Randomized Pragmatic Trials in Clinical Research: Myths and Realities

Frank W. Rockhold, PhD
Professor of Biostatistics and Bioinformatics
Duke University Medical Center

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Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

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Frank W Rockhold, PhD

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Boards: European Medicines Agency Technical Advisory Group, California Institute for Regenerative Medicine, Frontier Science Foundation, CEPI Vaccine Advisory, DataVant Scientific Advisory, Spencer Health Solutions Scientific Advisory, Athira Pharma Scientific Advisory, Doctor Evidence Medical Strategy, Editorial Advisory Board of *Pharmaceutical Statistics*

Equity Interest: GlaxoSmithKline, Ciox, Athira, Spencer, Doctor Evidence, Clover


HISTORY LESSON
'Those who cannot learn from the past are condemned to repeat it!'
~George Santayana
ADAM ZYGLIS ©2012 CAGLECARTOONS.COM THE BUFFALO NEWS

Substantial Evidence Amendment
(FDA Draft December 2019)

- Original document is from the 1962 Kefauver-Harris Amendment to the 1906 Food and Drug Act and updated in 1999
- fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products
- Applies to drugs and biologics only

History of Substantial Evidence Doctrine

FDA Statutory standard

In 1962, Congress required for the first time that drugs be shown to be effective as well as safe. A drug's effectiveness must be established by "substantial evidence," which is defined as:

"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."

Was updated 1999 and now 2019

Substantial Evidence Amendment
(FDA Draft December 2019)

"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)

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**

Substantial Evidence Amendment
(FDA Draft December 2019)

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

- **Placebo concurrent control**
- **Dose-comparison concurrent control**
- **No treatment concurrent control,**
- **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.***

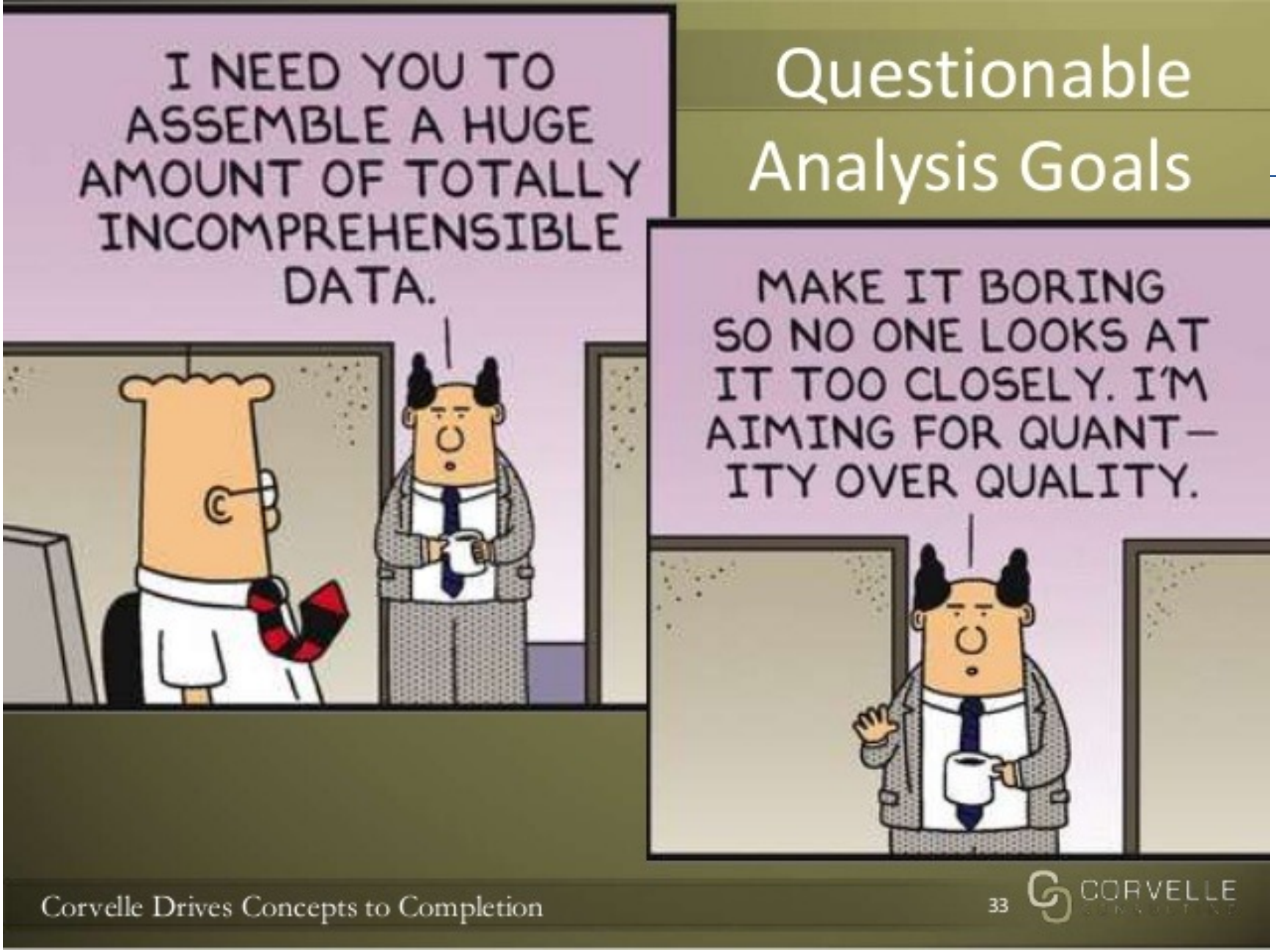
RWD Regulatory, Scientific, & Ethical Issues

