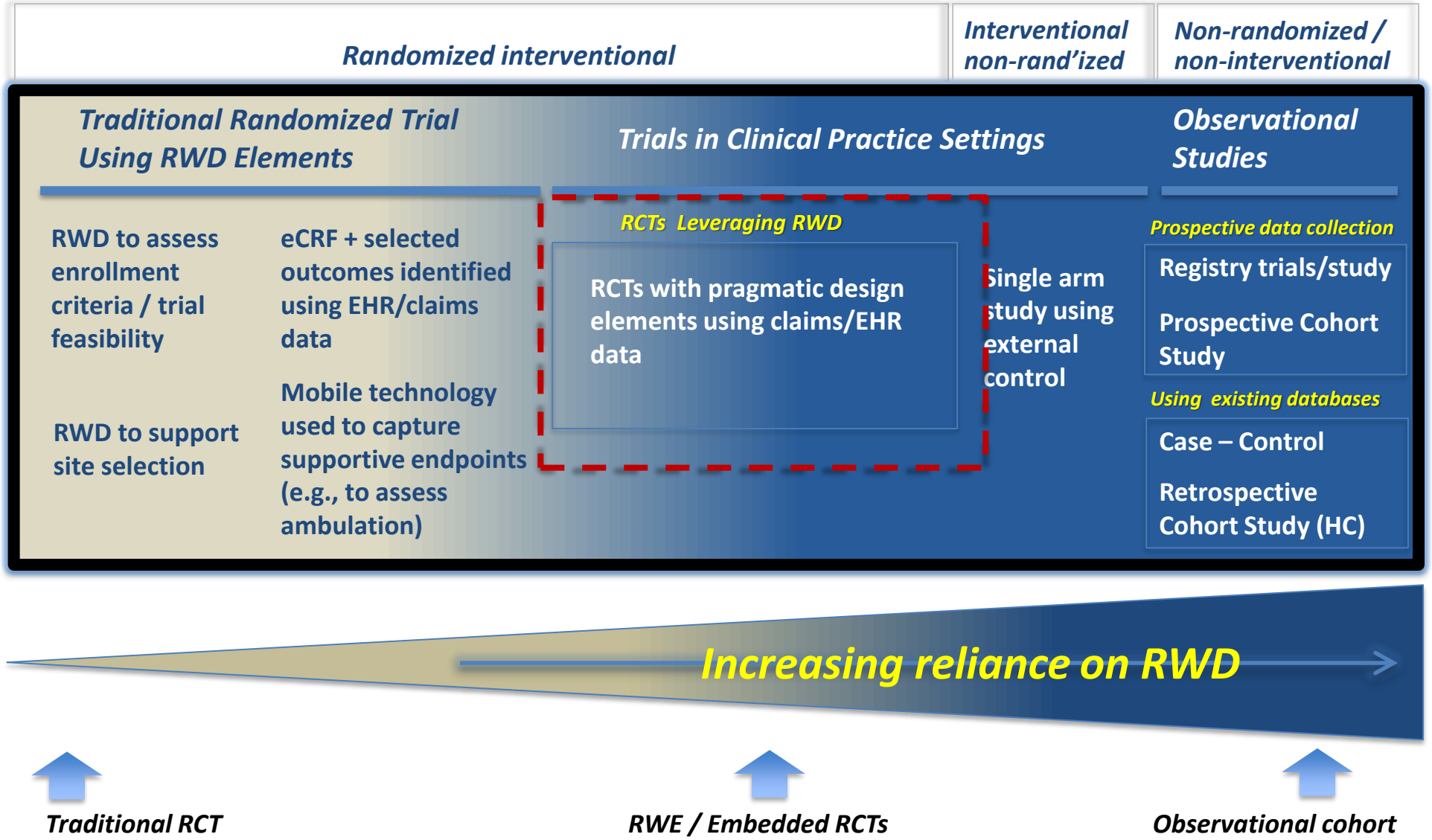
***Federal Food, Drug, and Cosmetic Act 1962 (*21 USC Sec. 355)**

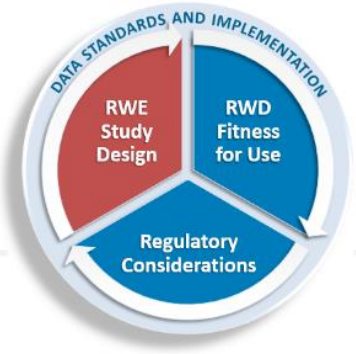
What is an "adequate and well-controlled investigation"?

Selected Key Characteristics*
There is a **clear statement of objectives** of the investigation and **methods of analysis**
The study uses a **design** that permits **a valid comparison** with a **control to provide a quantitative assessment of drug effect**: placebo-control, dose-comparison control, no treatment control, active-treatment control, historical control
Adequate measures are taken to **minimize bias** on the part of the subjects, observers, and analysts of the data
The **methods of assessment** of subjects' response are **well defined and reliable**
The **method of selection** of subjects provides adequate assurance that they have the disease/condition being studied
The **method of assigning patients** to treatment and control groups **minimizes bias** and is intended to **assure comparability of the groups** with respect to pertinent variables. Ordinarily…assignment is by randomization…
There is an **analysis of the results of the study adequate to assess the effects of the drug**

*From 21 CFR 314.126

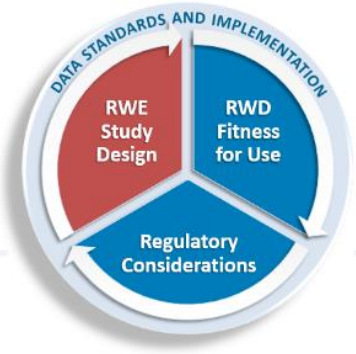
Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies





Use of RWD in RCTs

Factors when considering embedding a randomized trial in clinical settings in order to access RWD:



Use of RWD in RCTs

Factors when considering embedding a randomized trial in clinical settings in order to access RWD:

- **What types of interventions and therapeutic areas might be well-suited to routine clinical care settings?**
- **How will RWD be captured in these settings?**
  - **Impact on lags in data capture**
- **Blinding/Masking?**
- **Bridging between regulatory endpoints and clinical practice**
- **Site inspections and monitoring**

Adopting “Pragmatism” into Regulatory RCTs

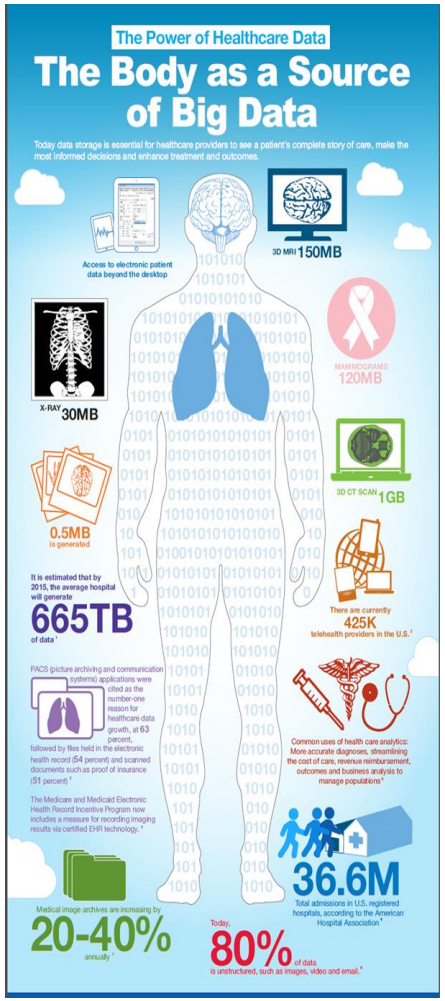
- The issue is **reliability – persuasiveness** – of the results, not trial methodology
- **Randomization** supports strong causal inference
- **Blinding** supports strong causal inference vs unblinded
- **Appropriate enrollment criteria** assures patients have the target condition (that the study objective is aimed to address)
- A **well-constructed endpoint** means that the study can determine if the purported effect of the drug is observed, and that effect is meaningful to patients
- **Reliable data**, that accurately collects the patient experience, and is accurately transferred into the analysis datasets supports **reliable conclusions**
- **Adequate monitoring** means complete collection of **important, relevant** efficacy and safety endpoints

