The Pragmatic Trial in Development: The Salford Lung Study(s)

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Conflict of Interest Statement –

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Key Topics

- What is driving the need for Pragmatic Clinical Trials (PCTs)?
- Recap: what's different about PCTs?
- Running a PCT in Salford, UK
- Summary, Challenges and Learning's

Why the Drive 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

Designing a randomized pragmatic clinical trial (PCT)

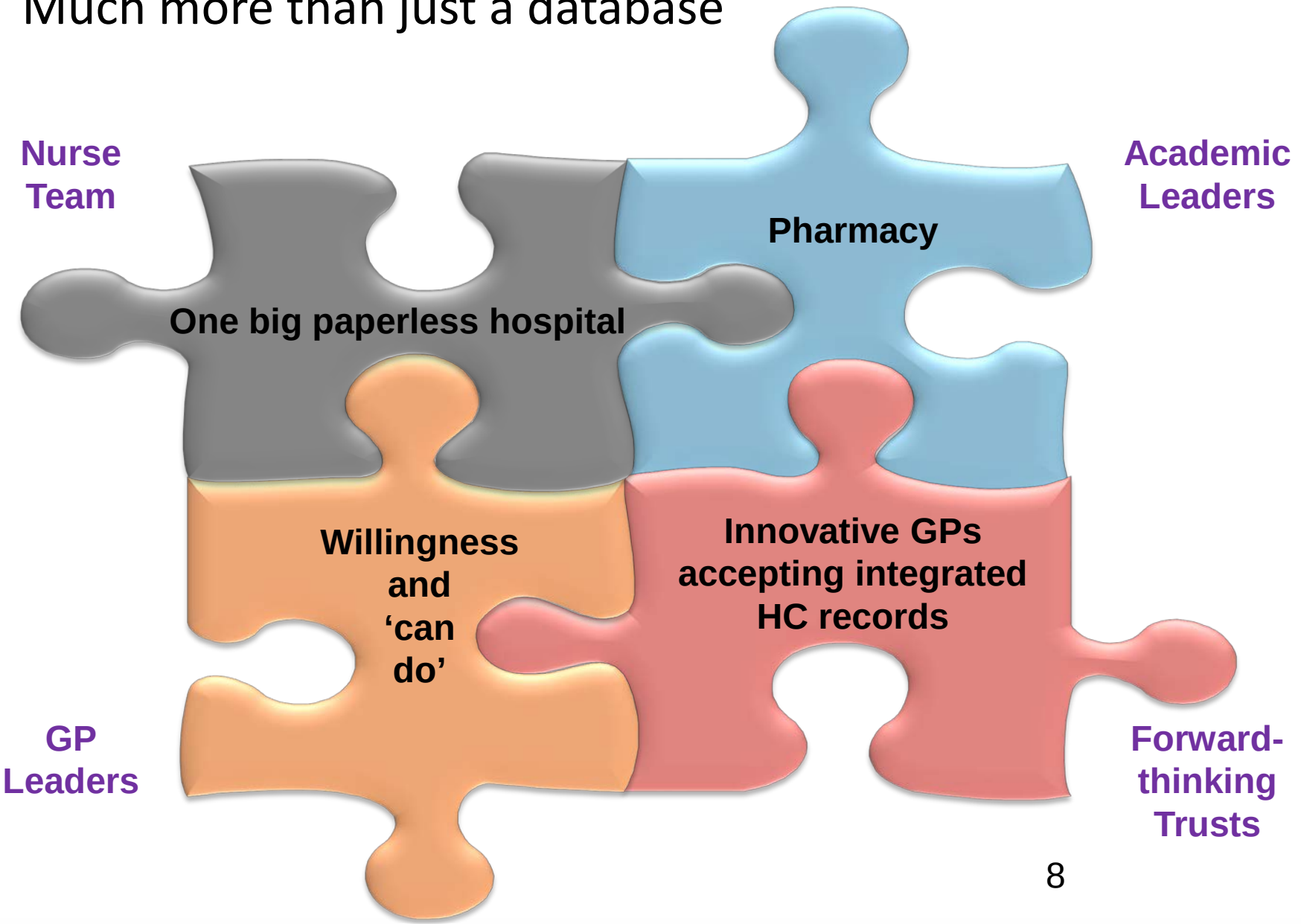
RCT		PCT
Intentionally homogeneous to maximise treatment effect	Eligibility Criteria	Heterogeneous - representative of normal treatment population
Randomisation and blinding	Randomisation and blinding	Randomisation only
Clinical measures, intermediate endpoints, composite endpoints, clinical outcomes	Endpoints	Clinical outcomes, PFOs, QoL, resource use
Protocol defines the level and timing of testing. Physicians blinded to data	Tests and diagnostics	Measured according to standard practice
Fixed standard of care or placebo	Comparison intervention	Standard clinical practice
Conducted only by investigators with proven track record	Practitioner expertise	Employment of a variety of practitioners with differing expertise and experience
Visit schedule and treatment pathway defined in the protocol	Follow up	Most or all visits at the discretion of physician and patient.
Patients wishing to change treatment must withdraw from the study	Continuity	Standard clinical practice – switching therapy according to patient needs
Compliance is monitored closely – strategies are employed to maintain high levels of compliance	Participant compliance	Unobtrusive measurement of patient compliance with no strategies to maintain compliance
Close monitoring of adherence – strategies are employed to maintain high levels of adherence	Adherence to study protocol	Unobtrusive measurement of practitioner adherence with no strategies to improve adherence
Intent to treat, per-protocol and compliers	Analysis	All patients included