1. The 21st 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

FDA-ASA Biopharmaceutical Section RWD Working Group

1. **The FDA/Industry group (with some academic assistance) group has met for almost two years.**
2. **We have completed 3 papers Just Published in Statistics in Biopharmaceutical Research, 1 Feb 2021**
    1. ***Levenson M et al: The Current Landscape in Biostatistics of Real-World Data and Evidence: Label Expansion.***
    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***
    3. ***Ho M et al, Landscape in Causal Inference Frameworks for Design and Analysis of Studies Using Real-World Data and Evidence***

Questionable Analysis Goals



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	Defined prospectively	Data, source, and purpose dependent
Collection methods & schedules	Prospectively specified in study protocols	Provider- and purpose-dependent, e.g., bill collection, clinical visits
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	❖ Data specifically for study purpose ❖ Framingham Heart Study ❖ Cardiovascular Health Study ❖ Data intended for other studies ❖ Nurses' Health Study ❖ Some registries ❖ Traditional Clinical Trials	❖ Clinical documentation ❖ Electronic health records ❖ Wearable devices ❖ Administrative ❖ Claims data ❖ Geocoding/census

Some thoughts on data from RWD Sources*

- 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 Physicians

*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
*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

- "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

- 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

- 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 and will be discussed under concordance

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

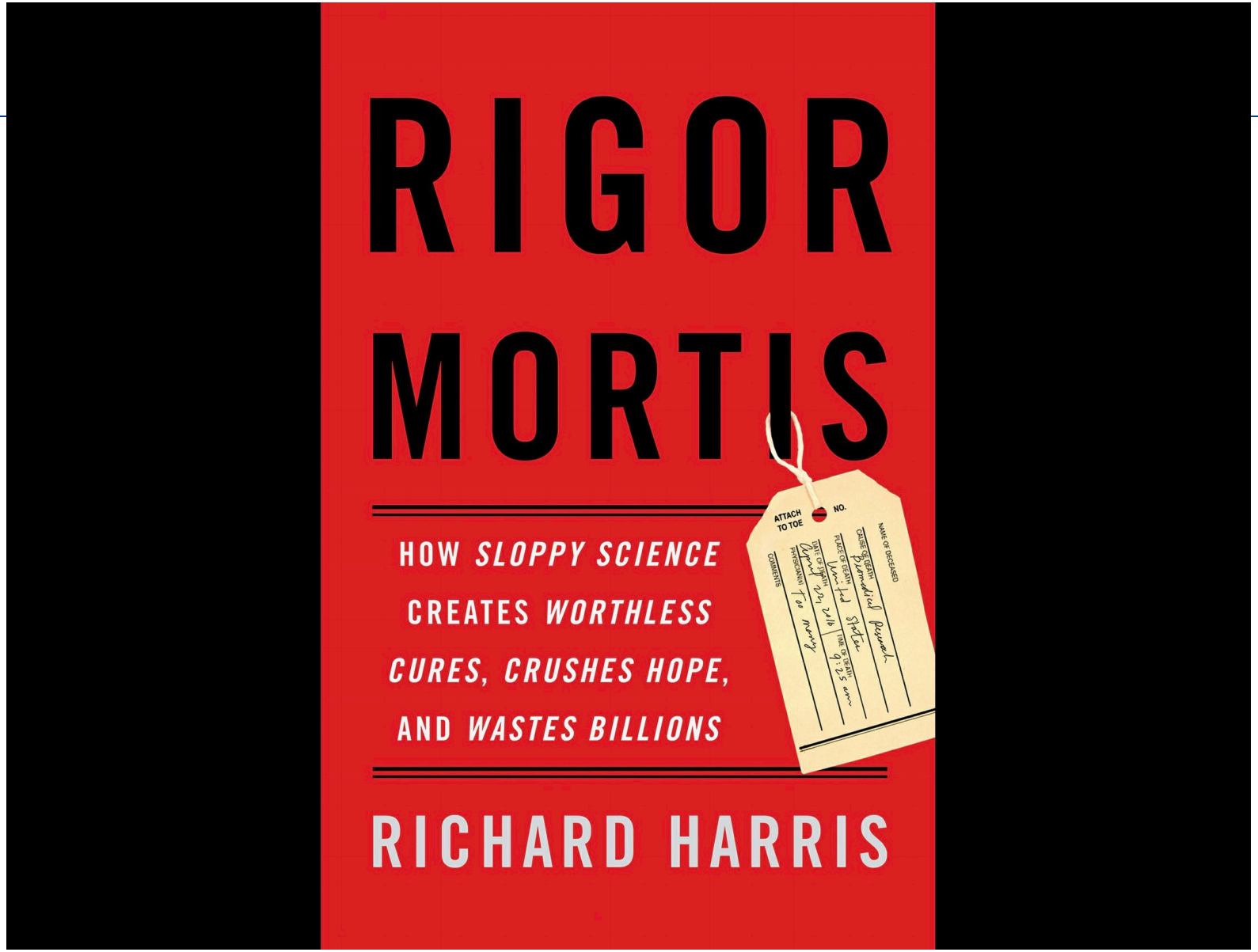
- Because RWD studies generally rely on health information that is extracted an EHR system, they are vulnerable to incomplete information due to data latency as well as data availability.
- Data latency is an issue because, while information is uploaded quickly to billing systems, clinical data may be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

Data Concordance (or lack thereof)

- If RWD is augmented by PRH, the level of concordance between the data reported by the patient and that entered in the EHR is important for ascertainment of events.
- Where the structure of the data element does not align perfectly, it may be possible to map one to the other (e.g. cigarettes per day vs packs per week)
- Though some types of data will require choosing one source or another, in other cases the sources may be combined. As discussed in data gaps section above.
- To assess if the patient has a given diagnosis or procedure, a combination of EHR data and the patient's memory may represent the best triangulation of ground truth.