RWD and Clinical Endpoint

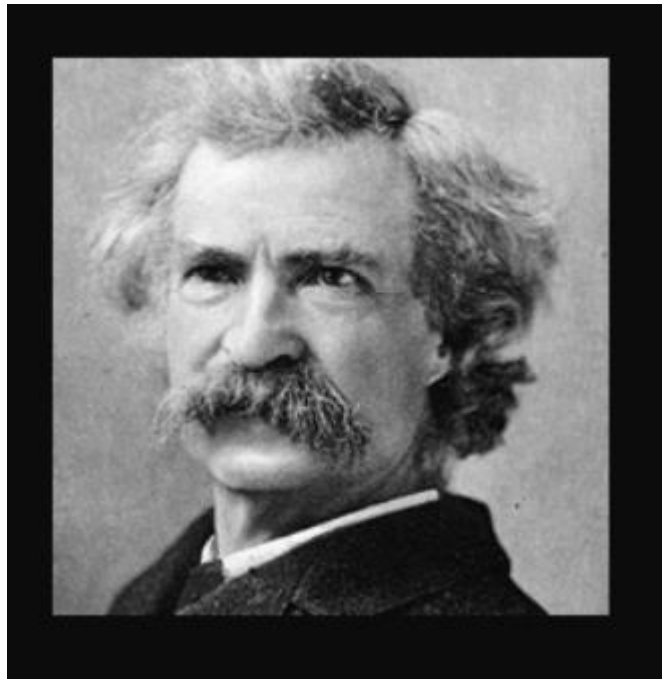
Biomarker

Clinical endpoint

Type of endpoint	Studies %	Examples of endpoints measured
Chemistry	21%	HBA1c, pregnancy test, GFR
Hematology	4%	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	1%	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	9%	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	10%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	10%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	13%	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	31%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score



Real World Data

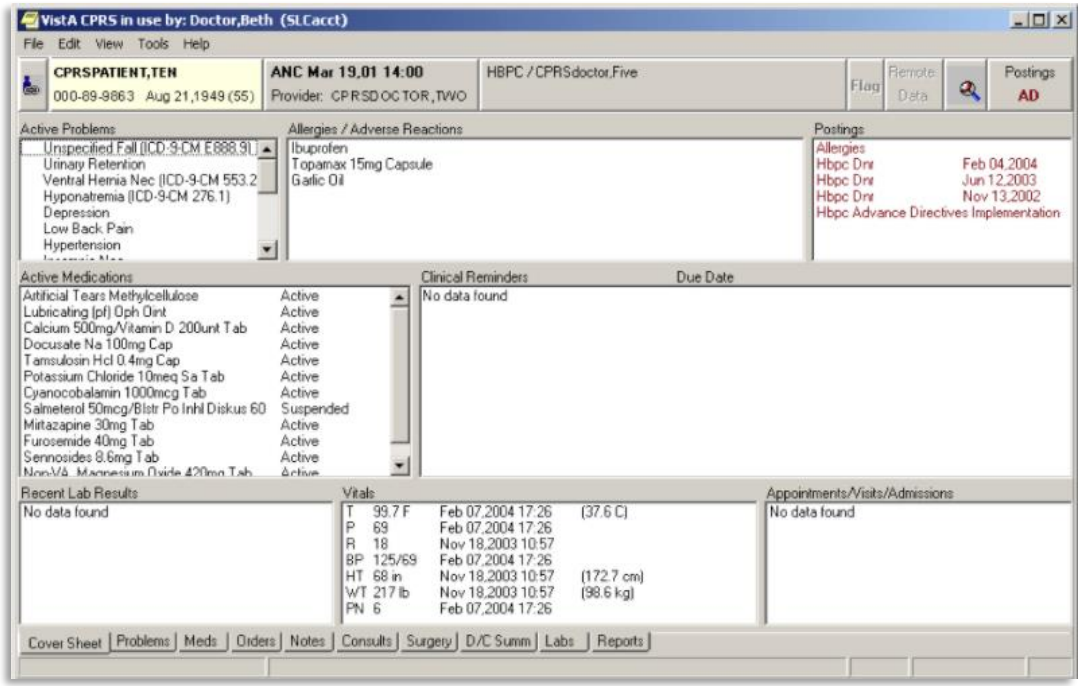


In the real world, nothing happens at the right place at the right time . . .

~ Mark Twain

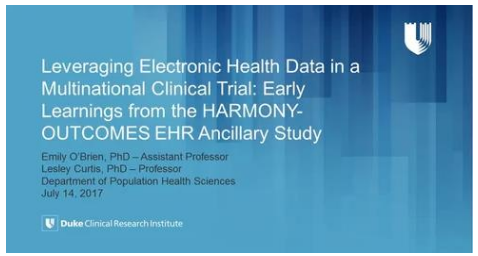
EHRs – Quality and Relevance

- Certain endpoints – labs, pathology, imaging are used in clinical practice and research
  - Challenge is curation of unstructured and inconsistent data format
- Timing of assessment in clinical practice may be variable
- Clinical outcome measures for disease progression may not be used or consistently recorded in practice
  - Are there ways to bridge that gap
- Interoperability will be necessary for studies outside of small populations
  - Including linkage to claims for longitudinal data

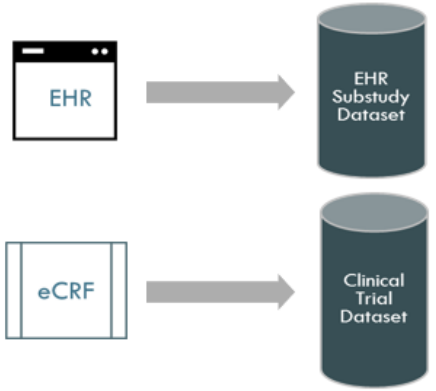


Demonstration Projects - Data

Comparing data collected from EHR to a Pragmatic Trial to assess fit-for-use

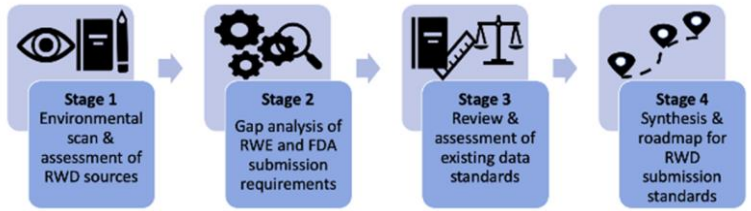


Developing a Reusable Framework for transforming raw data in fit-for-purpose data

