Within-registry trials: Do they work?

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University of Leeds, UK
Conflicts of interest

Grants, consultancy:
Abbott, Amgen, AstraZeneca, Bayer, BMS, Daiichy Sankyo, Novartis, Vifor Pharma

Publishing:
EHJ Quality of Care and Clinical Outcomes

Research funding:
British Heart Foundation, Horizon 2020, NHS England, National Institute for Health Research, Wellcome Trust
Chief Investigator of UKGRIS and ISCOMAT trials
Traditional RCTs are challenging

- Scientific & operational complexity
- Waning site & patient participation
- Regulatory issues
- Inefficient and costly

Jones WS. J Am Coll Cardiol 2016;68:1898-1907
Fanaroff AC. Am Heart J 2019; 214:184-193
RCT landscape inhibits research

- Regulatory obstacles, delays and costs
- Focus on regulation rather than innovation
- Therefore, fewer developments by industry and less research by academia

Growth in the Contract Research Organization (CRO) market since the creation of International Conference on Harmonisation (ICH) in 1990
Derivation of registry-RCTs

- Randomised Clinical Trial
  - Randomised
  - Narrow selection
  - Causal inference
  - Efficacy
  - Expensive

- Quality Registry
  - Observational
  - All comer
  - Hypothesis generating
  - Pragmatic
  - Low cost

RRCT
From challenges to solutions

<table>
<thead>
<tr>
<th>Current challenges</th>
<th>Goals for future RCTs</th>
<th>A pragmatic solution: Registry-based trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific and operational complexity</td>
<td>Simplify operational approach</td>
<td>Identify sites and candidates using health registry data</td>
</tr>
<tr>
<td>Waning site and patient participation</td>
<td>Large sample sizes with representative populations</td>
<td>Informed consent, randomization and patient comprehension via internet portal</td>
</tr>
<tr>
<td>Regulatory issues</td>
<td>Fewer restrictions</td>
<td>Follow up: Outcomes ascertained via patient report, electronic health records, and administrative claims</td>
</tr>
<tr>
<td>Inefficient and costly</td>
<td>Embed trials within routine clinical care processes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leverage electronic records and data</td>
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</tbody>
</table>
Data flow from registers to RCT timeline

Linkage with other public registries

- Subsequent events, e.g. new MI, heart failure (National Patient Registry)
- Adherence to treatment (National Registry of Drug prescriptions)
- Vital status and cause of death (National Cause of Death Registry)

Quality Registry

Hospitalisation

- Treatment A
- Treatment B

Data type:
- Baseline variables
- In-hospital treatment
- Discharge medication

Continuation of treatment A

Data analysis

- New hypothesis
- New generic drug indication
- Impact on clinical routine

Scheduled follow-up visits in routine clinical care

Data type:
- Treatment measures (blood pressure, blood samples)
- PROMs (patient-reported outcomes, symptoms)

Randomisation (R*)

Patient event (Myocardial infarction)
Population-based registers

**UK**
- Area: 243,610 km²
- Inhabitants: 65M; 259 p/km²
- 8M living in/around London

**Unique identifiers**
- 943 476 5870
  - Randomly generated at birth/point of first contact with NHS

**Sweden**
- Area: 447,435 km²
- Inhabitants: 10M; 23 p/km²
- 5M living in/around Stockholm, Göteborg and Malmö

**Unique identifiers**
- 390202-1439
  - Derived from DOB, place, sex

Data linkage for tracking care and outcomes
Disruptive technology in clinical research

The Randomised Registry Trial – The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D’Agostino, Sr., Ph.D.

Registry Randomised Clinical Trial - RRCT

- New concept for clinical research
- Integrates a randomised study with a clinical registry
- Complement to classical RCT

The success of the registry based randomised trials (RRCT) on patient recruitment & generating evidence in real life care
System-wide changes following RRCT

TASTE trial in Scandinavia
- Neutral results for routine thrombus aspiration use
- De-implementation of the intervention in Sweden
- Changes in practice anticipating guideline recommendations

Thrombus Aspiration

Uncertainty in efficacy and safety of a therapeutic strategy
- Variability in adoption rates across centers

Before TASTE  During TASTE  After TASTE

Use of thrombectomy before and after Taste

Buccheri S. Circ cardiovasc Int. 2019;12:e007381

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Objective vs subjective risk assessment: testing decision tree prompts for treatment of AMI

Chew D. Circ Cariovasc Qual Outcomes 2013;6:299
Chew DP. Am Heart J. 2015;170:995
Bebb O. Euro Heart J. 2018; 39 (42),3798
Everett C. BMJ Open. 2019;9(9):e032165
Recruiting ahead of time, target and budget: UKGRIS
Medications management at the transition between hospital and home for heart failure
Randomised trials based on health records: Spectrum of Studies

<table>
<thead>
<tr>
<th>Cost</th>
<th>Design &amp; Data</th>
<th>Study Population</th>
<th>Randomisation</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies (including registry studies)</td>
<td>$</td>
<td>Can be retrospective or prospective in design; data quality is variable</td>
<td>Typically unselected population (e.g., Medicare)</td>
<td>Without randomization, comparative effectiveness studies cannot be performed</td>
</tr>
<tr>
<td>Traditional RCTs</td>
<td>$$$$$-$$$$$$</td>
<td>Prospective design; data collection occurs at specialized study centers</td>
<td>Highly-selected patient population at study centers; may lead to results that are not generalizable</td>
<td>Randomization eliminates confounding bias</td>
</tr>
<tr>
<td>Registry-based RCTs</td>
<td>$-$$$$</td>
<td>Prospective design; data collection often occurs at diverse clinical sites</td>
<td>Typically designed to study a specific patient population (e.g., those undergoing PCI)</td>
<td>Randomization eliminates confounding bias</td>
</tr>
<tr>
<td>Large, pragmatic clinical trials</td>
<td>$-$$$$$</td>
<td>Prospective design; data is collected ubiquitously as part of clinical care</td>
<td>Depending on electronic infrastructure, can be broad or selective; can incorporate enrichment criteria</td>
<td>Randomization eliminates confounding bias</td>
</tr>
</tbody>
</table>

