Pragmatic Trials: how early in drug development?
Salford Lung Studies & IMI GetReal Project

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The need 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,... BUT there is currently an information gap in their decision making process.

Healthcare decision makers need to take a broader view and consider evidence of real world effectiveness from robust alternatives sources.

Pharmaceutical R&D needs to be able to deliver such evidence: RWE and early use of pragmatic trials can be part of 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
**Before phase 3**

**Potential Value**
- Background RWE on disease, treatments, care pathways, unmet need etc

**During phase 3**

**Predict Value of new Medicine**
- Comparative Trials. Pragmatic Trials, giving information on effectiveness
- More Focussed Context for current care and outcomes to inform initial assessments
- Evidence Synthesis to combine all sources of information: RCT + PCT + OBS

**After Launch**

**Confirm Value**
- Post Launch RWE on: use of new medicine, relative effectiveness, longer term outcomes

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**How much can be done pre-launch?**

**OR can we start Post-Launch sooner?**
### Designing a randomised pragmatic clinical trial (PCT)

#### 11 ways that Randomised Controlled Trials (RCTs) and PCTs can differ

<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>
</tr>
<tr>
<td>Protocol defines the level and timing of testing. Physicians blinded to data</td>
<td>Measured according to standard practice</td>
</tr>
<tr>
<td>Fixed standard of care or placebo</td>
<td>Standard clinical practice</td>
</tr>
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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>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Intent to treat, per-protocol and compliers</td>
<td>All patients included</td>
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Salford Lung Study Ambition

Study is 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 Rigour

- 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
- Exacerbation in last 3 years
- Consented

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

Randomised

New Rx open label

Visit 2
Routine respiratory review
Device instruction
CAT

Visit 6
Routine respiratory review
CAT

12 months of normal care

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

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

New Rx open label

Visit 2
Routine respiratory review
Device instruction
ACT

Visit 6
Routine respiratory review
ACT

12 months of normal care

Existing maintenance Rx, ICS, ICS/LABA

Randomised

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

A sub-sample of SLS patients (400 for each study) are being recruited for in-depth interviews, conducted post study-exit.

- To identify and assess patient centred outcomes beyond what is captured by standardised PROs:
  - symptoms, social and physical activity, sleep quality, self management of disease, disease progression over time, patient well-being and priorities, and demographic risk factors
- To evaluate how the above factors are impacted by treatment and relate to and complement other outcomes in the main SLS studies

Optional blood sample post study exit for genetics studies

- Large homogenous cohort with associated phenotypic data in a real life clinical setting
- Investigate genes associated with disease susceptibility, severity, progression & co-morbidities as well as response to study medicines

A matched “virtual cohort” study using data from patients elsewhere in UK (CPRD database)

- To understand representativeness of SLS population and changes in COPD Standard of Care over the study period
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
How the data is gathered
Scale of the Project

- 2800 COPD and 1425 asthma subjects recruited
- 88 GP sites
- 128 community pharmacies
- Specialist safety team covering 2 hospitals
- Over 300 study staff
- Over 3000 GP and pharmacy staff trained in GCP and research-ready

Bespoke eCRF and data monitoring system designed, built, and working
Electronic Clinical Monitoring

- >50 million rows of data
- >300 users
- 54,560 radiology results
- 51,940 patient visits
- 2 million clinical observations
- 2.8 million biochemistry and haematology results
- 4.97 million medications processed
- 9072 event alerts in last 12 mnths
- 977 SAE reports
- 15 data feeds per subject
- 977 SAE reports
- 9072 event alerts in last 12 mnths
- 4.97 million medications processed
- 2.8 million biochemistry and haematology results
- 2 million clinical observations
- 51,940 patient visits
- 54,560 radiology results
- >300 users
- >50 million rows of data

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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
Challenges and Learnings for PCTs