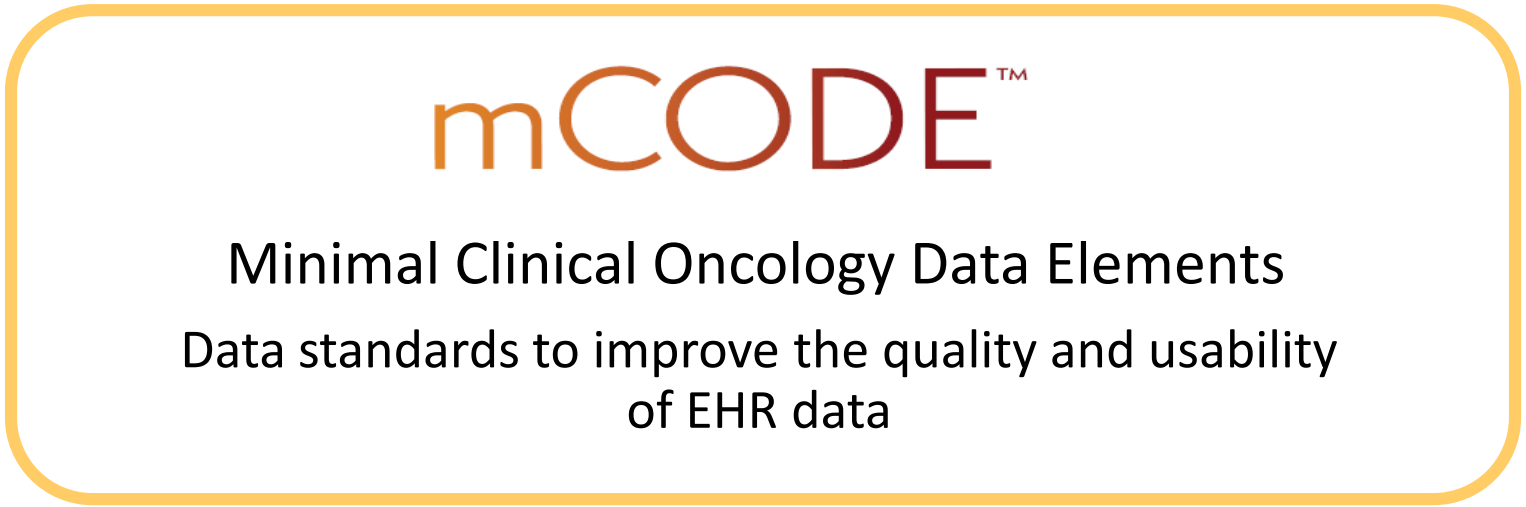


Creating a "One Source" EHR for Research and Clinical Care

Feasibility of transforming structured-based EHR data to FDA submission standards



Common EHR Data Structure



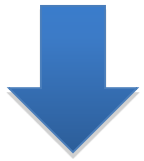
Courtesy of ASCO/MITRE

Common EHR Data Structure

mCODE™

Minimal Clinical Oncology Data Elements

Data standards to improve the quality and usability of EHR data

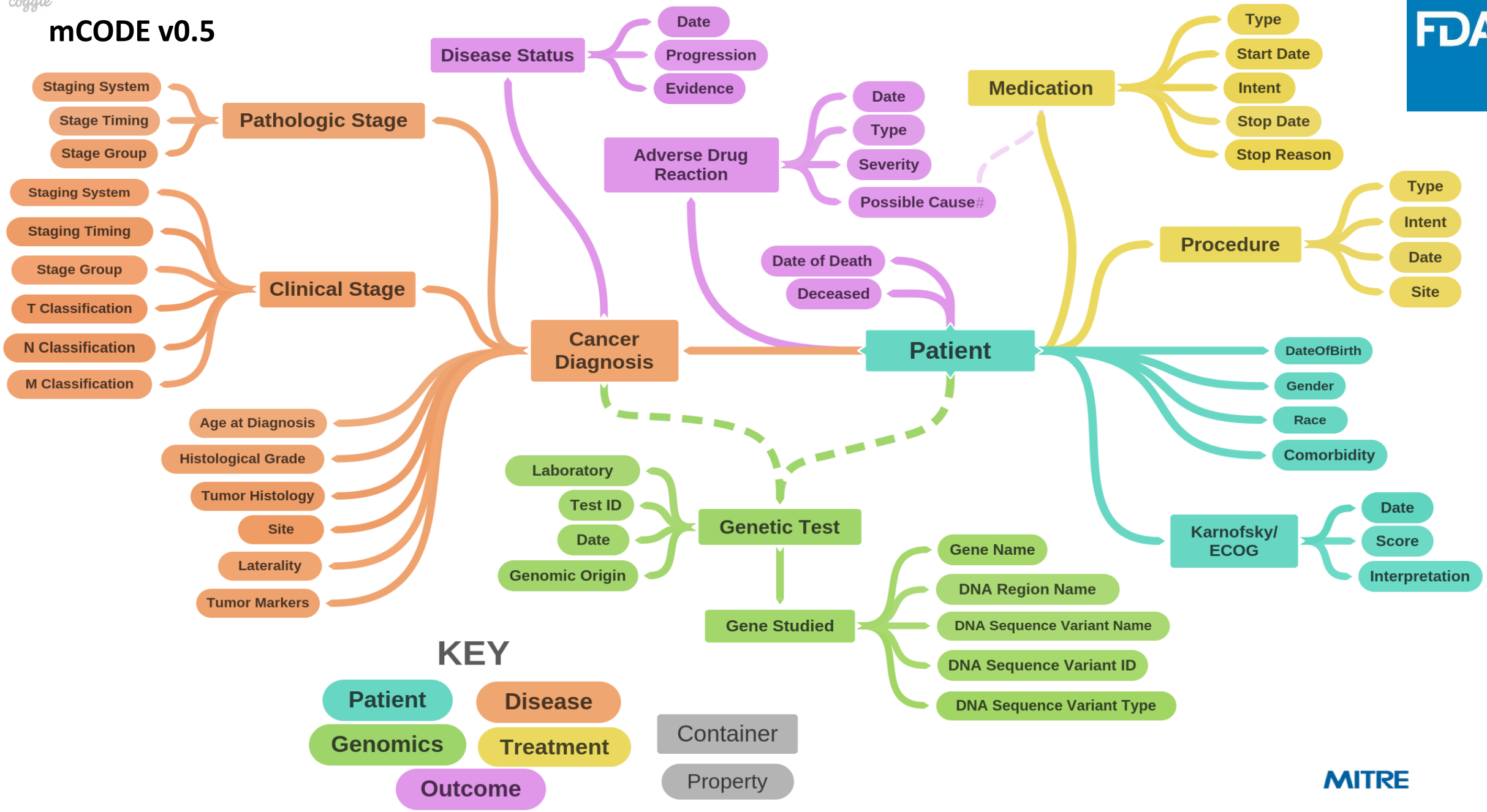


Collection of clinical trials data using the EHR

Courtesy of ASCO/MITRE

coggle

mCODE v0.5



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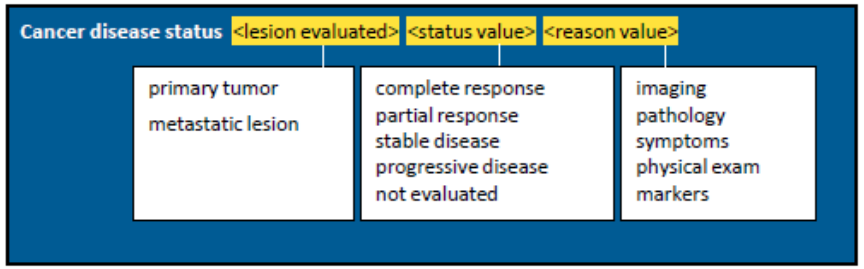
ICARE: Develop and validate mCODE-based outcome measures embedded in the EHR

Disease Status

Clinical Assessment

Based on the data available today (at the time of evaluation), categorize the patient's disease extent.

Question Format

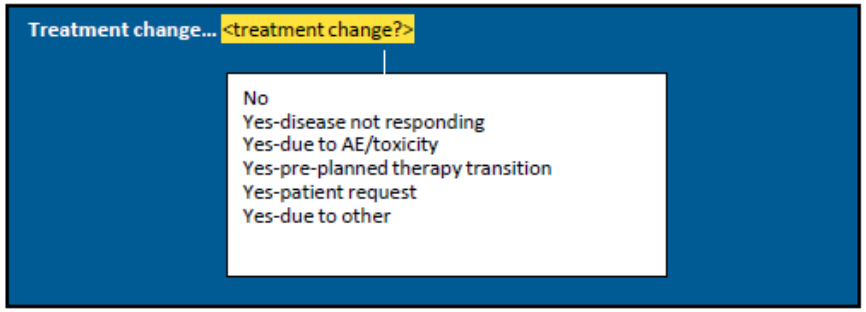


Treatment change

Clinical Assessment

Based on your evaluation today, are you making a change in treatment?

