

# Clinical Trials Using Patient Health Data: A Primer on Pragmatic Trials

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**Duke** Clinical Research Institute

FROM THOUGHT LEADERSHIP  
TO CLINICAL PRACTICE

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# Outline

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- **Brief overview of “Real World Data”**
- **Regulatory Environment**
- **Characteristics of RWD**
- **Use of Randomized Trials**
  - In this talk “RCT” refers to “Traditional CT” (TCT)
- **Pragmatic Clinical Trials**
- **Examples**
- **Summary and recommendations**



# “Real World” Data (RWD) in Clinical Research

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- RWD clinical research usually connotes “observational studies” using EHR and health claims data
- “RWD” can also be used with Randomized Clinical trials (RCTs)
  - Supplement RCT control group (recent FDA guidance\*)
  - Confirm results of RCT’s
    - Duplicate Project
  - FDA & EMA RWD Guidance's
- RCTs performed using RWD as primary source data are often referred to as Pragmatic Clinical Trials (PCTs)
  - Also Clinically Integrated or “Decentralized” Clinical Trials
- **Message: It should not be RCT vs RWD/OBS, but RCT teamed with RWD**

\*FDA Draft Guidance External Controls



# Substantial Evidence Amendment on RWD (FDA Draft December 2019)

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*“If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence.”*

This modification explicitly recognized the potential for FDA to find that one adequate and well-controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness



# Substantial Evidence Amendment (FDA Draft December 2019)

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## 1. Real World Data is discussed as follows:

“Confirmatory evidence could include, for example, adequate and well-controlled clinical investigations in a related disease area, certain types of real world evidence such as extensive data on outcomes that provide further support for the lack of effect seen in the control group in the randomized trial, compelling mechanistic evidence in the setting of well-understood disease pathophysiology (e.g., pharmacodynamic data or compelling data from nonclinical testing), or well-documented natural history of the disease. ”

## 2. Randomization is discussed in 20 places in the document and Well-Controlled is referred to 60 times

## 3. 2023 Draft Guidance on “One Adequate and Well-Controlled Confirmatory Evidence”



# Substantial Evidence Amendment (FDA Draft December 2019)

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Although randomized double-blinded, concurrently controlled superiority trials are usually regarded as the most rigorous design, other types of controls are as described in ICH E10\*:

- **Placebo concurrent control**
- **Dose-comparison concurrent control**
- **No treatment concurrent control (NB 2023 FDA Draft Guidance)**
- **Active treatment concurrent control,**
- **Historical control (a type of external control).**
  - **Of note, the first version of the rule published in 1970, historical controls and active treatment controls were included.**

\*ICH E10: Choice of a Control Group



# RWD Regulatory, Scientific, & Ethical Issues

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- 1. The 21<sup>st</sup> Century Cures Act specifically states that the act does not change the evidentiary standards.**
- 2. The regulatory framework related to safety is not based on the same substantial evidence criteria.**
- 3. The importance of pre-specification in producing credible real-world evidence is emphasized.**
- 4. Emphasis has been placed on the transparency in reporting of RWD research including pre-registration**
- 5. Impractical does not necessarily mean unethical- don't be seduced into prematurely abandoning randomization!**



# The need for randomized trials even in serious diseases: Lessons from COVID-19

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**“Giving a treatment with no experimental evidence of benefit and known toxicity to a patient does not fit into my definition of ‘compassionate’ care ”**

**Martin Landray MD, Oxford University, UK**



# FDA-ASA Biopharmaceutical Section RWD Working Group

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1. The FDA/Industry group (with some academic assistance 😊) group has met for 4+ years and we have 4 papers completed in *Statistics in Biopharmaceutical Research*, so far....

1. *Levenson M et al: The Current Landscape in Biostatistics of Real-World Data and Evidence: Label Expansion. 2021*
2. *Chen J, et al The Current Landscape in Biostatistics of Real-World Data and Evidence: Use of RWD/RWE to Inform Clinical Study Design and Analysis, 2021*
3. *Ho M et al, Landscape in Causal Inference Frameworks for Design and Analysis of Studies Using Real-World Data and Evidence, 2021*
4. *Levenson M, et al: Statistical Consideration for Fit-for-Use Real-World Data to Support Regulatory Decision Making in Drug Development. 2022*

*Watch this space.....*



# Data Categories

	Research data sources	Transaction data sources
Generation & collection purposes	Objective specified in study protocols	Billing, administrative, clinical management
Examples	Completed RCTs, natural history studies, registries	Claims, EHRs, prescriptions
Data Quality	Data monitored per protocol	Provider- and purpose-dependent
Auditability	Legally auditable for clinical trials with source data	Framework for auditable EHRs & claims has yet to be setup
Outcome definition	<b>Defined prospectively</b>	<b>Data, source, and purpose dependent</b>
Collection methods & schedules	<b>Prospectively specified in study protocols</b>	<b>Provider- and purpose-dependent, e.g., bill collection, clinical visits</b>
Treatment regimen	Coded for research in protocols	Patients and providers dependent
Missing data vs. unavailable data	Data points are missing if they are not collected as specified in the study protocols	Data points that do not exist are not necessarily missing, e.g., a patient might feel well, with no need to see doctors

# Data Sources-

	Research data sources	Transaction data sources
Description	Collected primarily for research	Used secondarily for research
Examples	<ul style="list-style-type: none"><li>❖ Data specifically for study purpose<ul style="list-style-type: none"><li>❖ Framingham Heart Study</li><li>❖ Cardiovascular Health Study</li></ul></li><li>❖ Data intended for other studies<ul style="list-style-type: none"><li>❖ Nurses' Health Study</li><li>❖ Some registries</li></ul></li><li>❖ Traditional Clinical Trials</li></ul>	<ul style="list-style-type: none"><li>❖ Clinical documentation<ul style="list-style-type: none"><li>❖ Electronic health records</li><li>❖ Wearable devices</li></ul></li><li>❖ Administrative<ul style="list-style-type: none"><li>❖ Claims data</li><li>❖ Geocoding/census</li></ul></li></ul>