Concordance

- Handling discordant data is the specific use case and the relative importance of sensitivity versus specificity for an outcome.
- If one is looking at inclusion criteria for a very rare condition, it may be best to err on the side of accepting false positives in order to cast a wide net.
- If one intends to perform a case-control analysis, one may want to be very certain that patients designated as cases are indeed true cases.


RIGOR MORTIS
HOW SLOPPY SCIENCE CREATES WORTHLESS CURES, CRUSHES HOPE, AND WASTES BILLIONS
RICHARD HARRIS
ATTACH TO TOE
NO.
NAME OF DECEASED
CAUSE OF DEATH
PLACE OF DEATH
DATE OF DEATH
TIME OF DEATH
PHYSICIAN
COMMENTS

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

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.

Nonrandomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of "real-world evidence" about the efficacy and safety of new and existing treatments.[1-3] For drugs or procedures that are already being used widely, such observational studies may involve exposure of large numbers of patients. Consequently, they have the potential to detect rare adverse effects that cannot plausibly be attributed to bias, generally because the relative risk is large (e.g., Reye's syndrome associated with the use of aspirin, or rhabdomyolysis as- safety and efficacy because the potential biases with respect to both can be appreciable. For example, the treatment that is being assessed may well have been provided more or less often to patients who had an increased or decreased risk of various health outcomes. Indeed, that is what would be expected in medical practice, since both the severity of the disease being treated and the presence of other conditions may well affect the choice of treatment (often in ways that cannot be reliably quantified). Even when associations of various health outcomes with a particular treatment remain statistically significant after adjust-

n engl j med 382;7 nejm.org February 13, 2020

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

“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 Landry MD, Oxford University, UK

Principle Investigator, RECOVERY COVID-19 Trial

Pragmatic Clinical Trials Using RWD

- 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

Why the interest in Pragmatic Clinical Trials?

- Healthcare decision makers are searching for more clinically-effective treatments and cost-effective healthcare solutions for their budgets.
  - Access to real patient outcomes vs. current options
  - Evidence of real world effectiveness from robust data sources
  - These data are primarily from EHR's and Claims data
- To employ RWD/use of pragmatic trials one needs:
  - Assurance RWD / PCT evidence is founded on sound science
  - Adequate RWD / PCT research infrastructure
  - Understanding of RWD among healthcare decision makers
- The hope is they will be easier to run and therefore less expense

A Little More History

- 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

Pragmatic Trial Considerations

- The *questions* should be for real world and "pragmatic" real world use and inference
- "Investigator" vs GP
  - Is patient recruitment faster and easier?
  - What is the research role of the HealthCare Practitioner in a PCT?
- Is it less expensive?
  - In total probably but per information unit unclear
  - Data management vs healthcare informatics
  - Could also teach us how to make "classic" RCTs more efficient
- Is the approach useful for safety studies?
- Is the approach useful for unapproved drugs?

Importance of Question before data

Simple Definition of Pragmatic Trials

"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

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

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)

