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

Frank W. Rockhold, PhD
Professor Biostatistics and Bioinformatics
Duke University School of Medicine

Cardiac Safety Research Consortium
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Frank W Rockhold, PhD

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

Much more than just a database

Pharmacy

Innovative GPs accepting integrated HC records

One big paperless hospital

Willingness and ‘can do’

Nurse Team

GP Leaders

Academic Leaders

Forward-thinking Trusts
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

- 2800 patients
  - Patients in primary care, aged 40+
  - GP diagnosis of COPD
  - Taking ICS, LABA, LAMA alone or in combination
  - Consented

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)

Randomised

Visit 2
- Routine respiratory review
- Device instruction
- CAT

Visit 6
- Routine respiratory review
- Device instruction
- CAT

12 months of normal care

New Rx open label

Existing maintenance Rx, ICS, LABA, LAMA

Constant real-time data collection of all HC interventions/safety monitoring
Study outline for asthma

- 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

- Visit 2
  - Routine respiratory review
  - Device instruction
  - ACT
  - FEV₁

- Visit 6
  - Routine respiratory review
  - Device instruction
  - ACT
  - FEV₁

- New Rx open label

- 12 months of normal care

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

- 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

Subject

Out of Hours
Community
Other Hospitals
Other GPs
Participating GPs
Research Nurses
Participating Pharmacies
Participating Hospitals

Linked Database System

Daily Extracts
Direct Reports
Periodic Extracts
Daily Summaries
Triage & Analysis
Expediting Reports
Data Looks

Safety Team
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
  - randomised
  - active control
  - 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