# Some thoughts on data from RWD Sources\*

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- **Data Gaps: "Missing" or just not needed for patient care**
- **Endpoint Ascertainment - the source document is the document**
- **Data Latency**
- **Data Concordance (or lack thereof)**
- **Clinical Trial Site Investigators vs Practicing Clinicians**
  - **Clinically Integrated or Decentralized CTs**

\*1. Rockhold FW, et al (2020) Design and analytic considerations for using patient-reported health data in pragmatic clinical trials: report from an NIH Collaboratory roundtable, *J Am Med Inform Assoc*, 27(4), 634–638

2. Rockhold F.W., Goldstein B.A. (2020) Pragmatic Randomized Trials Using Claims or Electronic Health Record Data. In: Piantadosi S., Meinert C. (eds) *Principles and Practice of Clinical Trials*. Springer, Cham

# Gaps in Data

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- **“Missingness” is a term often incorrectly used in the RWD framework.**
- **It is carried over from trial terminology in a CRF where the concept of “missing” is clear if that element is blank.**
- **In an RWD/pragmatic study, the information may be not available for research because it was not necessary for the patients’ medical care.**
- **It is not clear what these gaps or “missingness” imply in this context.**
- **Standard CT imputation methods are likely not appropriate**



# Gaps in Data

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- In EHR data, these “gaps” become important, because the presence of data elements is usually informative, a process we’ve referred to as ‘informed presence’ \*
- This typically manifests itself in that we have more information on sicker patients.
- The protocol needs to be clear about what information is reasonably expected to be in an RWD source and how gaps will be defined when an “expected” value is unavailable.

\*Goldstein BA et al (2019) J Am Med Inform Assoc 26(12):1609–1617

# Data gaps- more

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- **The reliability of an outcome tied to reimbursement may be different from one that is clinically driven, like the collection of vital signs during an ambulatory visit.**
- **These differences can affect the way that an outcome could become missing or incomplete.**
- **Collecting information on outcomes from multiple sources, including patient-reported health data (PRH) , may address this incompleteness**
- **Best practices for integrating multiple sources and reconciling differences between them have not yet been defined**



# Data Latency (for RWD “real-time” data)

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- **Because RWD studies generally rely on health information that is extracted an EHR system, they are vulnerable to incomplete information due to data latency as well as data availability.**
- **Data latency is an issue because, while information is uploaded quickly to billing systems, clinical data may be less current than that from, say, a CRF in an RCT (TCT).**
- **This introduces special considerations for ongoing surveillance of event rates or adverse events in the study.**



# Data Concordance (or lack thereof)

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- If RWD is augmented by patient reported data, the level of concordance between the patient report and the EHR is important for ascertainment of events.
- If the data do not align perfectly, it is possible to map one to the other (e.g. cigarettes per day vs packs per week)
- To assess if the patient has a given diagnosis or procedure, a combination of EHR data and the patient's memory may be the best triangulation of ground truth.



# The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P., and Richard Peto, F.R.S.

Metrics

February 13, 2020

N Engl J Med 2020; 382:674-678

DOI: 10.1056/NEJMsb1901642

249 Citing Articles Letters

## Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler ✉, Francesco Pignatti, Brigitte Schwarzer-Daum, Ana Hidalgo-Simon, Irmgard Eichler, Peter Arlett, Anthony Humphreys, Spiros Vamvakas, Nikolai Brun, Guido Rasi

First published: 16 October 2020 | <https://doi-org.proxy.lib.duke.edu/10.1002/cpt.2083> | Citations: 69

Collins, R., Bowman, L., Landray, M., & Peto, R. (2020). The Magic of Randomization versus the Myth of Real-World Evidence. *N Engl J Med*, 382(7), 674-678

H. G. Eichler, F. Pignatti, B. Schwarzer-Daum, A. Hidalgo-Simon, I. Eichler, P. Arlett, et al., Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth, *Clin Pharmacol Ther* 2021 Vol. 109 Issue 5 Pages 1212-1218

# Pragmatic Clinical Trials\* Using RWD

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- **Greater access to data from EHR's & Claims data to observe outcomes directly in the healthcare environment**
- **Pragmatic trials can embed randomization into the “RWD” environment**
- **PCTs are based on sound well controlled randomized clinical trial principles**
- **There is a hope they will be easier to run and therefore less expensive than “classic” RCTs**

\*1. Schwartz, D. and Lellouch, J., *Explanatory and pragmatic attitudes in therapeutical trials*. J Chronic Dis, 1967. 20(8): p. 637-48.  
2. Loudon, K., Treweek, S., Sullivan, F., Donnan, P., Thorpe, K.E., and Zwarenstein, M., *The PRECIS-2 tool: designing trials that are fit for purpose*. BMJ, 2015. 350: p. h2147



# Simple Definition of Pragmatic Trials

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***“Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.***

***Robert Califf, MD***

***Commissioner US Food and Drug Administration***

\*Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials. 2015 Oct;12(5):436-41