Jones WS. J Am Coll Cardiol 2016;68:1898-1907
# RCTs from eHRs

<table>
<thead>
<tr>
<th>SCOT-HEART Trial</th>
<th>PROMISE Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>4,146</td>
</tr>
<tr>
<td><strong>Follow Up</strong></td>
<td>Electronic Health Records</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Certainty of diagnosis of angina due to coronary heart disease</td>
</tr>
<tr>
<td></td>
<td>5-Year CHD Death or non-fatal MI</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>£0.5 Million</td>
</tr>
<tr>
<td><strong>Long-term Follow-up</strong></td>
<td>£718</td>
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Lancet 2015;385:2383-2391

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“On average, treatment effect estimates for subjective outcome events assessed by onsite assessors did not differ from those assessed by Adjudication Committees.”

In the real world, what matters is what the healthcare system sees and experiences not what is adjudicated.

Cochrane Database of Systematic Reviews 2016;3: MR000043
eHR data as the (composite) outcome

Reliable results from electronic health records
ASCEND trial: Effect of (a) aspirin vs. placebo, and
(b) omega-3 fatty acids vs. placebo on Vascular Events*

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>812 (10.8%)</td>
<td>903 (12.0%)</td>
<td>0.89 (0.81-0.98)</td>
</tr>
<tr>
<td></td>
<td>692 (9.2%)</td>
<td>761 (10.2%)</td>
<td>0.90 (0.82-1.00)</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>855 (11.4%)</td>
<td>860 (11.4%)</td>
<td>1.00 (0.91-1.10)</td>
</tr>
<tr>
<td></td>
<td>723 (9.7%)</td>
<td>730 (9.7%)</td>
<td>1.00 (0.90-1.10)</td>
</tr>
</tbody>
</table>

Vascular Event: MI, ischaemic stroke, TIA, vascular death (exc. intracranial haemorrhage), or arterial revascularization

Adjudicated follow-up
Electronic health record follow-up only

Jane Armitage, (via D Newby) Personal Communication: Unpublished Data
The need for internationally recognised definitions of disease derived from eHRs

“An anonymous Tweeter brought the unusual ICD codes to light. But investigators were quick to provide answers on numbers.”

“When is an MI not an MI? Sometimes in SCOT-HEART, apparently.”

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EuroHeart: an ESC initiative

EuroHeart is an ESC coordinated and sponsored programme that:

- Supports continuous development of quality of care based on individual patient data.
- Is based on development of and collaboration between national programmes that use common data sets and quality criteria.
- Integrates tools for device surveillance.
- Integrates tools for randomised clinical trials (RRCT).
- Provides an optional common IT-infrastructure.
- Is aligned with the ESC mission to reduce the burden of CVD.
EuroHeart – the project

EuroHeart is an ESC coordinated and sponsored programme that:

- Covers the common disease areas ACS-PCI, valve disease, heart failure and atrial fibrillation.
- Starts with development of standardised data sets and quality indicators for diseases and devices.
- During the pilot phase, it tests the system in 2 – 4 countries.
- Will develop a data science centre localised with options for remote data access.
- Will include representatives from the interested countries in the development and in all subcommittees.
Potential Pilot Phase countries

- Sweden
- Iceland
- United Kingdom
- Scotland
- Ireland
- Poland
- Romania
- Serbia
- Czech Republic
- Hungary
- Portugal
- Germany
- Austria
- Italy
- Israel
- Estonia
- Bosnia and Herzegovina
- Greece
- France
- The Netherlands
- Denmark
- Norway

EuroHeart – Eols
## EuroHeart – schedule

### EuroHeart - Milestones

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec, 2019</td>
<td>Decision on protocol and standardized variables for ACS-PCI</td>
</tr>
<tr>
<td>March, 2020</td>
<td>Final decision on 2 – 4 pilot countries</td>
</tr>
<tr>
<td>April, 2020</td>
<td>IT-platform ready for development of ACS-PCI registry</td>
</tr>
<tr>
<td>June, 2020</td>
<td>Launch of the EuroHeart ACS-PCI</td>
</tr>
<tr>
<td>Sep 1, 2020</td>
<td>Report on the first included patients at the ESC Congress 2020</td>
</tr>
<tr>
<td>June, 2021</td>
<td>Decision on protocol &amp; variables for valve disease</td>
</tr>
<tr>
<td>Sep 1, 2021</td>
<td>Report on the 1-year outcomes of the ACS-PCI registry at ESC</td>
</tr>
<tr>
<td>Oct, 2021</td>
<td>EuroHeart ACS-PCI registries running in all pilot countries</td>
</tr>
<tr>
<td></td>
<td>Start of development of TAVI registry</td>
</tr>
<tr>
<td>Dec, 2021</td>
<td>Decision on expansion of the EuroHeart system</td>
</tr>
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</table>
Registry-based RCTs

• Ideal for simple important clinical questions
• Cheap, real world and highly relevant for healthcare systems
• Many advantages over and above ‘gold-standard’ double blind RCTs
• Less resource intensive and more inclusive than registry-based RCTs
• Relies on strong and widespread registries / eHR systems to be in place

Are registries-based RCTs the future gold-standard for real world testing and implementation of therapies?