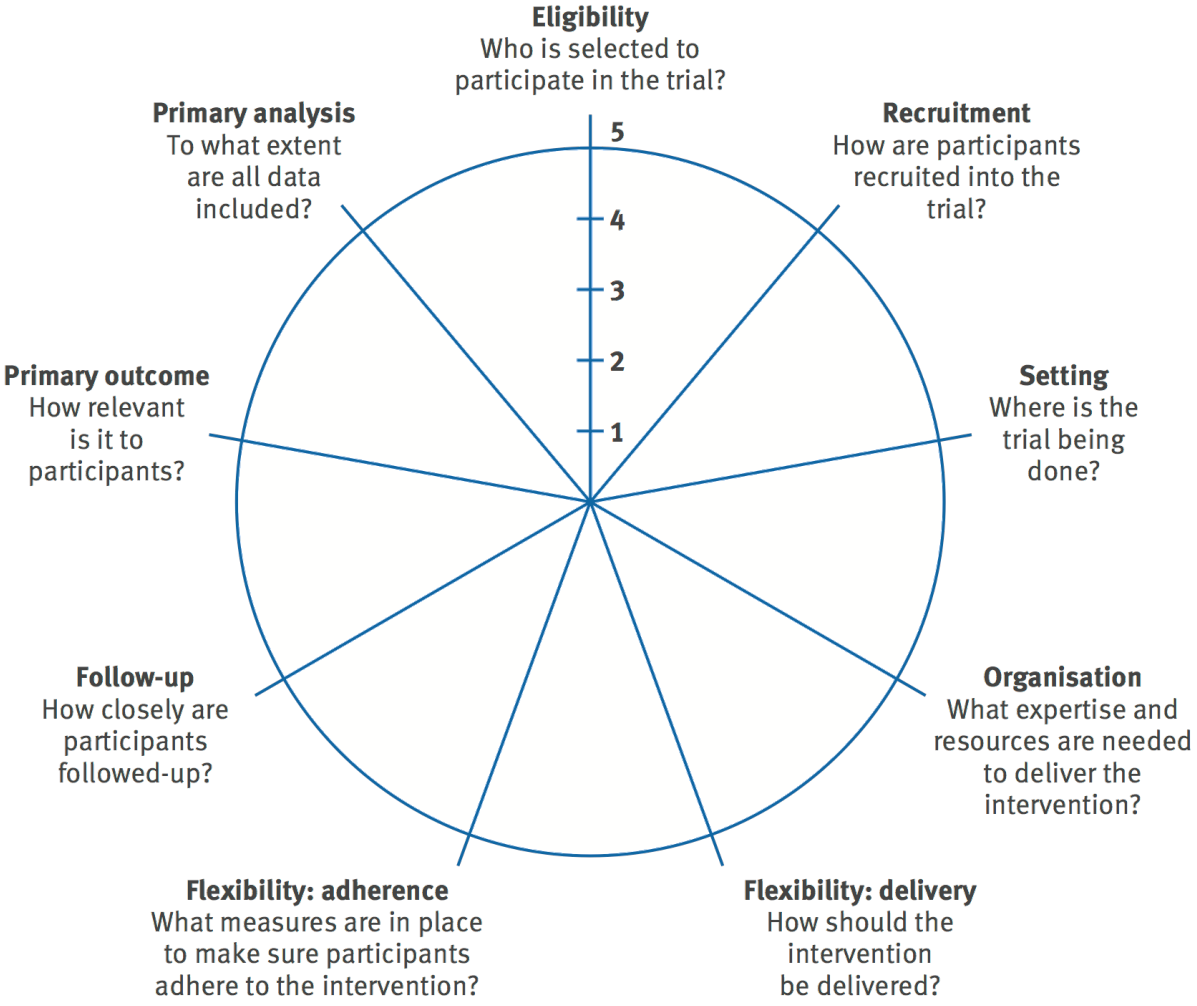


Table 1 Ways that randomized controlled trials (RCTs) and PCTs can differ

Classic RCT	Criterion	P"R"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*

- "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
- 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

Salford Lung Study Ambition

- Study as near to “real world” as possible using a pre-license medicine
- 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

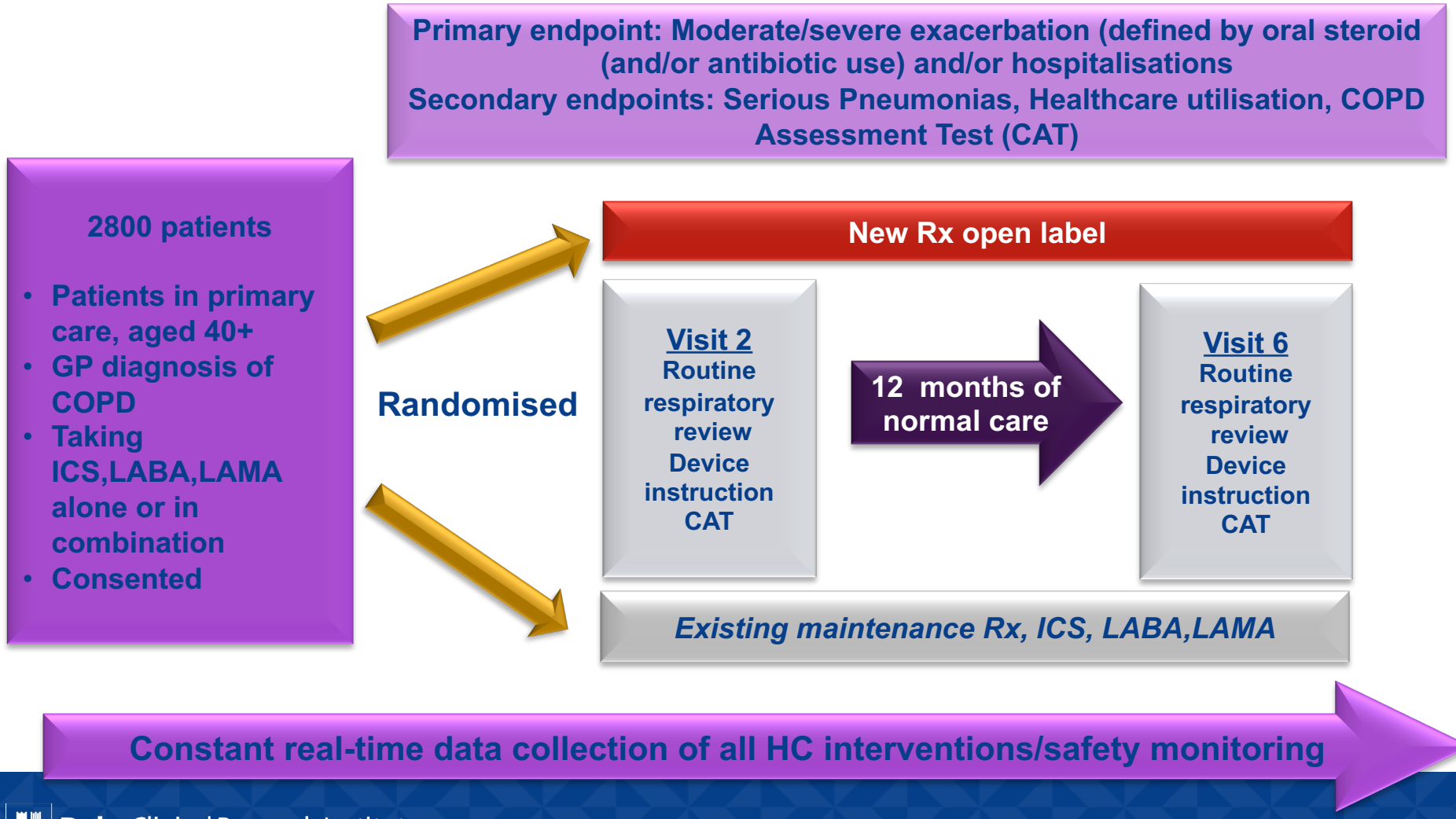
Running a PCT in Salford, UK: Study of an experimental drug in Asthma and COPD*

- 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 Healthcare Infrastructure: More than just a database