Question Format



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

MITRE

FDA

NCI National Clinical Trials Network
a National Cancer Institute program

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Patient-Generated Health Data (Digital Health Tools)

FDA MyStudies

- **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
- **Web-based Configuration Portal (WCP)**
  - Enables support of multiple types of medical product effectiveness and safety studies with minimal software development
- **Secure Storage Environment**
  - Generates secure tokens
  - Separates registration information and responses
  - Partitioned for multisite, decentralized, or distributed models

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625228.htm
https://www.fda.gov/Drugs/ScienceResearch/ucm624785.htm
https://github.com/PopMedNet-Team/FDA-My-Studies-Mobile-Application-System

FDA MyStudies

- Google Cloud and FDA MyStudies: Harnessing real-world data for medical research

Jameson Rogers, Ph.D.
Product Manager, Google Cloud Healthcare & Life Sciences

January 7, 2020

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Get $300 free credit to spend over 12 months.

FREE TRIAL

Google Cloud is committed to helping customers conduct life-saving research that results in new medications, devices and therapeutics by unlocking the knowledge hidden in real-world data. That's why we're supporting the goals of the U.S. Food & Drug Administration, by making the FDA's open-source MyStudies platform available on Google Cloud Platform. By building on the platform developed by the FDA, we hope to stimulate an open ecosystem that will improve the ability of organizations to perform research that leads to better patient outcomes. This collaboration continues our long history of open-source work, and our commitment to producing easy-to-use tools that serve the healthcare and life sciences community.

Because of the FDA's focus on real-world evidence, drug and device organizations are increasingly looking to incorporate patient-generated data into regulatory submissions for new products and treatment indications. But until recently, there haven't been mobile technologies or methodologies to help collect, store and submit this kind of data in a regulatory compliant manner. In order to address this gap, the FDA developed MyStudies,

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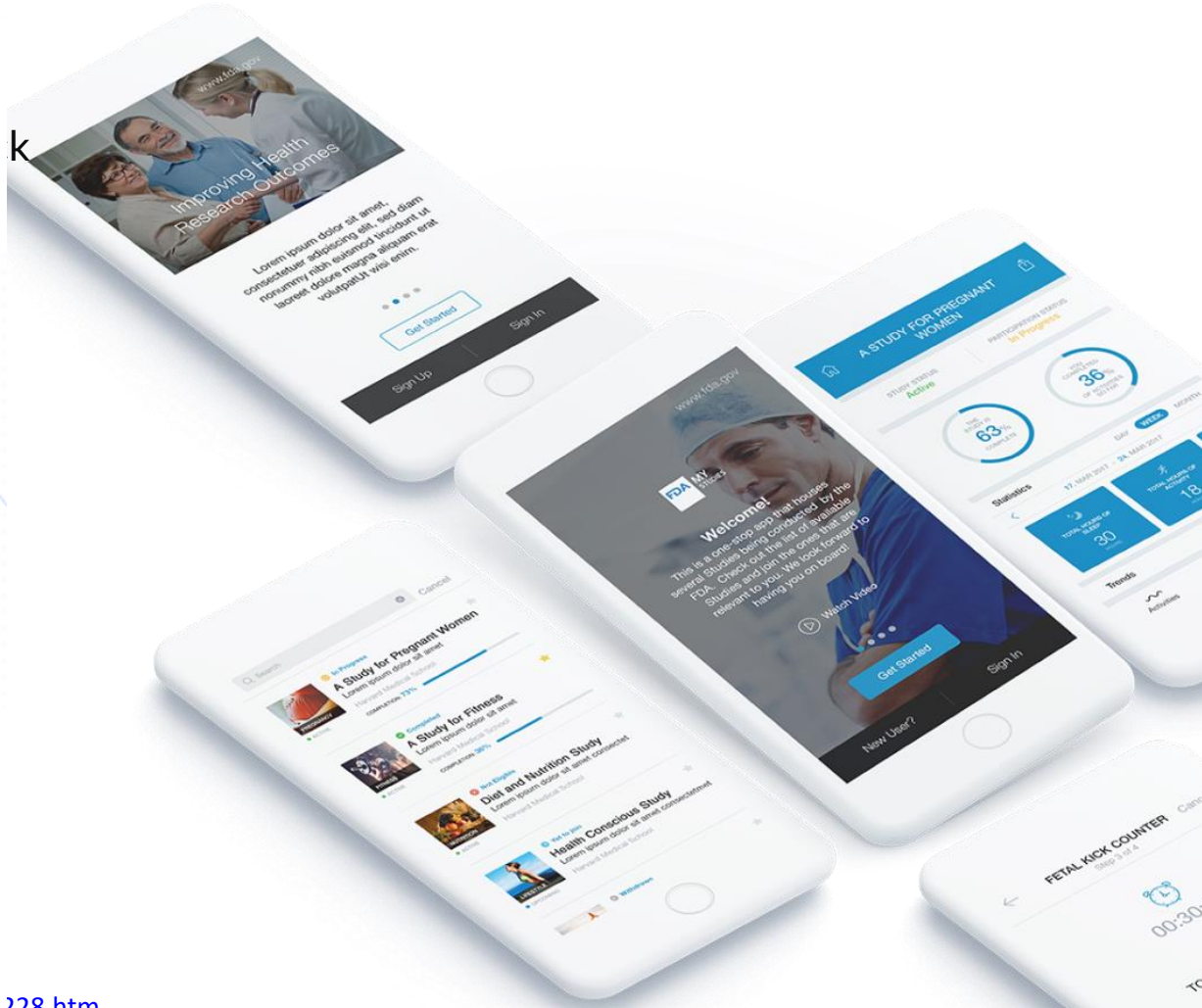

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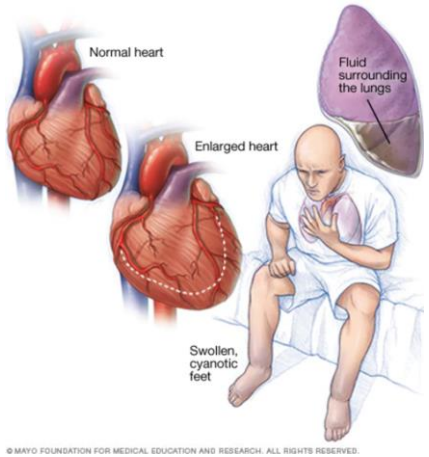
plication-System

Demonstration Projects – RWE Tools

Developing tool to improve data collection from mobile technology-wearables and accelerometers



Evaluating the performance of wearables and health platforms for real-world surveillance surrogate endpoints