# A Little More History

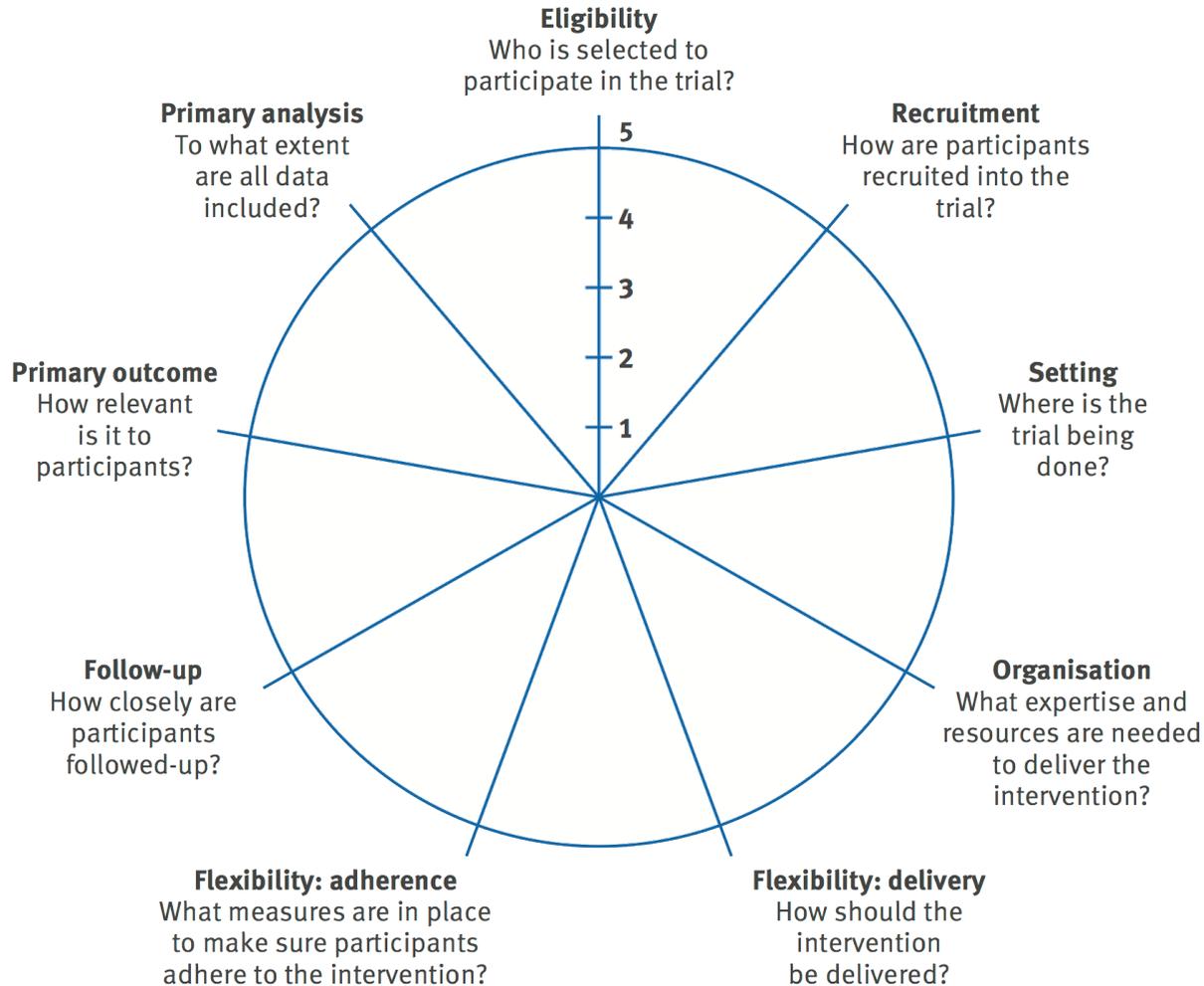
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- **1967** The Term “Pragmatic Clinical Trial” was coined
- **“Large Simple Trials”** with huge public impact
  - **1987** GISSI series of randomized clinical trials (RCTs) were launched in thrombolytics (first trial 12,000 patients)
  - **1988** ISIS series of RCTs in thrombolytics starting with 17,000 patients
  - **1993** GUSTO Trial- a randomized trial of 41,000 patients in thrombolytics with a 2-page case report form.
  - **Prior to EHR access** these trials used brief CRF’s
- **2016 ADAPTABLE-** 20,000 randomized comparing aspirin dose. All data from EHR’s and patient portal. PCORI’s flagship “Pragmatic Clinical Trial”.
- **They share randomization, simplicity, broad inclusion criteria, and a “real world effectiveness” approach and differ in data source**



# PRECIS-2

(Loudon, K., Treweek, S., Sullivan, F., Donnan, P., Thorpe, K.E., and Zwarenstein, M., *The PRECIS-2 tool: designing trials that are fit for purpose. BMJ, 2015. 350: p. h2147* )



**Table 1** Ways that randomized controlled trials (RCTs) and PCTs can differ

Classic RCT	Criterion	P <sup>o</sup> R <sup>o</sup> CT
Intentionally homogeneous to maximize treatment effect	Eligibility criteria	Heterogeneous – representative of normal treatment population
Randomization and double blind	Bias control	Randomization and rarely blinding
Clinical measures, intermediate endpoints, composite endpoints, clinical outcomes	Endpoints	Clinical outcomes as reported in the health system
Protocol defines the level and timing of testing	Routine follow-up tests	Measured according to standard practice
Fixed active control or placebo	Comparison or intervention	Standard clinical practice
Conducted only by trained and experienced investigators	Trial “investigator”	Practitioners with differing and limited experience
Visit schedule defined in the protocol	Longitudinal follow-up	Visits at the discretion of physician and patient
Compliance is monitored closely	Protocol compliance	Passive or indirect monitoring of patient compliance
Close monitoring of adherence	Adherence or treatment	Passive or indirect monitoring of practitioner adherence
Intent to treat, per protocol and completers	Estimand	All patients included ITT



# Pragmatic Clinical Trials\*

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- “Real world” and more patient focused than classic RCT
- Principle hypothesis: Effectiveness vs efficacy (and both are important)
  - Treatment strategy: literal meaning of intention to treat
- Patient level randomization or cluster randomized trials
- Pragmatism is on a spectrum and not a binary label as sometimes applied in the literature
- I will give examples of 3 different PCT designs