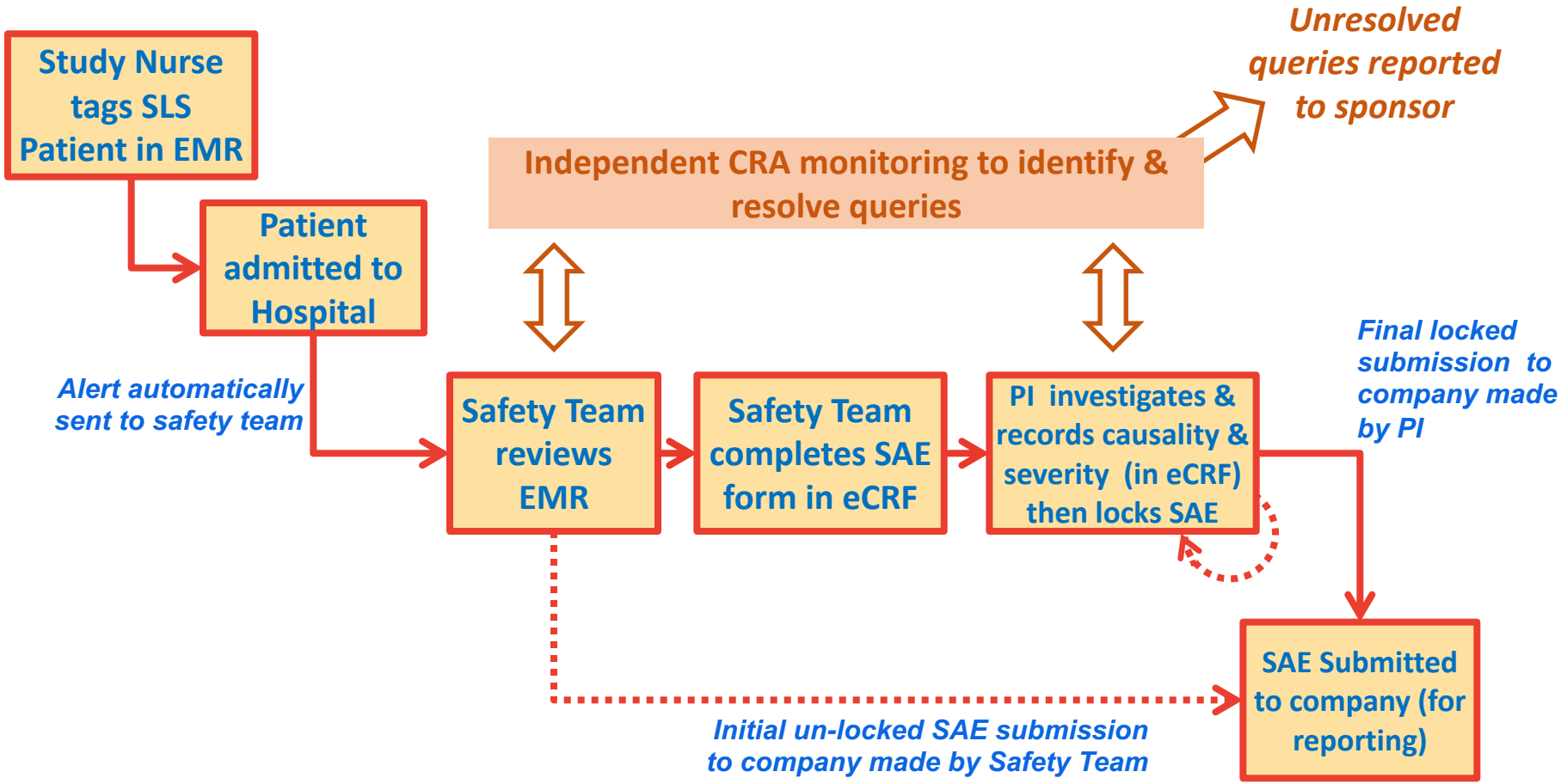
Study outline for COPD



Key Facts on COPD Study
(Findings similar for Asthma study)

- 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



Challenges and Learning's

- Importance of partnership
  - Industry/ NHS / University / EHR provider
- Working with research-naive “investigators”
- Recruitment and Consent has some challenges
- Data journey:
  - from EHR to Research Dataset (eCRF or not?)
  - Collaboration with EHR provider to implement changes
- Applying GCP
- Benefits and effects of Safety Monitoring