FDA MyStudies in a Juvenile Idiopathic arthritis trial to capture an endpoint

CARRA
Childhood Arthritis and Rheumatology Research Alliance

LimitJIA

pcori

FDA MyStudies to support the Crohns and Colitis Registry

CROHN'S & COLITIS FOUNDATION

IBD PLEXUS

Adopting “Pragmatism” into Regulatory RCTs

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- **Randomization** supports strong causal inference
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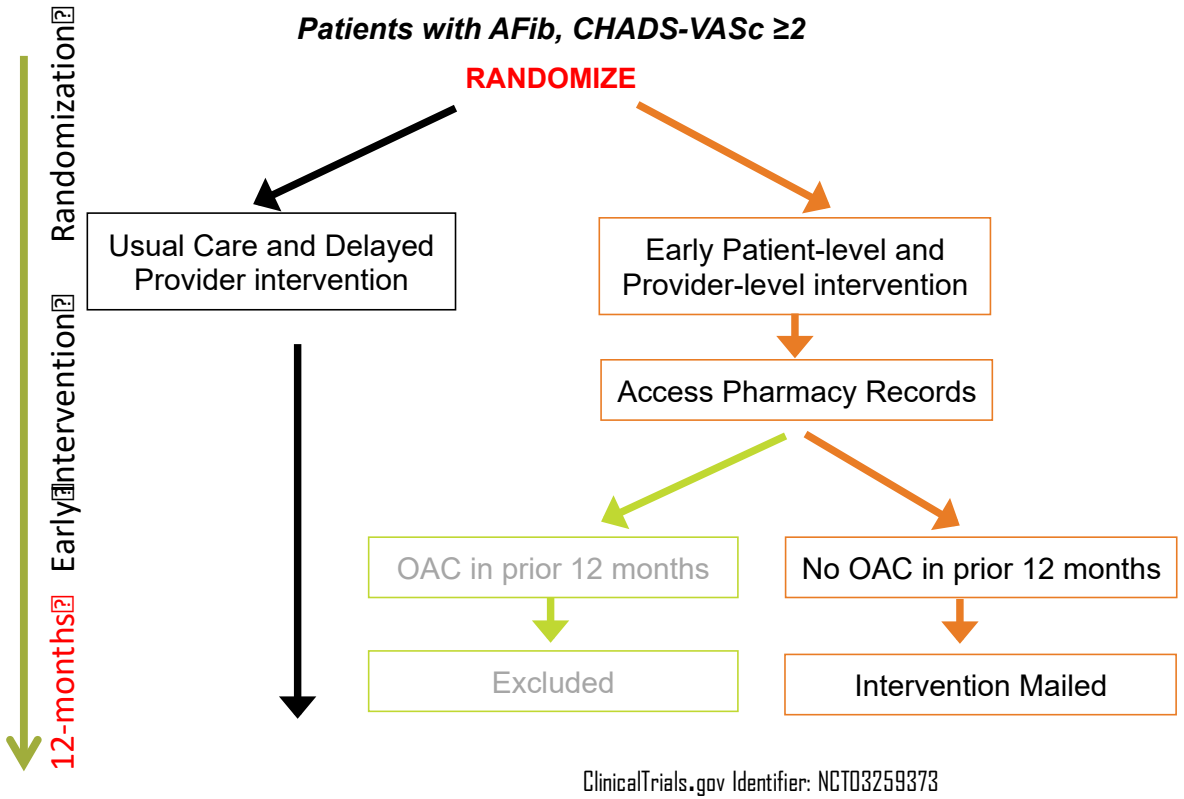
FDA-Catalyst Demonstration Project: IMPACT Afib Trial

IMplementation of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation



Test the ability of an education intervention to increase the appropriate use of oral anticoagulants in a patient population with atrial fibrillation (afib) at high risk of stroke

Enrollment of approximately 80,000 individuals in the early and late intervention arms

- Atrial fibrillation /CHADS –VASc ≥2
- No oral anticoagulant
- No contraindications

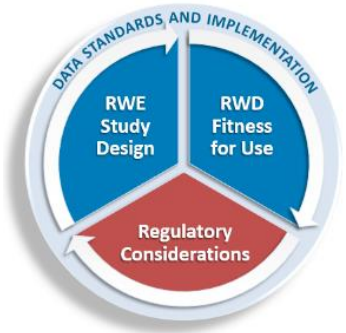
Endpoint – initiation of oral anticoagulation

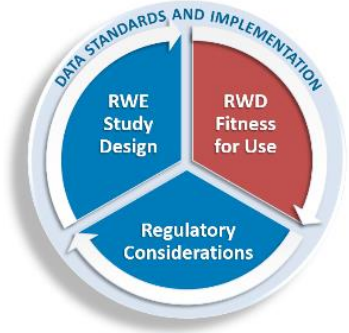
- Stroke, hospitalization, bleeding

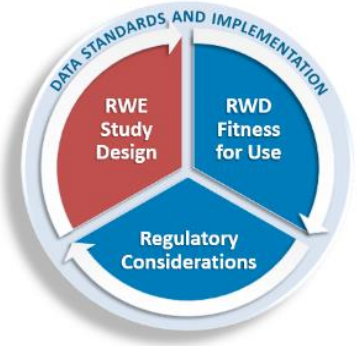
https://www.sentinelinitiative.org/FDA-catalyst/projects/implementation-randomized-controlled-trial-improve-treatment-oral-anticoagulants-patients

RELIANCE Trial

ClinicalTrials.gov Identifier: NCT04069312







- **RofLumilast or Azithromycin to prevent COPD Exacerbations**
  - Randomized “real world” trial; 1,600 adults in each arm
  - Azithromycin - macrolide with anti-inflammatory properties
  - Roflumilast - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
  - Both guideline recommended but Roflumilast is FDA approved for this indication
- **Population**
  - Clinician considering treatment intent to intensify therapy with roflumilast or azithromycin
  - > 40 years with severe COPD or associated chronic bronchitis
  - Current or past smoker – 10 pack/ years
  - Hospitalized with COPD exacerbation in past 12 months
  - Current medications include long acting – muscarinic antagonist, beta agonist or inhaled corticosteroid
  - No contraindications to the medications
- **Primary outcomes**
  - All cause hospitalization
  - All cause mortality
- **Follow-up**
  - 6-36 months, no visits, call center, Patient Portal, Site EMR
  - CMS linkage through FDA-Catalyst for outcomes and exposures

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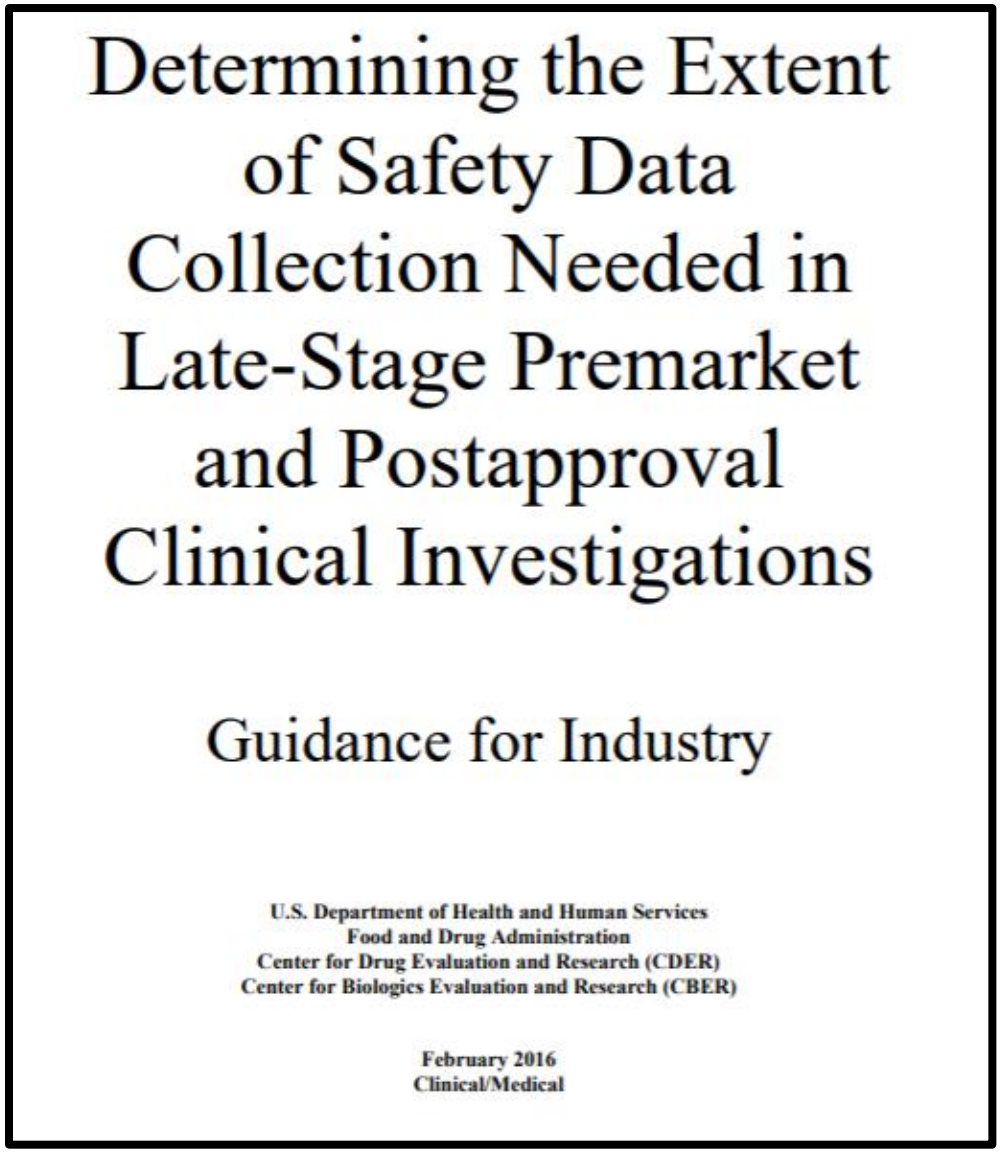
Safety Monitoring in Post Approval Investigations



- **It may be appropriate to use a selective approach to safety data collection for common, non-serious adverse events that have already been well-characterized through data collection in earlier stages**

- **Excessive safety data collection may**

  (1) discourage the conduct of these types of trials by increasing the resources needed to perform them and

  (2) be a disincentive to investigator and patient participation in clinical trials.

