

What is driving the desire for Pragmatic Clinical Trials?

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Duke Clinical Research Institute

FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE

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- Equity Interest: GlaxoSmithKline



Pragmatic Clinical Trials*

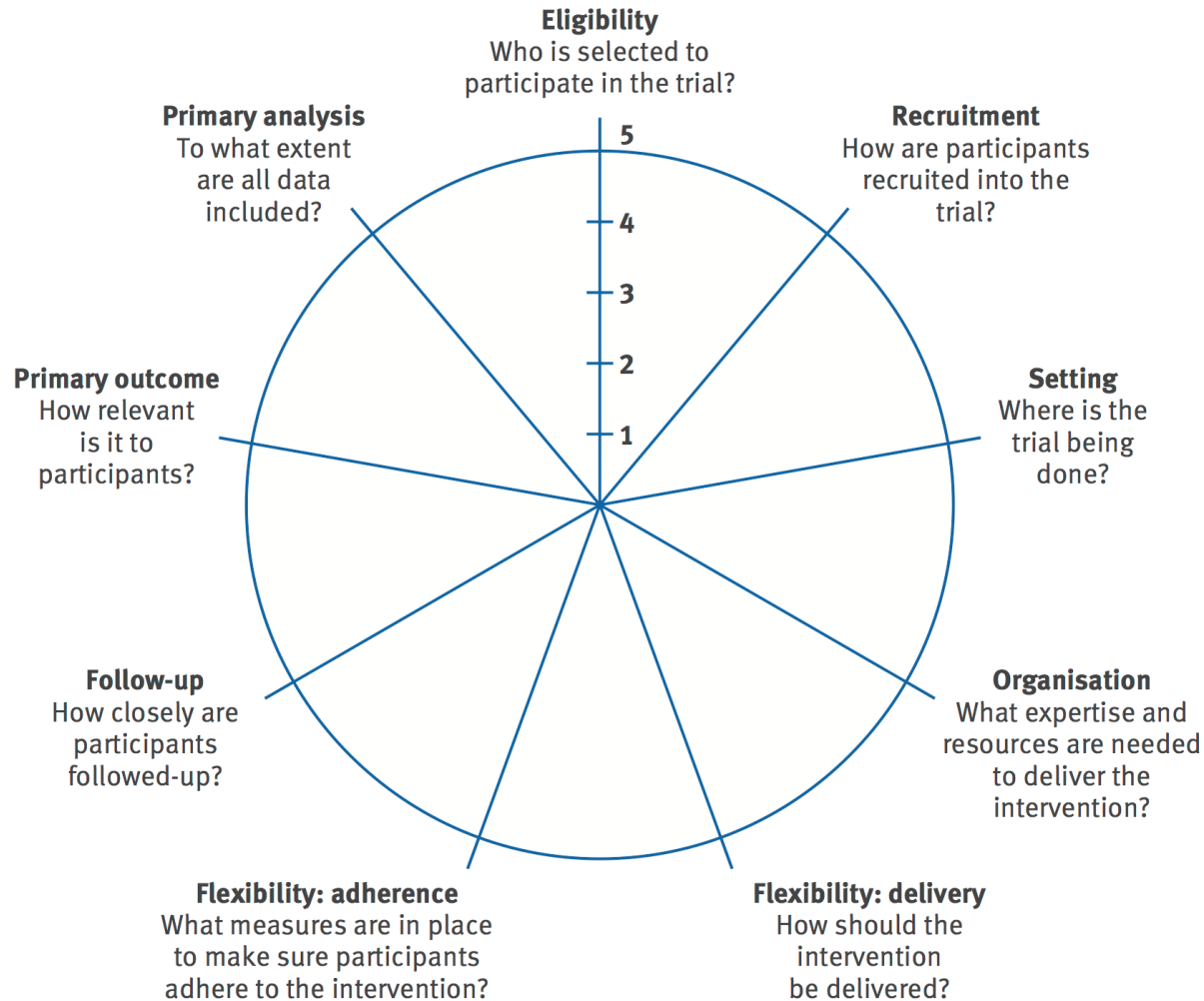
- Think real world and more patient focused.
- Think a different hypothesis: Effectiveness vs efficacy (and both are important)
- Think Treatment strategy
- Think true meaning of intention to treat
- Patient level randomization vs cluster randomized trials
- Two Examples- one of an unapproved therapy and one of a commonly used therapy