\* Lentz TA, Curtis LH, Rockhold FW, Martin D, ....., Ellenberg SS. Designing, Conducting, Monitoring, and Analyzing Data from Pragmatic Randomized Clinical Trials: Proceedings from a Multi-stakeholder Think Tank Meeting. Ther Innov Regul Sci. 2020 Jun 8

# Clinically Integrated (Decentralized) Clinical Trials

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- **Clinically integrated trials are designed to co-locate clinical research studies and routine, everyday clinical care delivery – e.g. in a hospital setting, office clinic, or at home.**
- **A clinically integrated trial is not a type of trial design, but rather an operational approach to conducting clinical trials that integrates clinical research and routine care delivery**
- **As such, clinically integrated trials represent a subset of pragmatic trials and concepts within pragmatism in clinical trials.**
- **Further components include:**
  - **Decentralization of trials utilizing digital elements**
  - **Point-of-care (POC) trials based on direct interaction with patients at the time and place (i.e., ER visit) of routine clinical care for discussion of participation in pragmatic clinical trials**



# Running a PCT in Salford, UK: Study of an experimental drug in Asthma and COPD\*

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- 7000 patients from a single city
  - Well defined NHS area with a strong academic centre
  - Minimal exclusion criteria
  - Active patient recruitment
  - Randomised, open label design, 1 year follow up
  - Free choice mixed comparator arm
  - No protocol restrictions on follow up care
  - Just start and finish visits (+safety if required)
  - Fully integrated EHR for all data collection & safety monitoring
  - Utilising community pharmacy for study drug supply
- \*Nawar Diar Bakerly, et al, ,The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease, Respiratory Research 2015, 16:101



# Salford Lung Study

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- **Study as near to “real world” as possible using a pre-license medicine for Asthma and COPD**
- **Embrace heterogeneity of patient population**
- **Normalise the patient experience as much as possible**
- **Pragmatic – “usual care” in each arm**
- **Relevant endpoints collected**
- **Maintain Scientific Rigor**
  - **Interventional**
  - **Randomised**
  - **Controlled**



# Study outline for COPD

**Primary endpoint: Moderate/severe exacerbation (defined by oral steroid (and/or antibiotic use) and/or hospitalisations)**  
**Secondary endpoints: Serious Pneumonias, Healthcare utilisation, COPD Assessment Test (CAT)**

2800 patients

- Patients in primary care, aged 40+
- GP diagnosis of COPD
- Taking ICS, LABA, LAMA alone or in combination
- Consented

Randomised

New Rx open label

**Visit 2**  
Routine respiratory review  
Device instruction  
CAT

12 months of normal care

**Visit 6**  
Routine respiratory review  
Device instruction  
CAT

Existing maintenance Rx, ICS, LABA, LAMA

Constant real-time data collection of all HC interventions/safety monitoring



# Salford Healthcare Infrastructure: More than just a database



# Key Facts on COPD Study

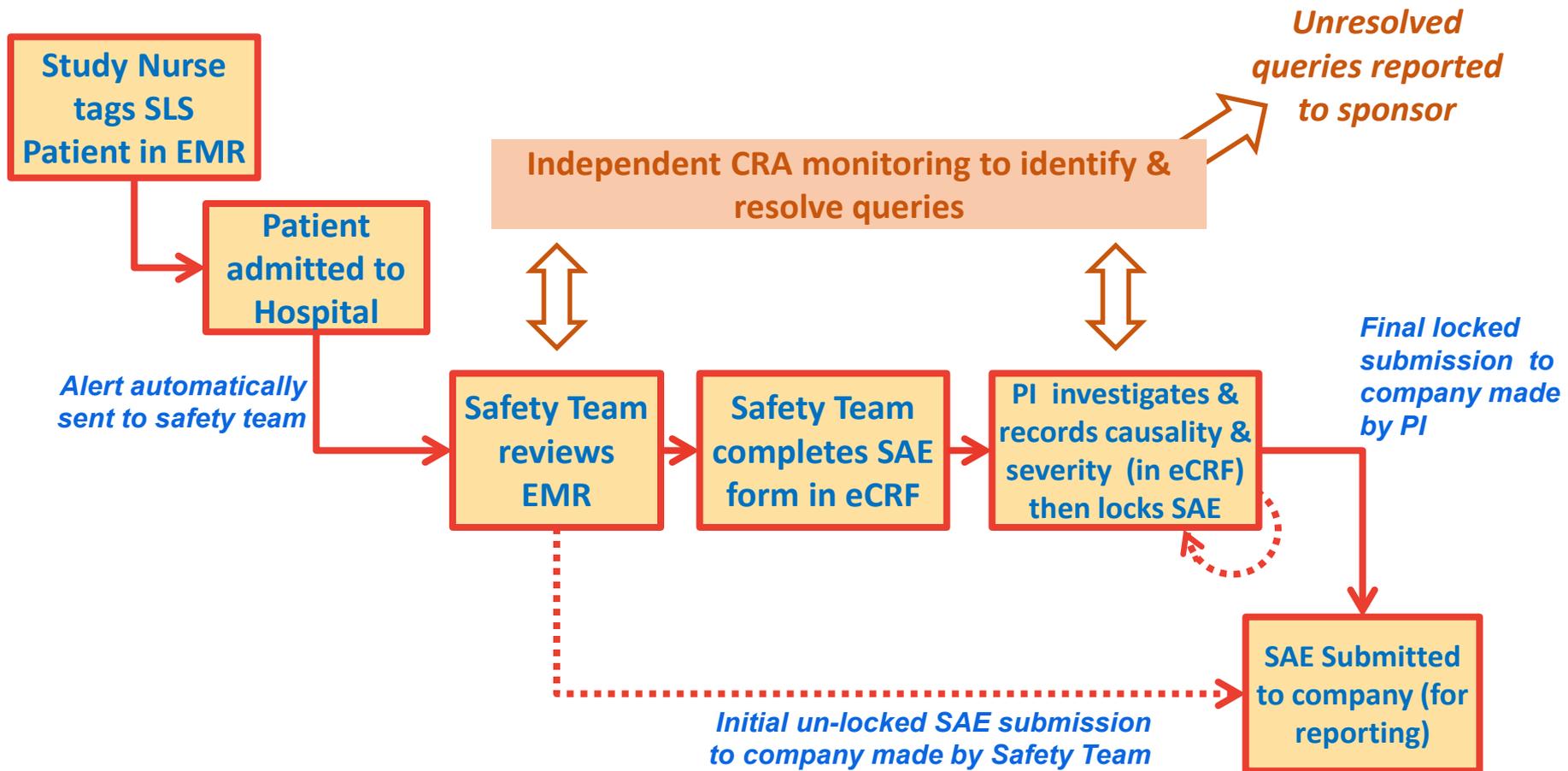
## (Findings similar for Asthma study)