- **Selective safety data collection may**

  (1) facilitate the conduct of larger trials without compromising the integrity and the validity of trial results or losing important information

  (2) facilitate investigators' and patients' participation in clinical trials, and

  (3) help contain costs by making more-efficient use of clinical trial resources.

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High-Dose Influenza Vaccine to Reduce Clinical Outcomes in High Risk Cardiovascular Patients INVESTED NCT02787044

Orly Vardeny et al. Am Heart J. 2018 August ; 202: 97–103

High-Dose Influenza Vaccine to Reduce Clinical Outcomes in High Risk Cardiovascular Patients INVESTED NCT02787044

- **Pragmatic clinical trial of 9300 patients over 4 influenza season to compare the effectiveness of an annual vaccination strategy of high-dose trivalent versus standard-dose quadrivalent influenza vaccine in patients with a history of recent heart failure or myocardial infarction hospitalization**

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- **Endpoint time to first occurrence of death or cardiopulmonary hospitalization**
- **Surveillance for hospitalization or death will include one telephone call completed by site personnel during influenza season and another phone call during the summer following influenza season.**
  - **Participants will also be asked to inform local site personnel of hospitalizations at any time they occur.**

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- **Surveillance for hospitalization or death will include one telephone call completed by site personnel during influenza season and another phone call during the summer following influenza season.**
  - **Participants will also be asked to inform local site personnel of hospitalizations at any time they occur.**
- **Masking: to minimize cross-over related to perceived benefit of one vaccine formulation over another, participants, site investigators, study personnel, persons performing follow-up surveillance, and study statisticians will remain masked to the identity of the treatment from the time of randomization until database lock**

Orly Vardeny et al. Am Heart J. 2018 August ; 202: 97–103

Prospective, Randomized, Active-controlled, Open-label, Flexible Dose Study of Paliperidone Palmitate Compared With Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults With Schizophrenia Who Have Been Incarcerated (PRIDE) NCT01157351

- **The PRIDE study design had both explanatory and pragmatic features**
  - **Explanatory analysis to demonstrate that treatment with Paliperidone palmitate (PP) significantly delayed treatment failure versus daily oral antipsychotics**
  - **Pragmatic features:**
    - **Population with history of incarceration, flexible treatment management**
    - **Pragmatic analysis included all data related to treatment failures from randomization until the end of the 15-month period regard-less of whether subjects were maintained on their initial randomized treatment**
  - **Treatment failures:** composite measure any of the following events:
    - **arrest or incarceration**
    - **psychiatric hospitalization**
    - **suicide; discontinuation of treatment due to inadequate efficacy, safety, or tolerability;**
    - **treatment supplementation with another antipsychotic due to inadequate efficacy;**
    - **increase in psychiatric services to prevent imminent psychiatric hospitalization.**

L. Alphs et al. / Schizophrenia Research 170 (2016) 259–264

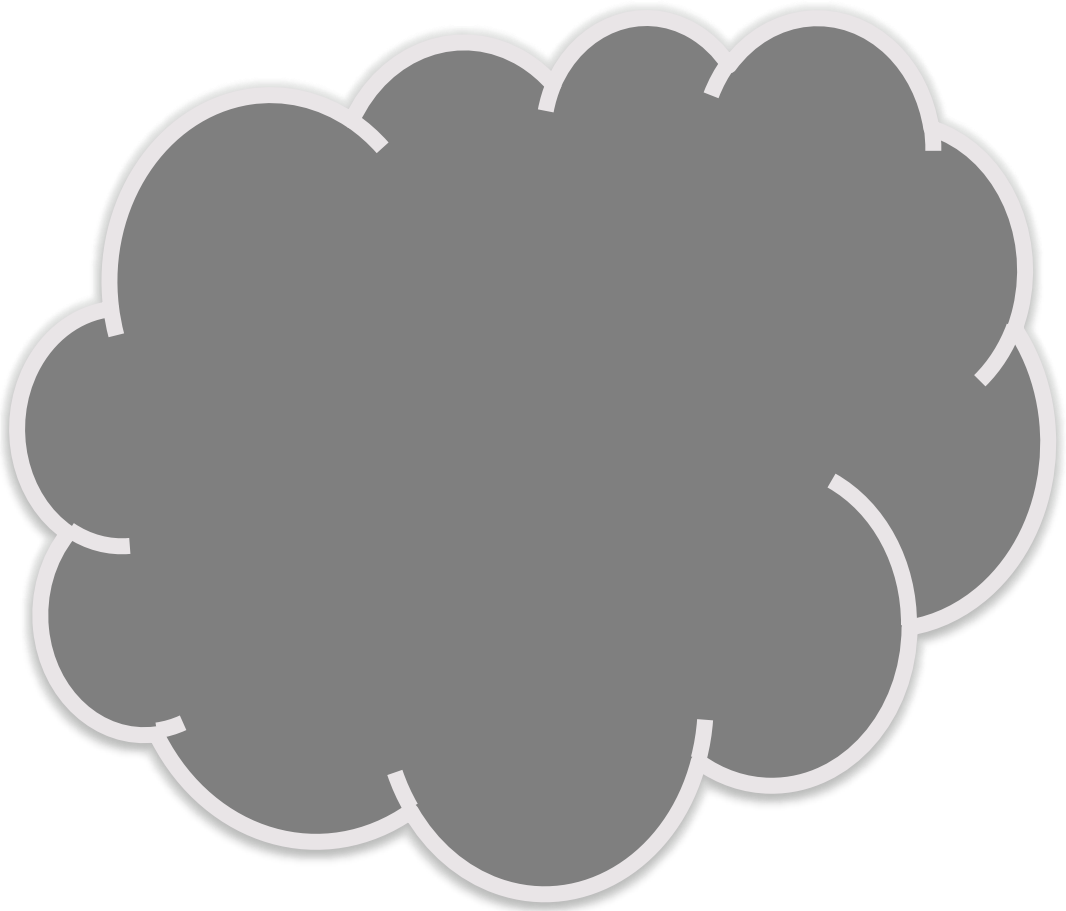
FDA Labeling - Paliperidone Palmitate

- **The primary study end point was time to first treatment failure, as determined by an independent event-monitoring board that was blinded to individual subject treatment assignment.**
- **All treatment failures used for the pragmatic analysis were identified and reported by investigators who were not blinded to their study medication**
- **There was little difference in timing or number of events when determined by these blinded raters.**