RIGOUR OF RCT START UP
“MESSINESS” OF OBSERVATIONAL DATA FOLLOW UP
BRAND NEW IT / DATA ISSUES

• Importance of partnership
  • Industry/ Healthcare Providers/ Academics/ EHR provider
• Create a broad network of investigators (including research-naive investigators for low interventional protocols)
• Map a clear Data journey from EHR to Research Dataset
• Collaborate with EHR provider to facilitate research
• Develop practical solutions for GCP & monitoring requirements
• Create Recruitment and Consent processes “fit for purpose”
Developing Solutions

- Industry needs new research partners
  - Applying clear criteria for due diligence and feasibility
  - Run pilot retrospective studies before more complex observational studies and interventional PCTs
- Synergy possible from collaborations and networks
  - Common infrastructure and standards
  - Scale and connectivity
- Work together to increase acceptability of study innovation and RWE in regulatory and coverage decision making
  - Experience in Europe (EMA/HTA; IMI GetReal; IMI-2)
  - NewDIGS
  - FDA openness?
INCORPORATING REAL-LIFE CLINICAL DATA INTO DEVELOPMENT STRATEGIES
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

Universities, research organisations, public bodies, non-profit groups
- Universitair Medisch Centrum Utrecht, the Netherlands
- Academisch Ziekenhuis Groningen, the Netherlands
- Zorginstituut Nederland, the Netherlands
- European Medicines Agency, UK
- European Organisation for Research and Treatment of Cancer, Belgium
- Haute Autorité de Santé, France
- University of Manchester, UK
- National Institute for Health and Care Excellence, UK
- Panepistimio Ioanninon, Greece
- Universitét Bern, Switzerland
- University of Leicester, UK

Small and medium-sized enterprises (SMEs)
- LA Santé Epidemiologie Evaluation et Recherche, France

Patients’ organisations
- International Alliance of Patients' Organizations, UK

EFPIA companies
- GlaxoSmithKline Research and Development Ltd, UK
- Amgen NV/SA, Belgium
- AstraZeneca AB, Sweden
- Bayer Pharma AG, Germany
- Boehringer Ingelheim International GmbH, Germany
- Bristol Myers Squibb EMEA sarl, US
- Eli Lilly, UK
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- Merck KGaA, Germany
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- Takeda Development Centre Europe Ltd, UK

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“What combination of possible studies will provide the most valuable information to customers controlling access - in order to maximise the probability of positive access outcomes?" What is the feasibility of the study options pre-launch and what would be required as commitments post launch? How do options reconcile with the regulatory process?"

“With all the available data, would we predict an improvement in patient outcome or care pathway efficiency over and above current practice in my healthcare system - with a reasonable level of certainty?"

“Would we accept the uncertainty for a period of time while waiting for studies to complete or for new studies to be run?”
Decision-making framework required!

R & D decision

Phase 3a
“optimise”

Phase 3b
“supplement”

Conditional Licensing
?

Conditional Access
?

Phase IV
“commit”

Regulatory decision

HTA decision

Rx decision

Joint Scientific Advice!
R&D DECISION MAKING

Is evidence of effectiveness critical for access/uptake?

To what extent does this study/analysis plan generate valuable information about real-world effectiveness?

Is the envisioned study/analysis plan technically feasible?

Will the study/analysis plan be accepted by regulators and HTA agencies?

What impact does this study have in the need for other studies? (e.g. post launch)?

HTA DECISION MAKING

Is evidence of effectiveness critical for a clear recommendation?

To what extent does this study/analysis generate valuable information about real-world effectiveness?

Is the presented study/analysis technically robust?

Is the study/analysis acceptable?

How does this study inform the need for other studies post launch?

What other criteria matter when allocating resources between competing options?
GetReal

Real-Life Data in Drug Development

WP1
Acceptability
Decision Frameworks
Policy Agenda

WP2
Understanding the efficacy-effectiveness gap
simulation of trials to improve design

WP3
Overcoming practical barriers to running real-world studies pre launch

WP4
Identifying best practice and creating new methods for evidence synthesis and predictive modelling

R&D decisions on development
HTA Guidance and Acceptability

Joint Scientific Advice
MAPPS
Training and Education

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