* 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., Zwarenstein, M., Sullivan, F., Donnan, P., and Treweek, S., *Making clinical trials more relevant: improving and validating the PRECIS tool for matching trial design decisions to trial purpose*. Trials, 2013. **14**: p. 115.
3. 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



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*)



Designing a randomised pragmatic clinical trial

Ways that Randomised Controlled Trials (RCTs) and PCTs can differ

Classic RCT

Intentionally homogeneous to maximise treatment effect

Randomisation and blinding

Clinical measures, intermediate endpoints, composite endpoints, clinical outcomes

Protocol defines the level and timing of testing.
Physicians blinded to data

Fixed standard of care or placebo

Conducted only by investigators with proven track record

Visit schedule and treatment pathway defined in the protocol

Patients wishing to change treatment must withdraw from the study

Compliance is monitored closely

Close monitoring of adherence

Intent to treat, per-protocol and completers

Eligibility Criteria

Randomisation and blinding

Endpoints

Tests and diagnostics

Comparison intervention

Practitioner expertise

Follow up

Continuity

Participant compliance

Adherence to study protocol

Analysis

P"R"CT

Heterogeneous - representative of normal treatment population

Randomisation and rarely blinding

Clinical outcomes, PROs, QoL, resource use

Measured according to standard practice

Standard clinical practice

Employment of a variety of practitioners with differing expertise and experience

Visits at the discretion of physician and patient.

Standard clinical practice – switching therapy according to patient needs

Passive monitoring of patient compliance

Passive monitoring of practitioner adherence

All patients included



What is driving the desire for Pragmatic Clinical Trials?

- Healthcare decision makers are searching for more clinically-effective treatments for patients and cost-effective healthcare solutions for their budgets.
- They need to have access to data which increases their confidence that new treatments will deliver better outcomes than current options,... AND they need to consider evidence of real world effectiveness from robust alternatives sources
- RWE and early use of pragmatic trials can help them to do this, but first there is a need for the research community to:
 - Ensure RWE / PCT evidence is founded on high-quality science
 - Develop a RWE / PCT research infrastructure
 - Increase understanding of RWE among healthcare decision makers
- The hope they will be easier to run and therefore less expensive



Pragmatic Trial Considerations

- By definition the questions should be real world and “pragmatic” real world use
- “Investigator” vs GP
 - Is patient recruitment really faster and easier?
 - What is the research role of the HCP in a PCT?
- Is it really 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?



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 recruitment / resource
- 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)
- Utilising 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 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