Event Type	INVEGA SUSTENNA® N=226 frequency (%)	Oral Antipsychotics N=218 frequency (%)	Hazard Ratio* [95% CI]
First Treatment Failures	90 (39.8%)	117 (53.7%)	0.70 [0.53, 0.92]
First Treatment Failure Component Events			
• Arrest and/or incarceration	48 (21.2%)	64 (29.4%)	
• Psychiatric hospitalization	18 (8.0%)	26 (11.9%)	
• Discontinuation of antipsychotic treatment because of safety or tolerability	15 (6.6%)	8 (3.7%)	
• Treatment supplementation with another antipsychotic because of inadequate efficacy	5 (2.2%)	6 (2.8%)	
• Need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization	3 (1.3%)	4 (1.8%)	
• Discontinuation of antipsychotic treatment because of inadequate efficacy	1 (0.4%)	9 (4.1%)	
• Suicide	0	0	
Arrest and/or Incarceration or Psychiatric Hospitalization Events, regardless of whether they were first events†	76 (33.6%)	98 (45.0%)	0.70 [0.52, 0.94]

COVID-19

COVID-19



HERO
Healthcare Worker Exposure Response & Outcomes

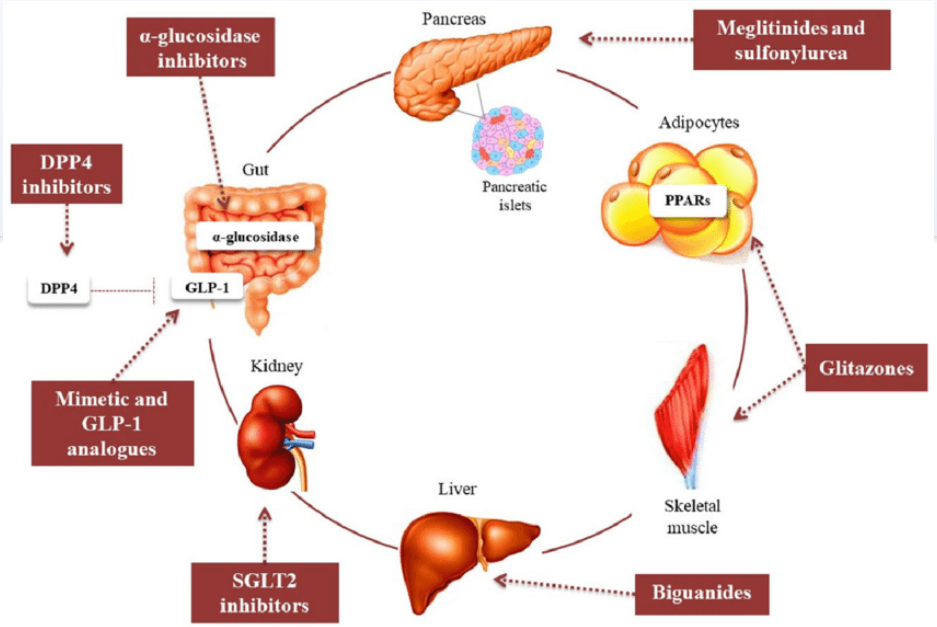
pcornet

- 15,000 Health Care workers
- Randomized, blinded
- Primary Endpoint
  - To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in healthcare workers (HCWs)
- Secondary Endpoint
  - Efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
  - Safety and tolerability of HCQ
- Under an FDA IND

Courtesy of Adrian Hernandez

Clinical Practice vs Clinical Trials

- Retrospective claims data comparing new users of glucagon-like peptide 1 receptor agonist (GLP-1 RA) or a dipeptidyl peptidase 4 (DPP-4) inhibitor, to quantify the gap between real-world (i.e., usual c



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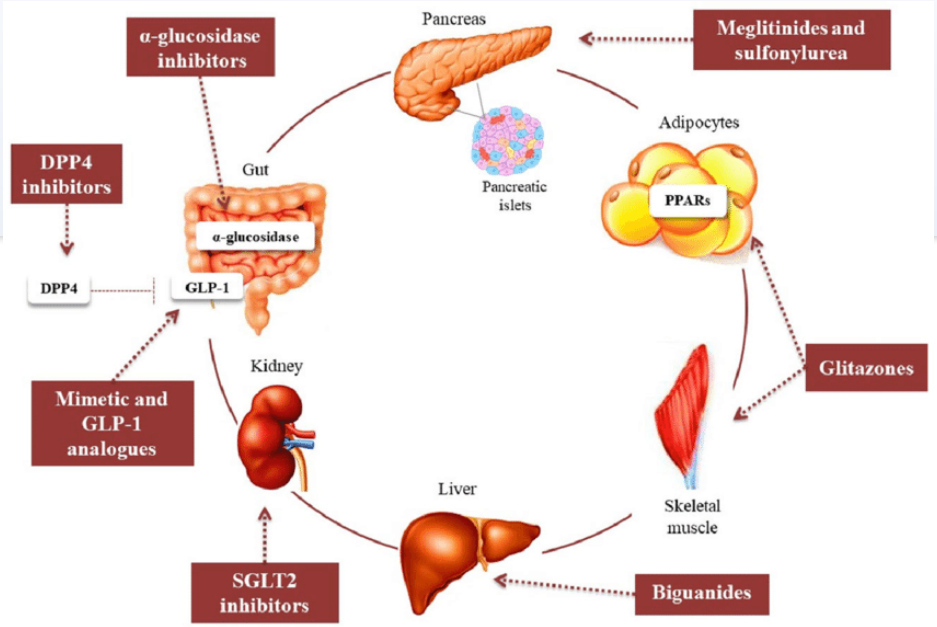
Clinical Practice vs Clinical Trials



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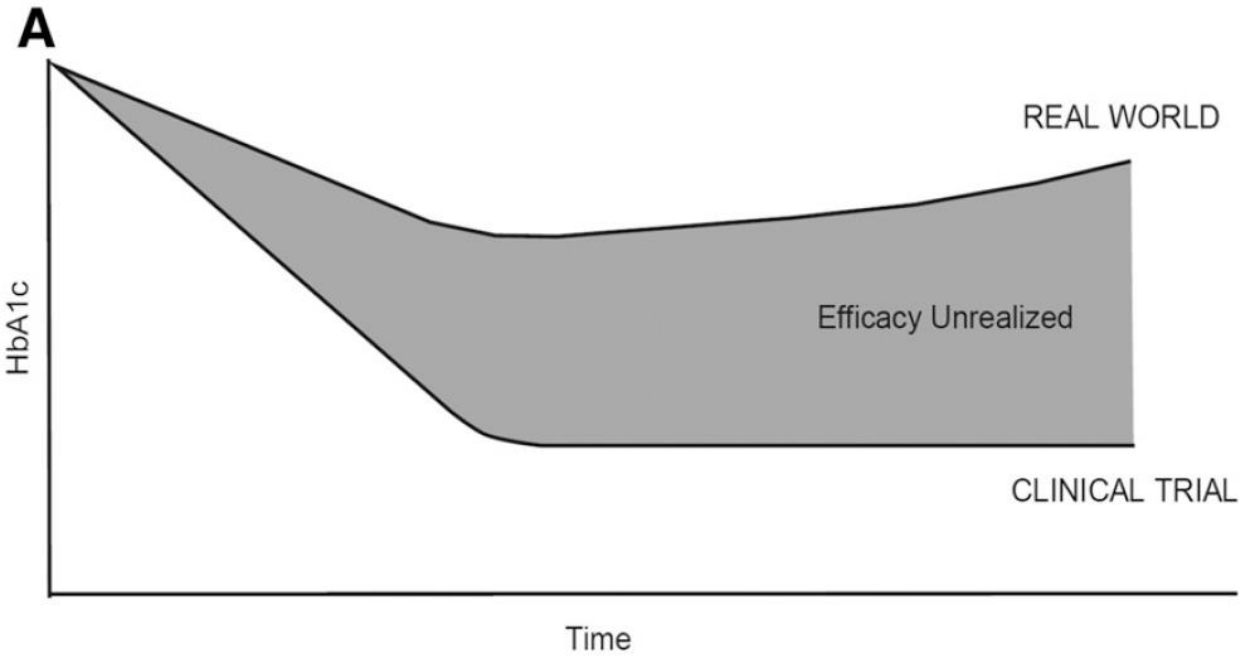