Salford Lung Study: 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

Much more than just a database



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

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

Study outline for asthma

Study designed to investigate efficacy of new Rx
Primary endpoint: Asthma control test (ACT)
Secondary endpoints: Serious Pneumonias, Healthcare utilisation

4036 patients

- **Patients in primary care, age 18+**
- **GP diagnosis of asthma**
- **Currently taking a maintenance treatment ; ICS alone or ICS/LABA combination**
- **Consented**

Randomised

New Rx open label

Visit 2
Routine respiratory review
Device instruction
ACT
FEV_1

12 months of normal care

Visit 6
Routine respiratory review
Device instruction
ACT
FEV_1

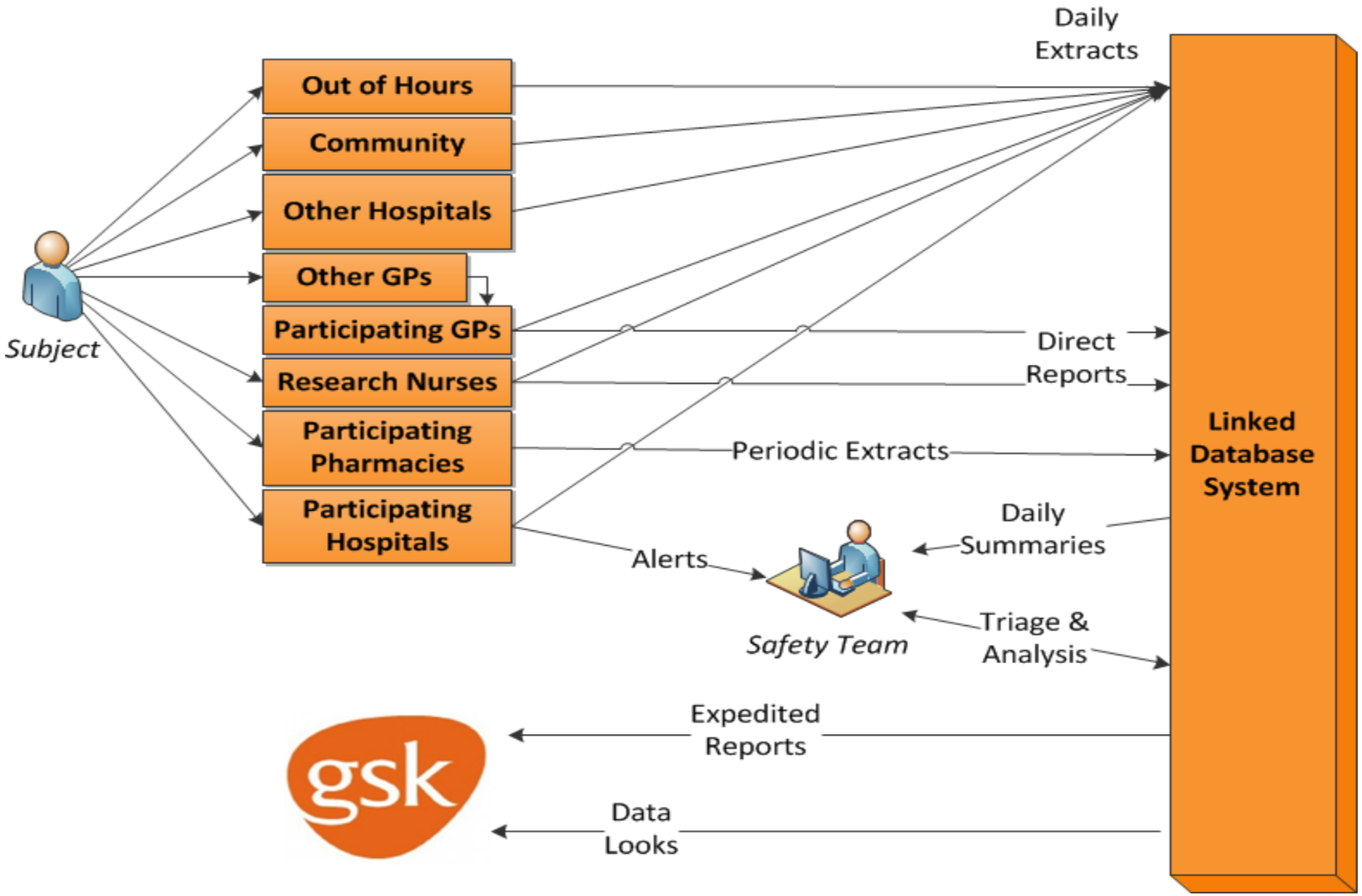
Existing maintenance Rx, ICS, ICS/LABA

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

Strengths and Weaknesses of study design

- 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 HRU data directly
- Breadth and depth of prescribing data available
  - prescribed, dispensed and collected
- 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 move out of area
  - unable to guarantee safety monitoring
- Volume and nature of SAEs
- Support needed for inexperienced site staff
  - GP and pharmacy sites

How the data were gathered



Large Interventional Asthma Study

- Setting up, training and green-lighting 203 sites
  - 120 PIs
  - 500+ contracts and addenda signed
  - >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

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 "high street" 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

Challenges and Learning's

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

Summary

- The Salford Lung Study is the first of its type in the world
- Maintained scientific rigor
  - o randomised
  - o active control
  - o robust primary endpoint
- It has, and continues to be an enormous logistical effort

- But.....
- It will offer important information for clinicians, healthcare decision makers and most especially patients
- And will provide valuable information about how to conduct real-world effectiveness studies in future