Summary: SLS

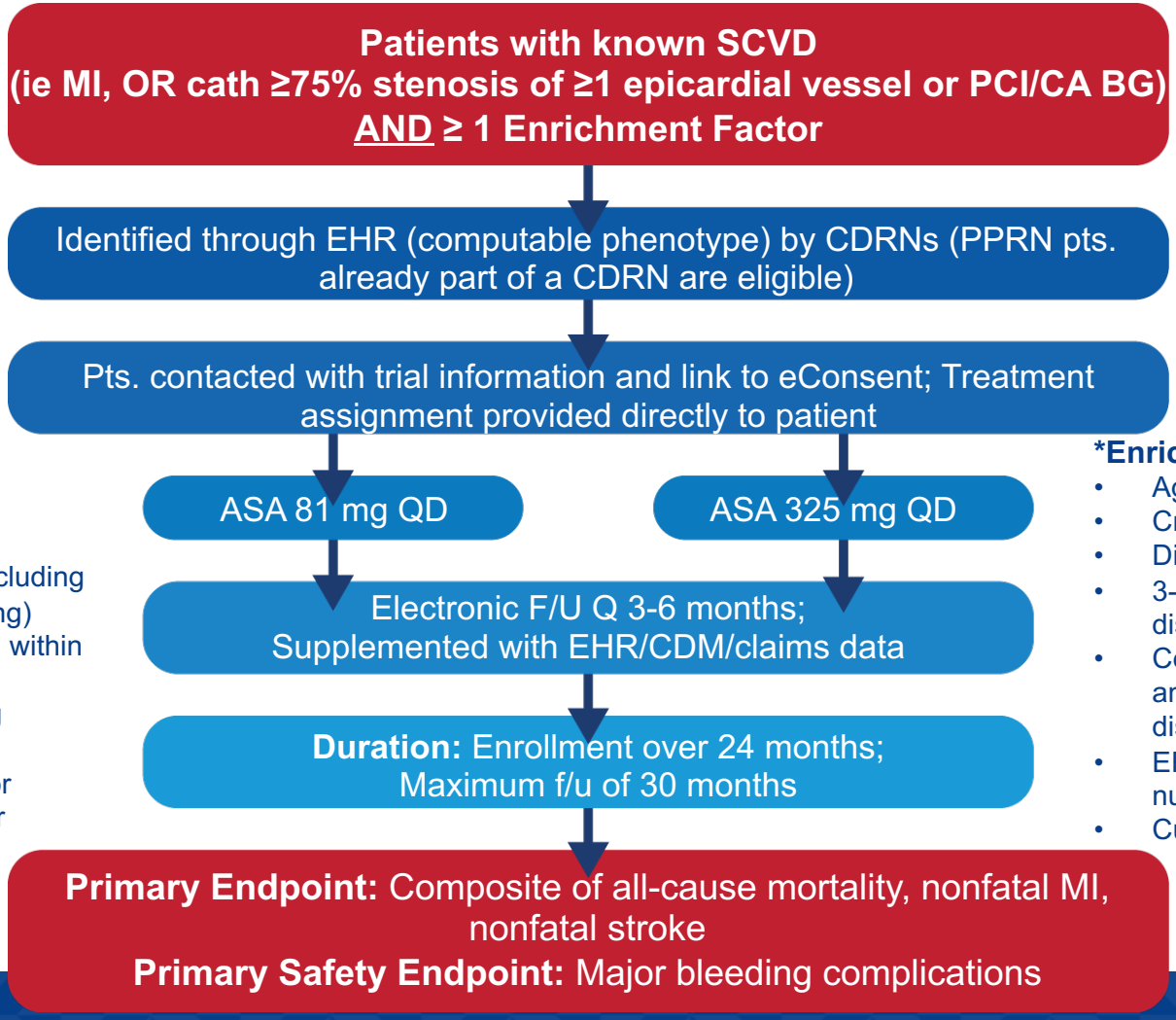
- The Salford Lung Study was the first of its type
- Maintained scientific rigor
  - randomised
  - active control
  - robust primary endpoint
- It was an enormous logistical effort and in a specialized setting
- Monitoring/reporting of adverse events required by regulators may interfere with clinical practice and affect the *pragmaticism*/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