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- **Setting up, training 203 “sites”**
  - **120 “PI’s”**
  - **>100 Pharmacies Trained (dispensing unapproved medicine)**
  - **>3000 site staff trained in ICH GCP**
- **3,500 patients seen in office and 2,800 patients recruited**
- **Over 3,800 site visits and reports written and reviewed**
- **Over 8,500 patient visits checked and verified**
- **Over 26,000 queries raised and closed**
- **Over 500 serious adverse events investigated**
- **25,000 parking tickets and 1 million cups of tea and coffee**



# Serious Adverse Event (SAE) Reporting Process



# Summary: SLS

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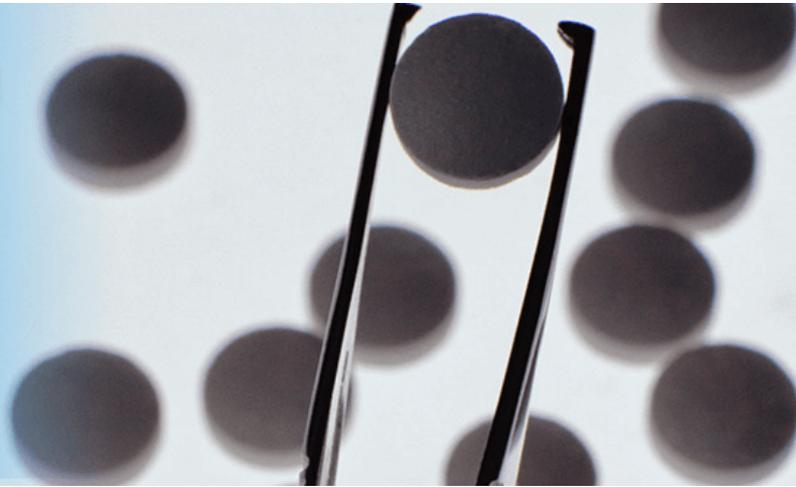
- **The Salford Lung Study was the first of its type**
- **Maintained scientific rigor**
  - **randomised**
  - **active control**
  - **robust primary endpoint**
- **It was an enormous logistical effort and in a specialized setting**
- **Monitoring/reporting of adverse events required by regulators may interfere with clinical practice and affect the *pragmatism/feasibility***
- **It offered important information for clinicians, healthcare decision makers and most especially patients**
- **Provided valuable information about how to conduct real-world effectiveness studies in the future**



# ADAPTABLE\*, the Aspirin Study – A Patient-Centered Trial

*60% of patients with heart disease take a 325 milligram dose each day while 36% take 81 milligrams.*

*Which dose should you take?*



*ADAPTABLE will compare two common aspirin dosages, 325mg and 81mg, and involve 20,000 patients across the U.S.*



[\\*Adaptable Results NEJM](#)