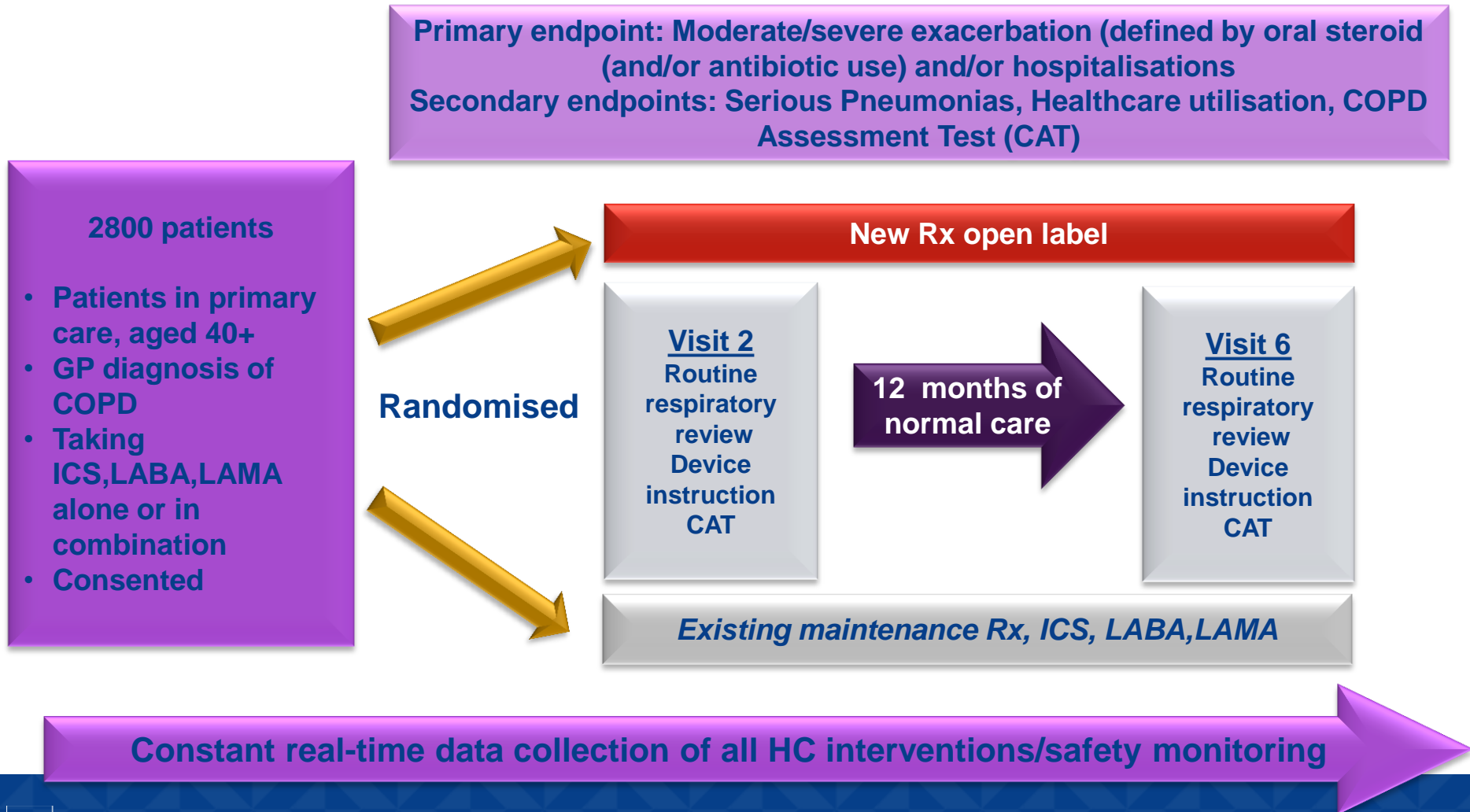
- Interventional
- Randomised
- Controlled