*theaspirinstudy.org

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

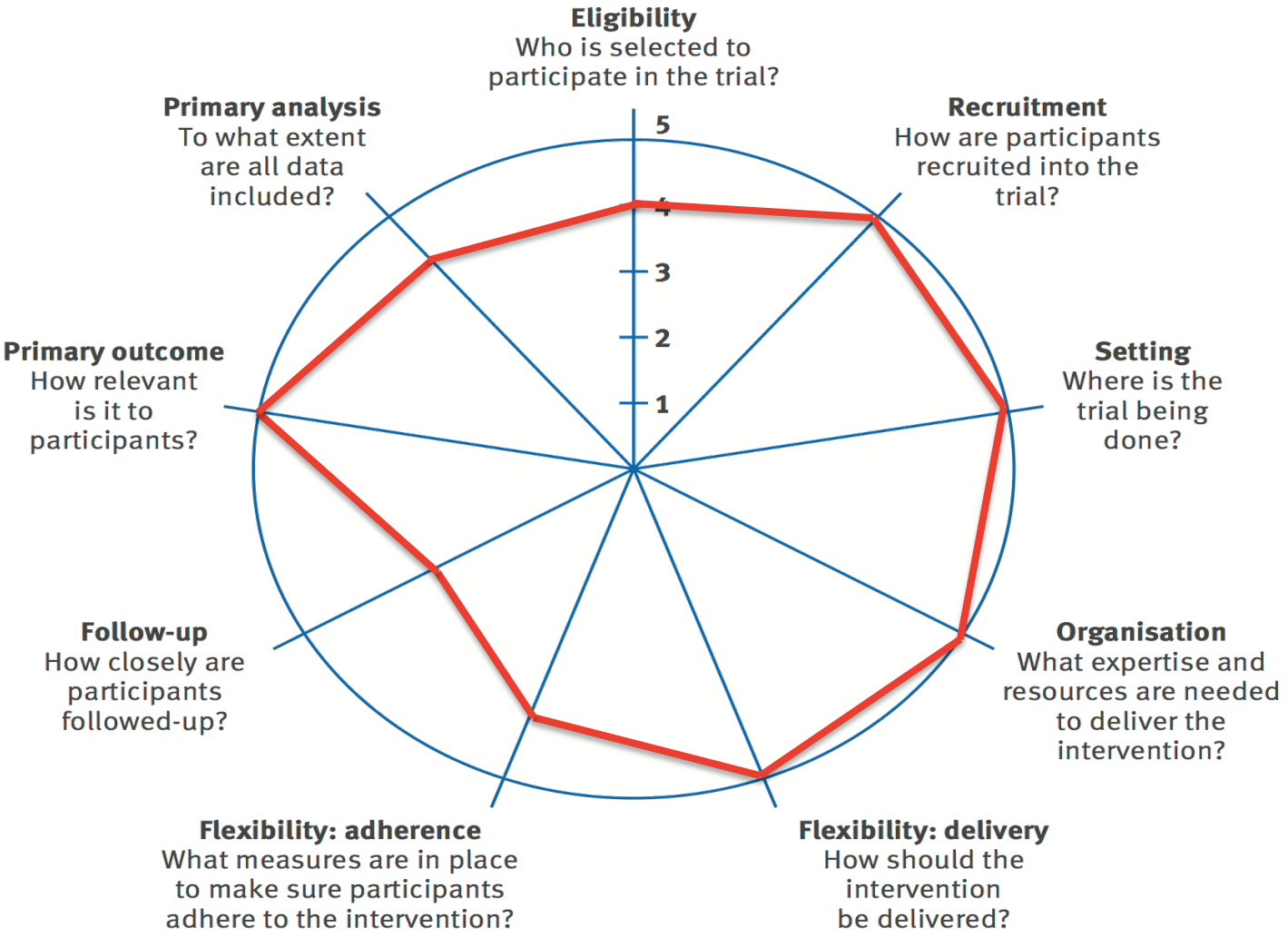
***Enrichment factors**

- 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

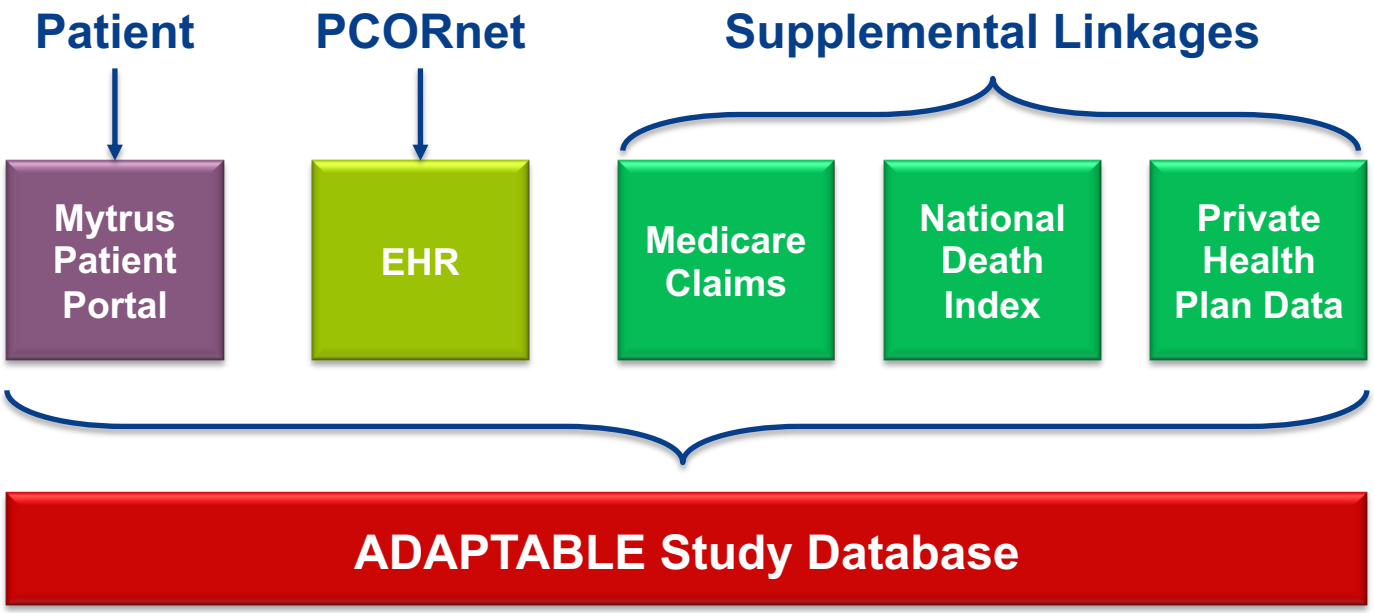
ADAPTABLE vs. A Classic Randomized Controlled Trial (RCT)

ADAPTABLE		RCT
Simple, inclusive, minimum risk, focus on population representation	**Eligibility**	Selective, focus on populations in more ideal circumstances
Heterogeneous - representative of real world treatment population	**Study Population**	Intentionally homogeneous to maximise treatment effect
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.	**Recruitment**	Potential participants identified and approached by their doctors or nurses from participating clinics
Participants randomize themselves, unblinded	**Randomization**	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
Participant Self-reported data	Instant	None
Electronic Records		
eHR from PCORnet DataMart	Quarterly	3 – 6 months
Medicare Claims Data	Annual	1 – 12 months
National Death Index	Annual	1 – 12 months
Private Health Plan Data	End of study?	

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

Endpoint Ascertainment

- 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

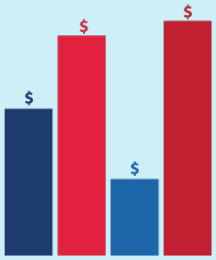
Endpoint Validation

- Are endpoints identified in eHR comparable to clinical endpoints confirmed by traditional adjudication process?
  - Events of interest: MI, stroke, major bleeding
  - Assess agreement: True Positive, False Positive, PPV
  - Provide insights on
    - Accuracy of coding algorithms
    - Data curation process
- Absence of events from eHR is not verified
    - Low event rate
    - No estimate of false negative rate of events

Handling Disagreement Across Different Data Sources

Patient Reported Events	EHR/PCORnet CDM: NO	EHR/PCORnet CDM: YES
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