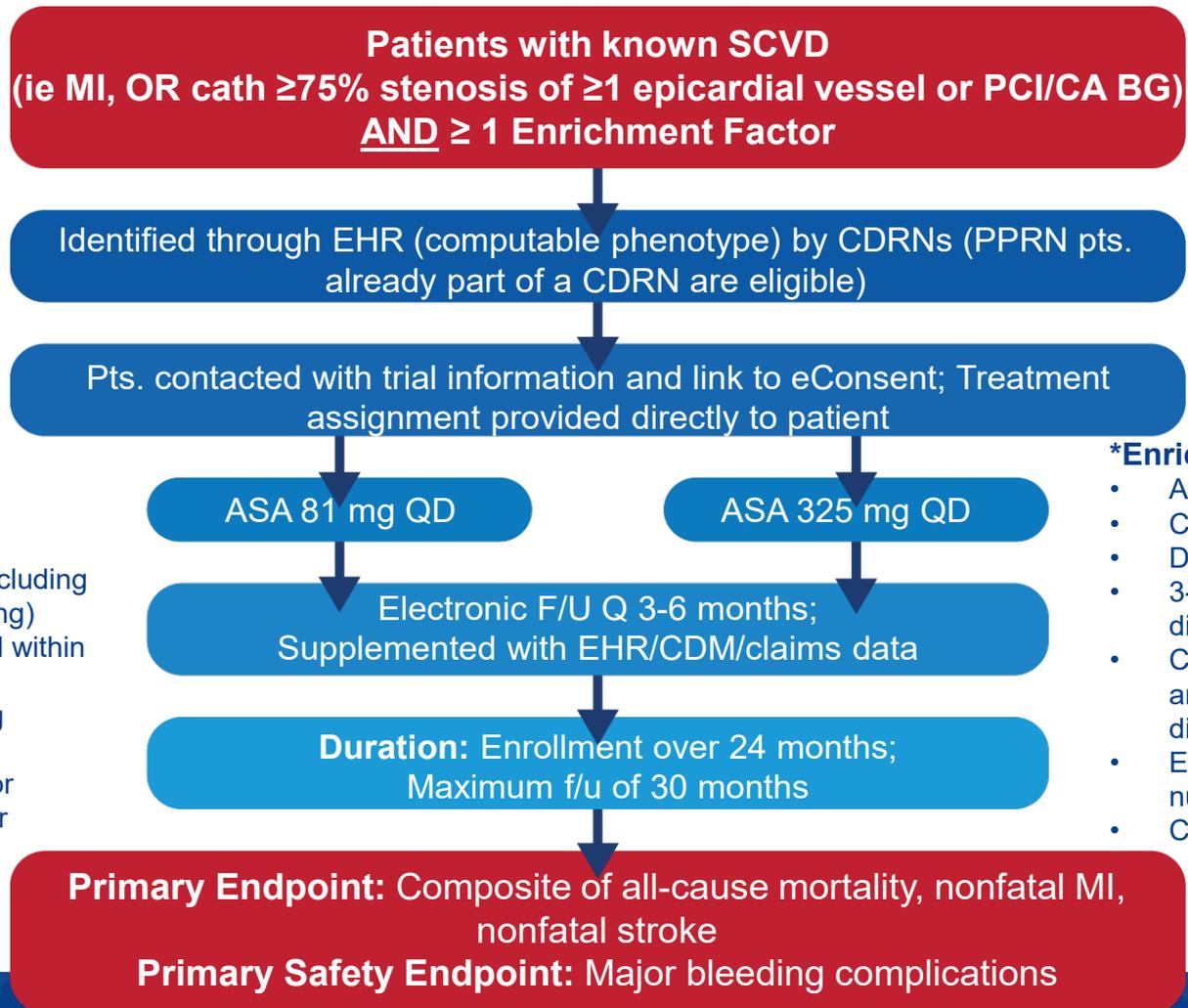




PCORnet seeks to improve the nation's capacity to conduct **clinical research** by creating a large, highly representative, national patient-centered network that supports more efficient clinical trials and observational studies.



# Study Design



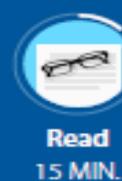
## Exclusion Criteria

- Age < 18 yrs
- ASA allergy or contraindication (including pregnancy or nursing)
- Significant GI bleed within past 12 months
- Significant bleeding disorder
- Requires warfarin or NOAC or Ticagrelor

## \*Enrichment factors

- Age > 65 years
- Creatinine > 1.5
- Diabetes (Type 1 or 2)
- 3-vessel coronary artery disease
- Cerebrovascular disease and/or peripheral artery disease
- EF < 50% by echo, cath, nuclear study
- Current smoker





You can re-watch the video at any time by clicking on the camera icon above.

A TEXT SIZE A

## ADAPTABLE Information

### Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE)

We are asking you to join a research study called ADAPTABLE. The information below explains the study so you can decide if you want to take part or not. Please read it carefully and take all the time you need to decide. Feel free to talk it over with your family, friends, and doctor. If there is anything you do not understand, be sure to ask questions.

#### WHY IS THIS STUDY BEING DONE?

For more than 40 years, doctors have been telling patients with heart disease to take aspirin. For these patients, taking aspirin every day can lower the risk of heart attacks and strokes.

Millions of Americans who have heart disease already take either regular (325 mg) or low-dose (81 mg) aspirin. Many studies have shown that both doses work and both are generally safe. The most common side effect of aspirin is an upset stomach. Aspirin can also make you bleed more easily. In rare cases (about 5 in 1,000 people), it can cause dangerous bleeding in the stomach, brain, or other places.

Even though both doses of aspirin are widely used, no one knows which is better. Regular aspirin has a higher risk of bleeding than low-dose aspirin. But no one knows if low-dose aspirin is both safer and works just as well as regular aspirin to prevent heart and blood vessel problems.

The goal of ADAPTABLE is to try to find out which dose of aspirin is better for patients like you who have heart disease. Patients who join this study will take either low-dose or regular aspirin every day. That way, we can learn which is better in terms of reducing the risk of heart attacks, strokes, bleeding, and death.

ClinicalTrials.gov: NCT02697916

# ADAPTABLE vs. A Classic Randomized Controlled Trial (RCT)

## ADAPTABLE

Simple, inclusive, minimum risk, focus on population representation

Heterogeneous - representative of real world treatment population

Reach out to a broad population: eligible pool by computable phenotype, subjects approached by emails, online portals, letters, social media, in-clinic visits, telephones, and live events.