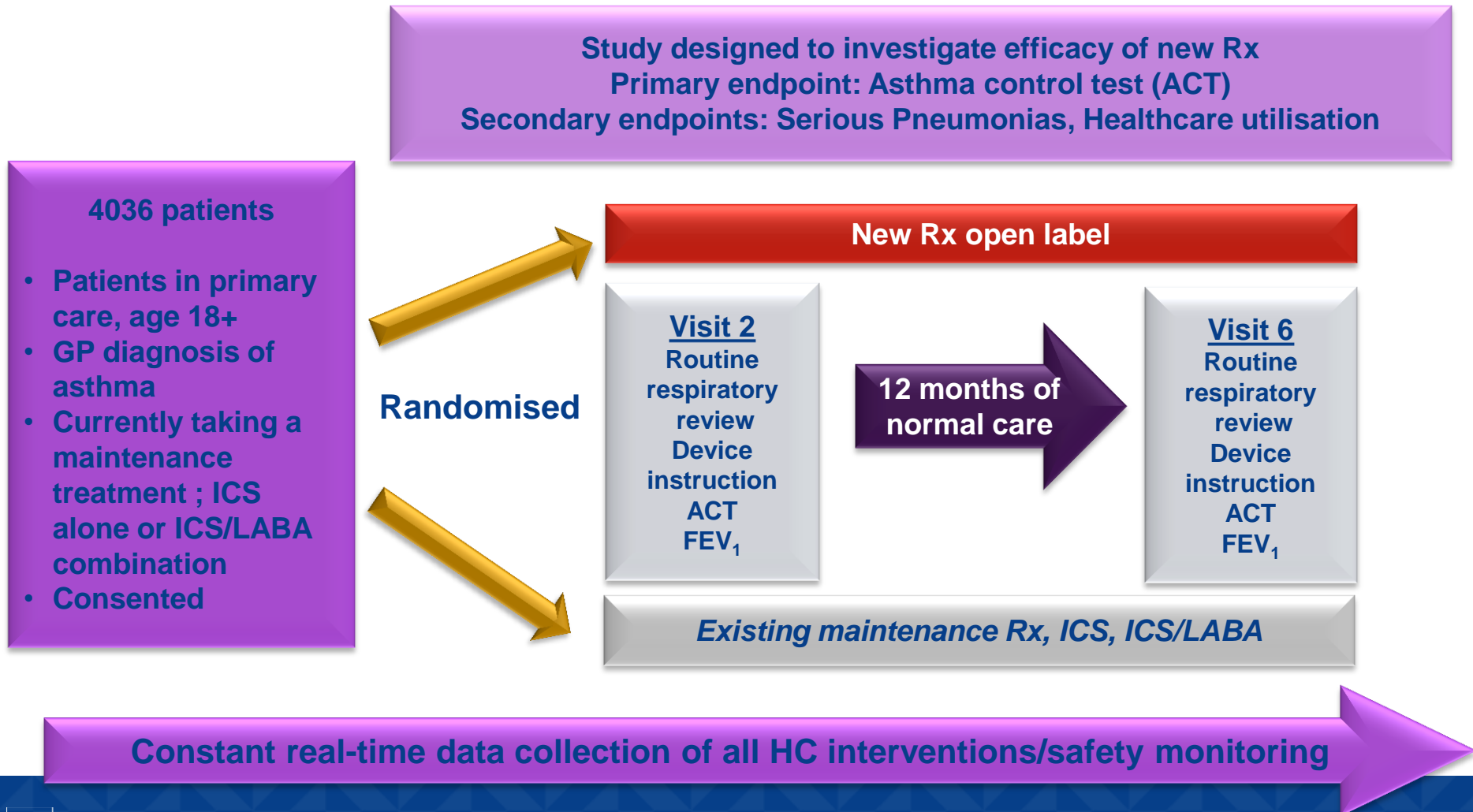
Much more than just a database



Study outline for COPD



Study outline for asthma



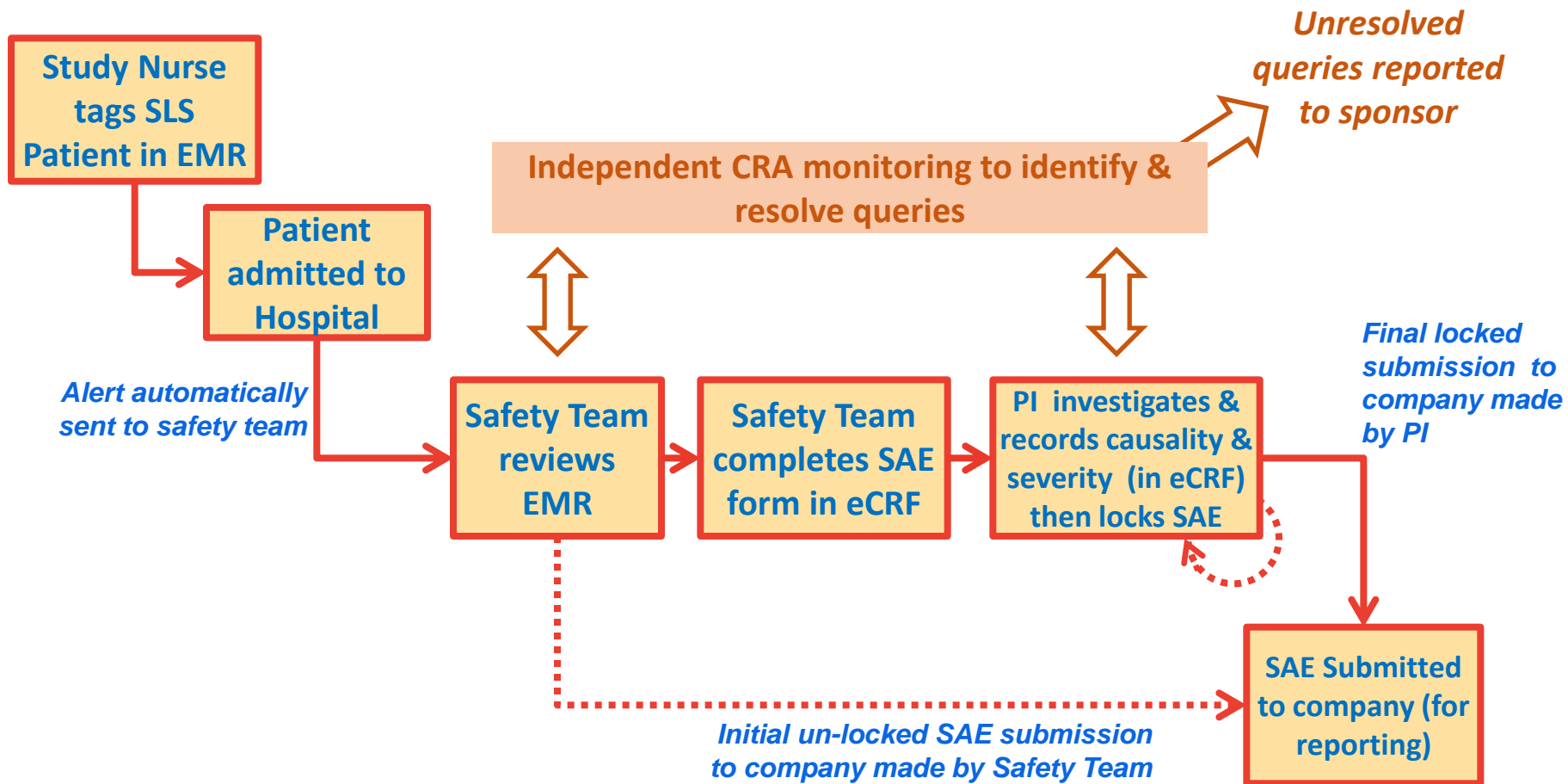
Key Facts on COPD Study

(Findings similar for Asthma study)

- Setting up, training 203 “sites”
 - 120 PIs
 - >100 Pharmacies Trained
- 40,000 letters sent
- 3,500 patients seen in office
- 2,800 patients recruited
- Over 3000 site staff trained in ICH GCP
- 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



Strengths and Weaknesses of study design

Strengths

- Subjects randomised to treatment arms
- Broad inclusion criteria
 - More representative study population
- Minimal interference with “normal” care
- More representative of “real world”
 - external validity
- Access to full EMR
 - breadth and depth of data
- Ability to collect utilization data directly
- Breadth and depth of prescribing data available
 - prescribed, dispensed and collected

Weaknesses

- Open label design
 - risk of bias?
- Salford population may not represent other COPD and asthma populations
- Challenge of recruiting sufficient subjects
 - not easy to open new sites
- Subjects lost if moved out of area
 - unable to guarantee safety monitoring
- Volume and nature of SAEs
- Support needed for inexperienced site staff
 - GP and pharmacy sites