75% of GAP Adherence

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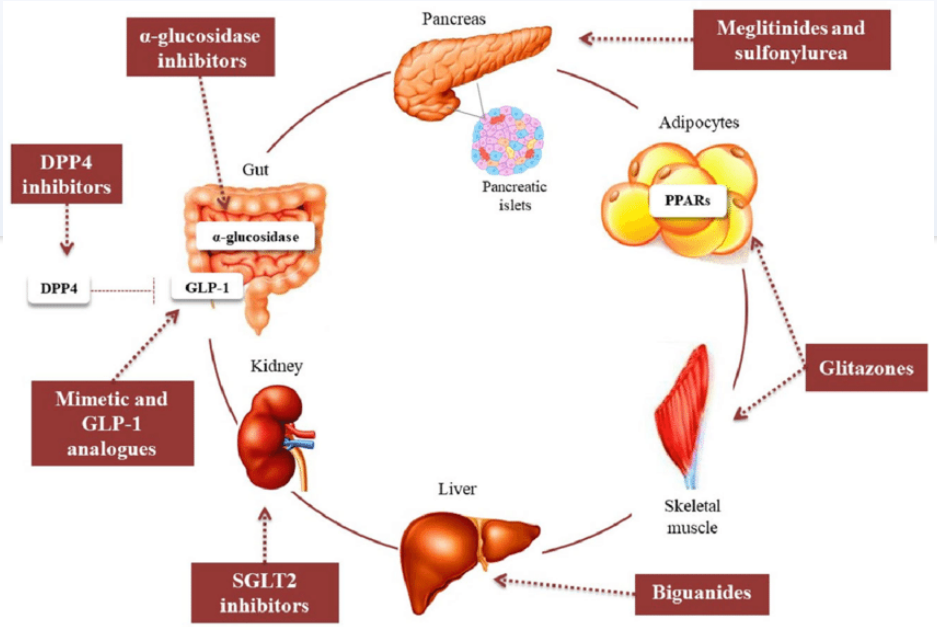

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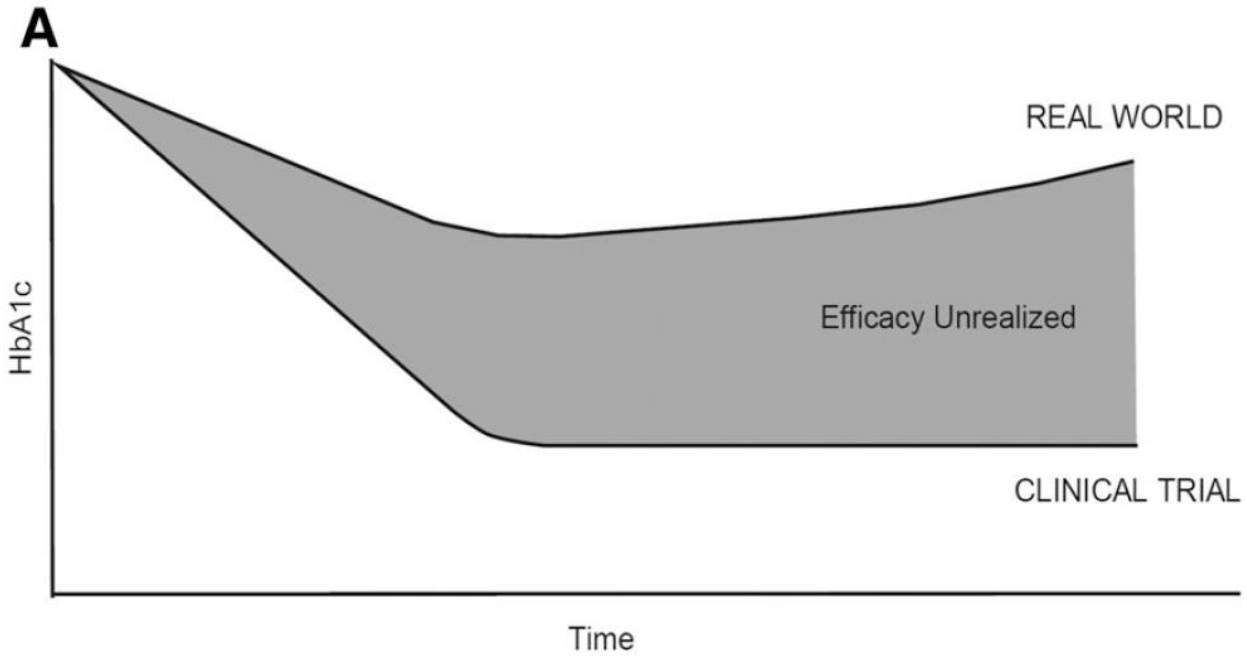

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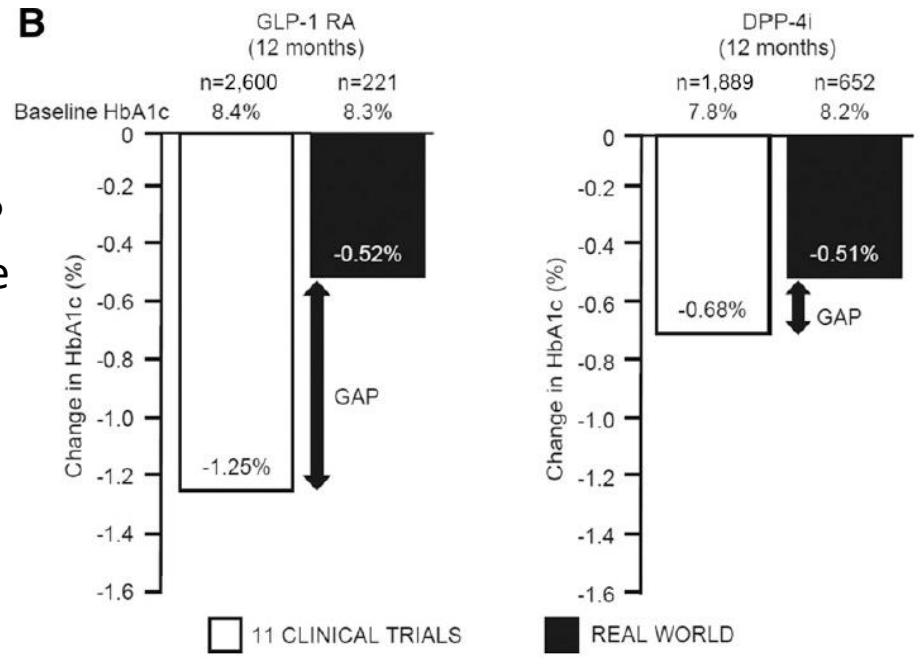

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Adopting “Pragmatism” into Regulatory RCTs

- The issue is **reliability – persuasiveness** – of the results, not trial methodology
- **Randomization** supports strong causal inference
- **Blinding** supports strong causal inference vs unblinded
- **Appropriate enrollment criteria** assures patients have the target condition (that the study objective is aimed to address)
- A **well-constructed endpoint** means that the study can determine if the purported effect of the drug is observed, and that effect is meaningful to patients
- **Reliable data**, that accurately collects the patient experience, and is accurately transferred into the analysis datasets supports **reliable conclusions**
- **Adequate monitoring** means complete collection of **important, relevant** efficacy and safety endpoints

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- How do we create a **research infrastructure** that can provide reliable, persuasive results?
- **Randomization methods** adapted to investigational sites
- **If blinding needed** – adapted to practices, such as central dispensing to patients
- **Simpler monitoring** – focused on endpoints that matter, but collected reliably
- **Endpoints utilizing digital tools**, in-home collection
- **Decentralized** sites
- **Enrollment criteria that are broad** but define properly the patient population
  - The issue isn't the enrollment criteria – it's doing studies in sites that bring in patients across a broader spectrum

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CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

Acknowledgements

- Peter Stein
- David Martin
- Dianne Paraoan
- Khair ElZarrad
- Juanita Marner


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