Participants randomize themselves, unblinded

### Eligibility

### Study Population

### Recruitment

### Randomization

## RCT

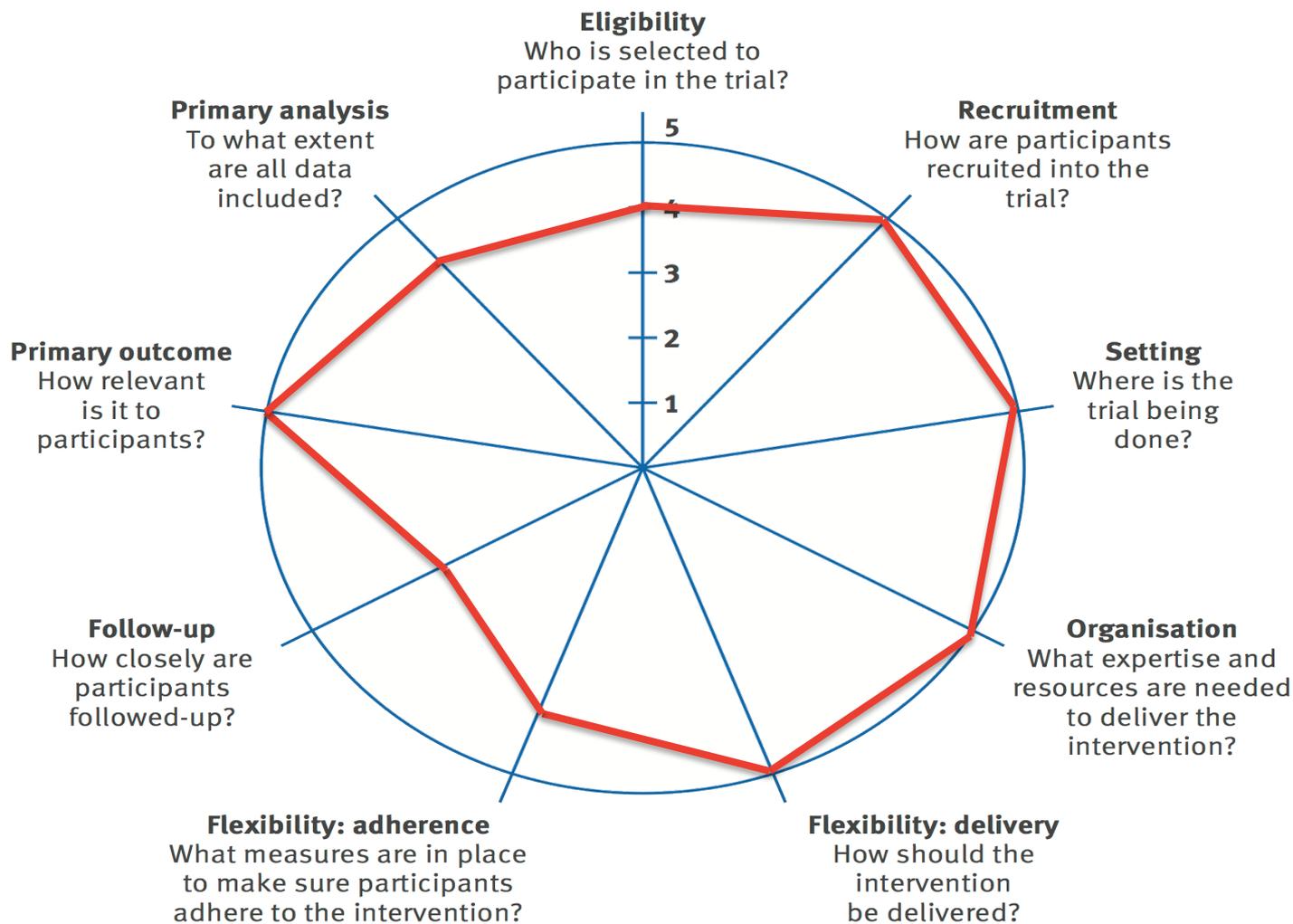
Selective, focus on populations in more ideal circumstances

Intentionally homogeneous to maximise treatment effect

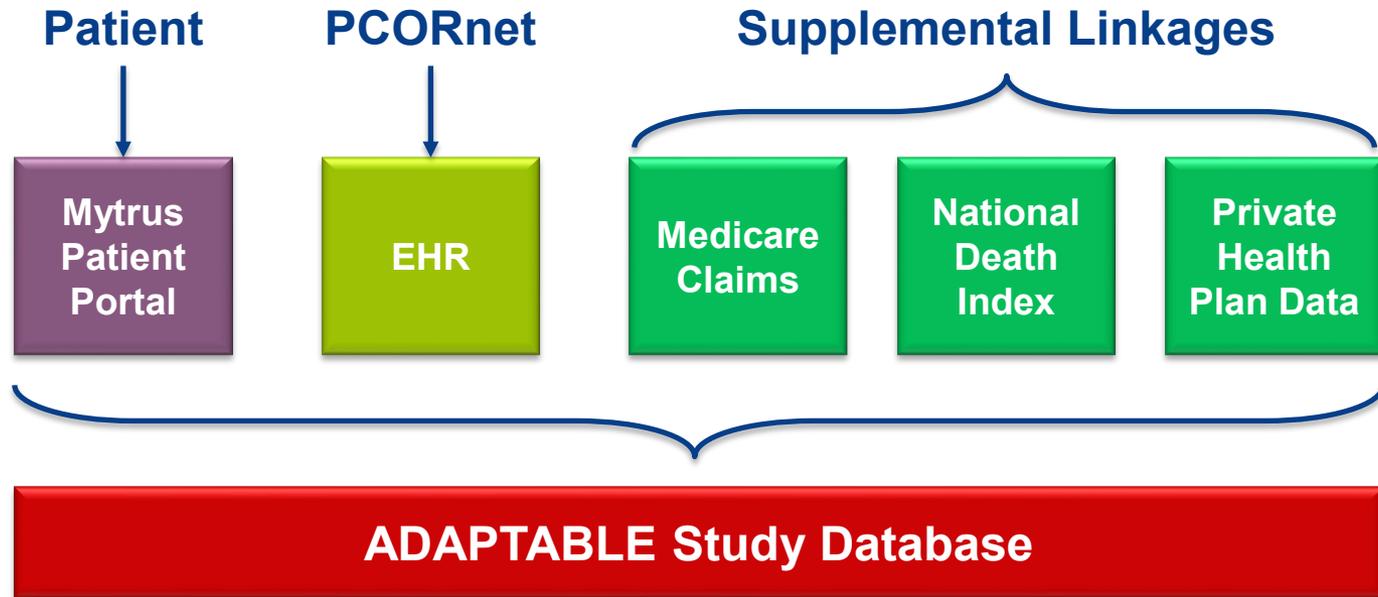
Potential participants identified and approached by their doctors or nurses from participating clinics

Sites randomize participants, often blinded

# ADAPTABLE – How Pragmatic is it?



# Information Flow



- Each data source arrives at the coordinating center via a different mechanism
- All will contribute to eventual study database
- Algorithm based decisions for discrepant data/event ascertainment

# Information Asymmetry

- Different participants with different sources of data contributing to endpoint ascertainment
  - Vary by site, Medicare & health plan coverage are not uniform
  - Vary by site or patient if fields are inaccurate or missing



# Information Latency

Data Source	Availability	Min – Max Delay
<b>Participant Self-reported data</b>	Instant	None
<b>Electronic Records</b>		
<b>eHR from PCORnet DataMart</b>	Quarterly	3 – 6 months
<b>Medicare Claims Data</b>	Annual	1 – 12 months
<b>National Death Index</b>	Annual	1 – 12 months
<b>Private Health Plan Data</b>	End of study?	