Challenges and Learning's

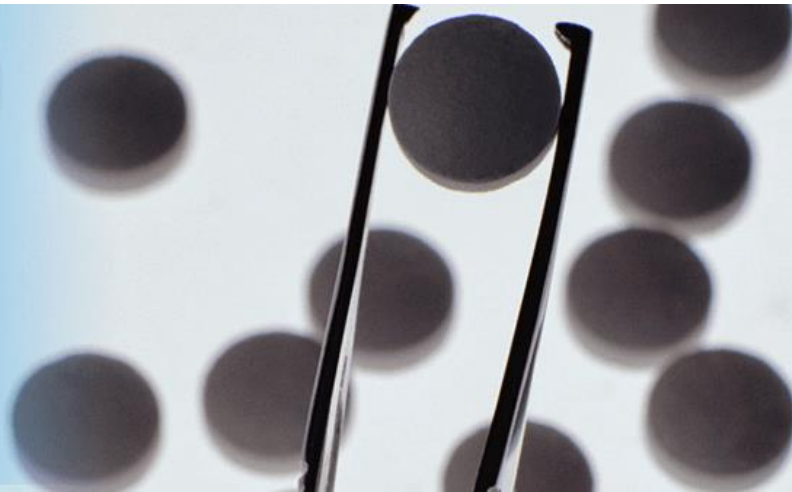
- Importance of partnership
 - Industry/ NHS / University / EHR provider
- Working with research-naïve “investigators”
- Recruitment and Consent has some challenges
- Data journey:
 - from EHR to Research Dataset (eCRF or not?)
 - Collaboration with EHR provider to implement changes
- Applying GCP
-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



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.

[*theaspirinstudy.org](http://theaspirinstudy.org)



Duke Clinical Research Institute



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.



“The benefits of aspirin for the treatment of CVD are well established, but the best dose of aspirin is uncertain and is not specified by clinical practice guidelines.”