Missing Follow-up

DCRI Call Center

Contact with the site

Patient Finder

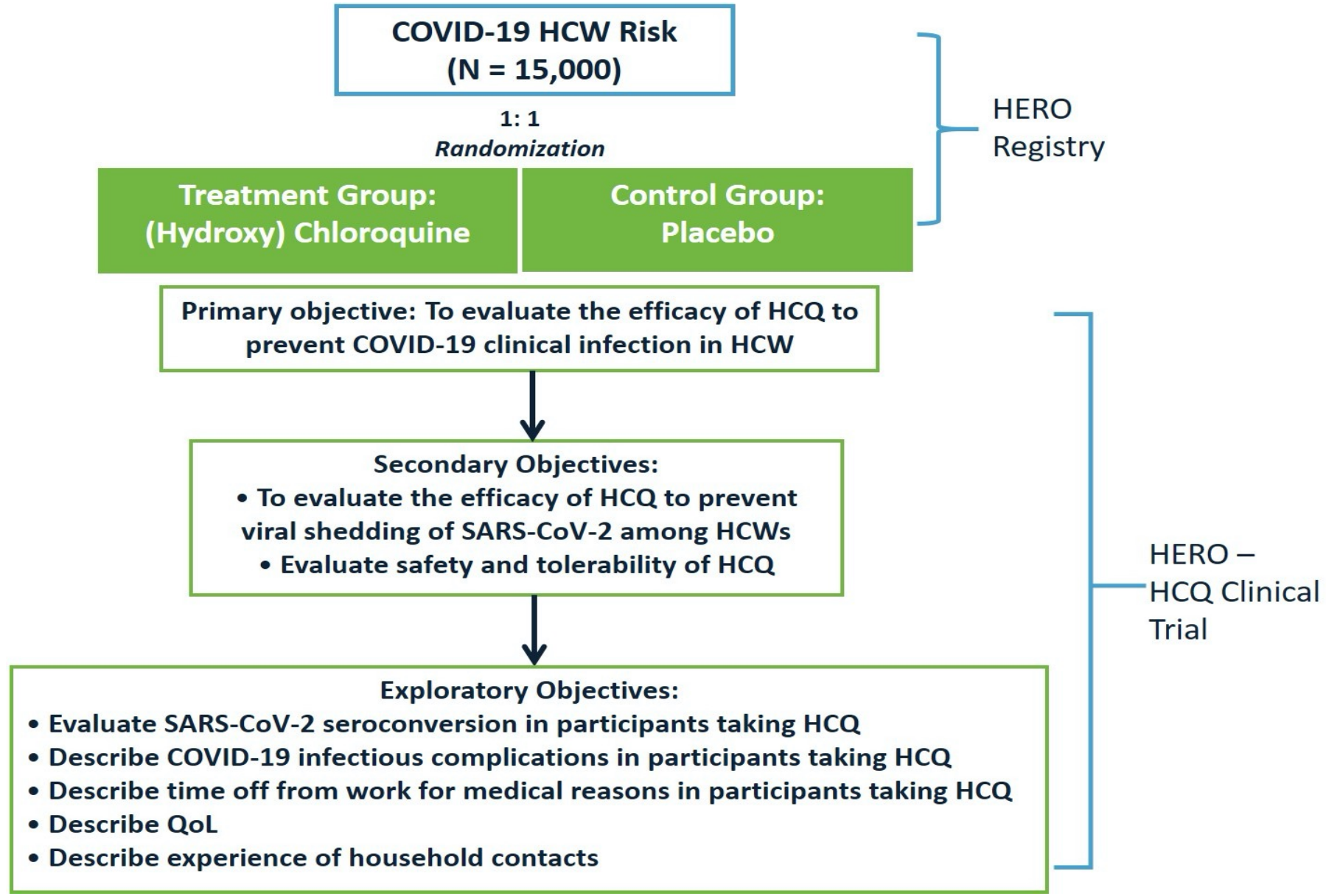
Social Security Death Index

Summary: ADAPTABLE

- ADAPTABLE was the first pragmatic mega-trial in the world designed to evaluate aspirin dose with 15,000 participants
- Attempts to mimic the real-world patient experience of a patient with heart disease
- Recruitment was a challenge
- Collects data through different sources and employs a multi-faceted approach to capture outcomes
- Maintained scientific rigor
  - randomised
  - active control
  - robust primary endpoint
- ADAPTABLE will tell us a great deal about the utility of the approach to perform "mega trials" in a very different way.

The HERO COVID-19 Program

- HERO COVID-19 Program: HERO-PCORI https://heroesresearch.org/
- The HERO program consists of two parts, a national registry and a randomized double-blind clinical trial run under a US IND.
  - The registry will seek to rapidly identify and enroll a large community of healthcare workers at risk for COVID-19 infection.
  - The clinical trial (HERO-HCQ), will randomize healthcare workers to 1 HCQ or placebo looking at the rate of infection
  - The study also will explore how well the drug can prevent further spread of the virus to others.
- 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
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
HERO –
HCQ Clinical
Trial

HERO Design and Operational Features

- 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

Summary: HERO

- HERO was designed and implemented rapidly in a time of many unknowns about the
- Attempts to mimic the real-world patient experience of a healthy participant with potential exposure to the COVID-19 virus
- Recruitment was a challenge for several reasons
- Collected data through different sources and employed a multi-faceted approach
- Maintained scientific rigor
  - randomised
  - blinded placebo control
  - robust primary endpoint
- HERO will tell us a great deal about the utility of the approach to launch trials rapidly in a time of urgency

Data and Safety Monitoring

- 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

- 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.
  - Recruitment was a challenge in all of the examples given
- Cost? For now, the focus should be on "how" and not "how much".
- Data management vs healthcare informatics- cost shifting.
- The approach can be useful for safety studies but there needs to be agreement on tradeoffs in event ascertainment.
- 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

- 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
- 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
- Develop an RWD / PCT research infrastructure
- Performing a pragmatic (RWD) trial is not be a euphemism for "sloppy" or "easy to conduct": This applies to the question and the conduct

Questions and discussion