**Implication: complete data for the study will become available 1 year after the last patient last follow up**



# Endpoint Ascertainment

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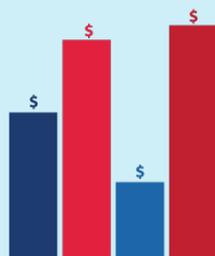
- **Are we capturing information completely and accurately?**
  - **A multi-faceted approach to capture outcomes**
  - **Endpoint validation and Endpoint reconciliation of MACE and Major Bleeding events**



# Handling Disagreement Across Different Data Sources

		EHR/PCORnet CDM	
		NO	YES
Patient Reported Events	NO	No Event	Event
	YES	Query	Event

📍 Patient reported hospitalizations that are not observed in eHR data will be queried via:



Medicare fee-for-service claims



Large national health plans (FDA's Mini-Sentinel initiative)



DCRI Call Center

# Summary: ADAPTABLE

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- **ADAPTABLE was the first pragmatic mega-trial in the world designed to evaluate aspirin dose with 15,000 participants**
- **Attempted to mimic the real-world patient experience of a patient with heart disease**
- **Data from multiple sources and a multi-faceted approach to capture outcomes and taught us a great deal about this approach**
- **Maintained scientific rigor**
  - **randomised**
  - **active control**
  - **robust primary endpoint**
- **While the open label approach was done to mimic the real world and save money, it turned out to be a major limitation of the trial due to treatment switching. A double-blind approach would have been cleaner scientifically and cost more and be “less pragmatic”**

# The HERO COVID Program

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- HERO COVID-19 Program: HERO-PCORI <https://heroesresearch.org/>
- The HERO program consisted of two parts, a national registry and a randomized double-blind clinical trial run under a US IND.
  - The registry rapidly identified a large (>100,000) community of healthcare workers at risk for COVID-19 infection.
  - The clinical trial (HERO-HCQ), randomized healthcare workers to HCQ or placebo looking at the rate of infection
  - The study also explored how well the drug can prevent further spread of the virus to others.
- First Design Meeting Sunday 3/22/20
- First patient randomized 4/22/20 (NCT NCT04334148). Concept protocol to randomization in 4 weeks!

**COVID-19 HCW Risk  
(N = 15,000)**

**1: 1  
Randomization**

**Treatment Group:  
(Hydroxy) Chloroquine**

**Control Group:  
Placebo**

HERO  
Registry

**Primary objective: To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in HCW**

**Secondary Objectives:**

- To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
- Evaluate safety and tolerability of HCQ

HERO –  
HCQ Clinical  
Trial

**Exploratory Objectives:**

- Evaluate SARS-CoV-2 seroconversion in participants taking HCQ
- Describe COVID-19 infectious complications in participants taking HCQ
- Describe time off from work for medical reasons in participants taking HCQ
- Describe QoL
- Describe experience of household contacts



# Design and Operational Features

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- **Rapid, large registry of healthcare workers – enrollment open to all**
- **Healthcare workers eligible for the HERO-HCQ trial will work at one of the 40 PCORnet sites participating in the trial**
  - **Pre-screened within the registry, and referred to their local site**
  - **Confirms HCW status, randomizes, and provide study drug**
- **Direct to participant data collection**
  - **Weekly web-based check-ins for symptoms, side effects**
  - **Call center rescue for missed check-ins.**
- **Baseline and end of study swab-checks for viral shedding**
- **Baseline and end of study serum for testing for sero-conversion**
- **Trial failed to randomize all patients due to numerous factors**

## \*HERO HCQ Results

# Data and Safety Monitoring of PCT's

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- **Role of a DMC in a pragmatic trial**
  - **Standard role**
  - **Additional focus: feasibility, protocol adherence, data validity**
  - **Involvement of patient representatives**
- **If and how can the DMC make critical recommendations with fragmented information during the study?**
  - **Interim analyses: differentiate a signal from noise with varied access to outcome data**
  - **Differential data lag times**
  - **Benefit to risk analysis**
- **Is the DMC protected?**
  - **Indemnification**



# Summary: PCT's

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- **PCTs answer questions that are more real-world effectiveness. Should be viewed as a supplement to RCT's.**
- **“Investigator” vs GP: impact on recruitment and event ascertainment.**
- **Cost? Speed? Time will tell and for now the focus should be on “how” and not “how much” or “how fast”.**
- **Data management vs healthcare informatics- cost shifting.**
- **Patient recruitment can face all the same challenges as an RCT**
  - **Clinically integrated trials are a point of care subset of PCTs**
- **The approach can be useful for unapproved drugs, but additional infrastructure is needed to meet regulatory reporting requirements.**
- **In the end these trials may prove most valuable to the ultimate customer- The patient**



# Recommendations

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- Be precise with the study question and then make sure the data are useful to answer it! And don't twist the question to fit the data
- PrCT's and OBS studies should be an "and" not an "or" discussion
- Understand the data- don't try to make RWD look like an RCT CRF
  - Develop an RWD / PCT research infrastructure
- Data gaps are not necessarily "missing" data
- Perform studies using RWD because of the clinical utility and scientific value and not driven solely by speed and cost
- Performing a pragmatic (RWD) trial is not be a euphemism for "sloppy" or "easy to conduct": This applies to the question and the conduct

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# Questions and discussion

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