Matthew Roe, MD, MHS | Adaptable Study Co-PI | Duke Clinical Research Institute

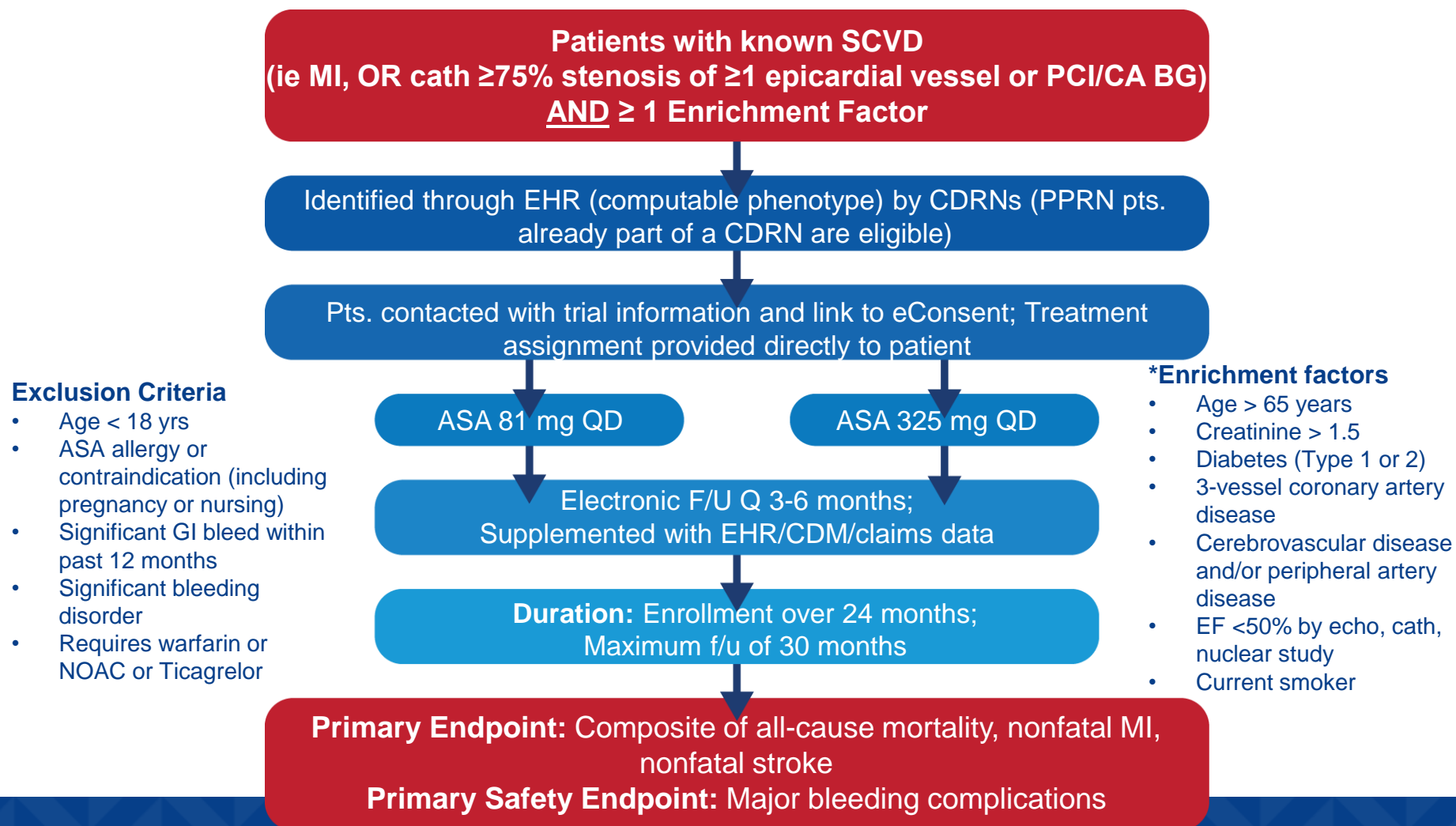


Patient Focused

- Patient focused ICF
- Patient focused randomization
- Patient focused data collection
- Patient participation in design and execution
 - Two patient representatives are voting members of the IDMC



Study Design




Adaptable

The Aspirin Study


Watch

Read

15 MIN.


Answer

5 MIN.


Join

3 MIN.


Inform

5 MIN.

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.

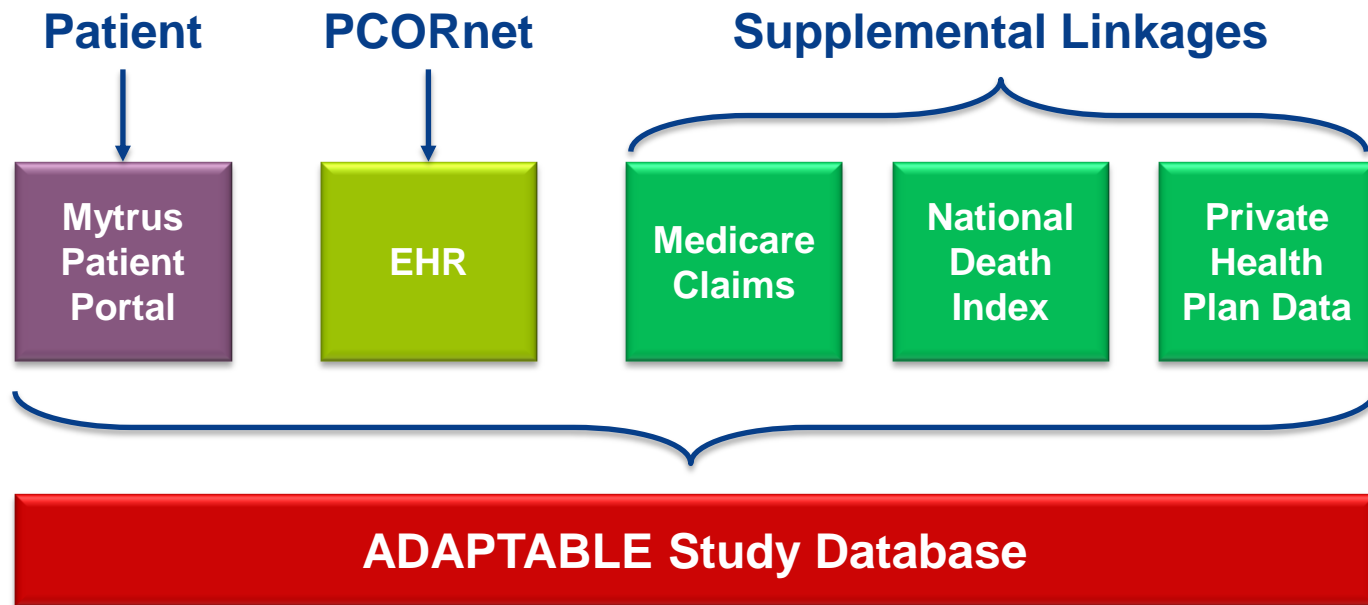
Even though both doses of aspirin are widely used, no one knows which is better. Regular aspirin has a higher risk of bleeding than low-dose aspirin. But no one knows if low-dose aspirin is both safer and works just as well as regular aspirin to prevent heart and blood vessel problems.

