Registry-based Randomized Clinical Trials

Reinhard Seifert
Biostatistician
Haukeland University Hospital, Bergen
Norwegian Registry for Invasive Cardiology
RRCT = Registry + RCT

Prospective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting.
Which Treatment is Best for Whom? High-Quality Evidence is Scarce

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Tricoci et al. JAMA. 2009;301(8):831-841
Background

A) Clinical decision needs evidence

B) Evidence obtained by
   i. Experiment (RCTs)
   ii. Observation (Registries)
   iii. Opinion (Experts)

C) RCTs are required but scarce

D) RRCTs receive attention as part of a solution
Registry-based randomized clinical trials—a new clinical trial paradigm

Stefan James, Sunil V. Rao and Christopher B. Granger

Abstract | Randomized clinical trials provide the foundation of clinical evidence to guide physicians in their selection of treatment options. Importantly, randomization is the only reliable method to control for confounding factors when comparing treatment groups. However, randomized trials have limitations, including the increasingly prohibitive costs of conducting adequately powered studies. Local and national regulatory requirements, delays in approval, and unnecessary trial processes have led to increased costs and decreased efficiency. Another limitation is that clinical trials involve selected patients who are treated according to protocols that might not represent real-world practice. A possible solution is registry-based randomized clinical trials. By including a randomization module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry. We believe that prospective registry-based randomized clinical trials are a powerful tool for conducting studies efficiently and cost-effectively.

James, S. et al. Nat. Rev. Cardiol. 12, 312–316 (2015); published online 17 March 2015; doi:10.1038/nrcardio.2015.33
Introduction

• RCTs provide highest levels of evidence, but
  – are limited in generalizability (selection bias)
  – only a minority of guideline recommendations are covered

• Observational data in electronic medical records and clinical registries is approaching real-time population coverage, but
  – is not considered adequate evidence (confounding)
Perspectives

(a) Paradigm change in clinical decision making and (RCT) trial design due to inherent limitations and technical advance

(b) Technological synergies between clinical registries and medical-, population-, device-registries
## Randomized Clinical Trials (RCTs) in Cardiovascular Disease

<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>
<td></td>
</tr>
</tbody>
</table>

Challenges with RCTs

Traditional clinical trials are increasingly challenging due to

• rising costs,
• increasing complexity and length, and
• burdensome institutional and regulatory requirements.

➔ Large proportions of international recommendations are based on lower-quality evidence

Traditioonal RCT
Solution

Use of existing clinical, medical and population registries to conduct large simple trials

• Enhanced patient enrolment
• Random allocation
• Baseline medical history
• Minimize additional data collection and monitoring
National clinical registries

- Reflect the complete patient population
- Integrate with other medical and population registries
- Build on flexible and extendable digital platforms
- Provide data for observational studies
Traditional purpose

Better quality of health care:

- Prevention
- Quality control
- Research
- Guidance for administration
- Monitoring incidence and prevalence
Challenges

There still is work to do for clinical registries in many countries:

- Primarily intended for quality improvement
- Traditionally focused on descriptive reports
- Delayed registration
- Ongoing integration with registries and devices
- Data quality
National clinical registries
Summary

Wide change in paradigms:

- Requirements for international guideline recommendations
- Conduct of RCTs
- Expectations from clinical registries and their usage
By including a randomization module in a large, all-inclusive clinical registry with unselected consecutive enrolment, some of the most important features of a prospective randomized trial can be combined with the inclusiveness and efficiencies of a large-scale all-comers clinical registry.

By including a randomisation module in a clinical quality registry, it is possible to combine some of the finest attributes of a prospective randomised trial with the best features of a [...] clinical registry including the key strength of unselected consecutive enrolment.

James et al. Heart 2012;98:1329-1331
An ideal opportunity [...] would be to embed randomization in the EMR [...] and to use the EMR as the case report form for data collection.

Antmann et al. JAMA 2012; 17:1743-44
Tasks of the registry

- Collect baseline and procedure characteristics
- Identify eligible patients
- Provide patient information
- Register patient consent
- Randomize
- Collect endpoint data
### Information for consent

#### Did the patient consent?

Are inclusion and exclusion criteria met?

---

**TASTE**

Did the patient consent?
Are inclusion and exclusion criteria met?