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.

We expect 20,000 patients **Please scroll to see all content** will take part in ADAPTABLE

ClinicalTrials.gov: NCT02697916

Information Flow



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

Summary 1

- The Salford Lung Study is the first of its type in the world
- Maintained scientific rigor
 - randomised
 - active control
 - robust primary endpoint
- It was an enormous logistical effort
- And.....
- It will offer important information for clinicians, healthcare decision makers and most especially patients
- And provides valuable information about how to conduct real-world effectiveness studies in the future



Summary 2

- ADAPTABLE addresses an important medical question
- ADAPTABLE will tell us a great deal about the utility of the approach to perform “mega trials” in a very different way.
- A very patient focused design and execution
- Data acquisition and ascertainment will teach us a great deal about the value and issues with this approach in the future.



Summary 3

1. PCTs answer questions that are more real world effectiveness. Should be viewed as a supplement to and not a replacement for “classic” RCT’s.
2. Two Examples showed the spectrum “pragmatism”.
3. “Investigator” vs GP: Has an impact on recruitment and event ascertainment.
4. Is it really less expensive? Time will tell and in short term the focus should be on “how” and not “how much”.
5. Data management vs healthcare informatics- resource and cost shifting. Lessons learned should be of value to all clinical trial conduct.
6. The approach can be useful for safety studies but there needs to be agreement on tradeoffs in event ascertainment.
7. The approach can be useful for unapproved drugs but additional infrastructure is needed to meet regulatory reporting requirements.
8. In the end these trials may prove most valuable to the ultimate customer- The patient



Questions and discussion

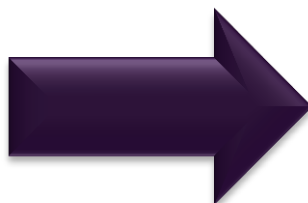


Efficacy to effectiveness

**Gold standard science
to answer specific questions**

Efficacy Trials

Double blind
Double dummy
Strict inclusion criteria
Exclusions
Adherence encouraged
Frequent reviews
Drugs provided
Traditional Efficacy
Endpoints



**Evidence representing
medicines in the real world**

Effectiveness Trials

Open label?
Broad population
All comers
Set in normal care
No extra review
Drugs prescribed and
collected in usual way
Health Outcome and
Utilisation Endpoints

i.e. Real life



Challenges and Solutions

- How to recruit patients?
 - “all comers”
 - broad inclusion criteria
 - pragmatic diagnostic criteria
 - few exclusions
 - How to ensure “normal” care of patients during the study?
 - minimal study procedures
 - normal prescribing and dispensing practices
 - How to monitor patients without carrying out frequent reviews?
 - minimize “Hawthorne” effect
 - ensure patient safety
 - ensure robust collection of end points
- ✓ Recruit patients through primary care
 - ✓ Study drug accessed through community pharmacy network
 - ✓ No additional review
 - ✓ No change to “care as usual”
 - ✓ Integrated electronic patient record (EMR) with real-time access ensures that data is complete wherever and whenever patient accesses healthcare