---

**PCI**

Operator

---

**Segment**

Segmentnummer
Graft
Nummer på stenos i samma segment
Ocklusion
Stenotyp
Stenosklass
Procedurtyp
Lokal framgång

---

Source: Stefan James
Two questions need to be answered:

Did the patient consent orally?
Are inclusion and no exclusion criteria met?

Source: Stefan James
Randomize and store data

TASTE

Did the patient consent?  
Are inclusion and exclusion criteria met?

PCI

Operator

Segment

Segmentnummer  
Graft  
Nummer på stenos i samma segment  
Ocklusion  
Stenostyp  
Stenosklass  
Procedurtyp  
Lokal framgång

Randomisera & Spara

Spara

Source: Stefan James
Required modifications

The clinician has to interact with the electronic registry before procedure

- Register patient
- Evaluate consent
- Randomize treatment

Additional IT-development

- Integration with medical and population registries (Central Health Registries)
- Added randomization module
- Guidance for informed consent
Conditions for success

The impact of registries on treatment and excellence of care depend on

- Data quality
- Completeness
- Coverage
- Integration of long-term outcome data
TASTE trial enrollment flow chart

- Enrolled in Denmark
  - N=247

- All patients with STEMI in Sweden and Iceland undergoing primary or rescue PCI. N=11,709 *)

- Enrolled in TASTE
  - N=7259

- Randomized in TASTE
  - N=7244

  - N=3621 assigned to thrombus aspiration
  - N=3623 underwent conventional PCI

  - N=3445 underwent conventional PCI
    - N=178 underwent thrombus aspiration

  - N=3621 were followed up
  - N=3623 were followed up

- Not enrolled
  - N=4697

- No patients (0) were lost to follow-up of the primary outcome!

- N=1162 underwent thrombus aspiration
  - N=1162 were followed up

- N=3535 underwent conventional PCI
  - N=3535 were followed up

Source: Stefan James
Study design

<table>
<thead>
<tr>
<th></th>
<th>Registry study</th>
<th>RCT</th>
<th>R-RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalizable</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Un-biased</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
## R-RCT vs traditional RCT

<table>
<thead>
<tr>
<th>R-RCT</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of therapeutic options used in routine clinical care</td>
<td>Approval of new pharmaceutical agents and medical devices</td>
</tr>
</tbody>
</table>
## Study design requirements

<table>
<thead>
<tr>
<th>Requirement</th>
<th>RCT</th>
<th>R-RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Approved devices/ medication</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Drugs for new indication</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Device, first in man</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>New drug</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
R-RCT Sweden

IFR SWEDHEART (n=2000) Completed enrollment
Instantaneous Wave-Free Ratio versus Fractional Flow Reserve in ACS
Clinical registry: Swedeheart
Funding: Volcano. Study

PROSPECT-2 (n=1)
Providing Regional Obse
Evaluate future events from angiography
Clinical registry: Swedeheart
Funding: The Medicines

DISCO (n=2480) ong
Evaluate if patients with depression will benefit from targeted therapy
Clinical registry: Swedeheart
Funding: Swedish Research Council

SOREG (n=2500) ongoing
Closure of the meso-defect occurring at gastric bypass operation will reduce postoperative ileus without increasing early severe complications

IAM (n=4400) ongoing
Influenza vaccination After Myocardial Infarction (IAMI trial)
Clinical registry: Swedeheart
Funding: Sanofi, Study sponsor: Örebro University Hospital

U-CARE (n=500) c
Evaluation of internet based depression in patients with depression
Clinical registry: Swedeheart
Funding: Swedish Research Council

TIMING (n=3000) soon to start enrollment
Evaluation of efficacy and safety of the time point for treatment with NOAK after ischemic stroke and AF
Clinical registry: Swedish Stroke Registry
Funding: Swedish Research council (VR), Study sponsor: UCR

FULL-REVASC (n=4000) soon to start enrollment
Ffr-gUIdance for st eLeVation myocardial infarction REVASCularization
Clinical registry: Swedeheart
Funding: Swedish Research council (VR), Study sponsor: Karolinska Institute

Source: Stefan James (UCR)
Consequences

Potential benefits for registries:

• Academic - increased impact as tool for knowledge discovery
• Administrative - increased funding
• Regulative - increased legitimacy
• Technological - increased integration
• Clinical - nuisance to necessity
Summary

- Fast inclusion of large patient numbers
- Focus on hard endpoints
- Complete follow-up
- Fraction of costs
- Important complement to RCTs

→ R-RCTs could potentially revolutionise clinical trials
Thank you