Prospective registry-based randomized clinical trials – the Swedish concept for pragmatic clinical trials

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Executive director, Uppsala Clinical Research Center
Uppsala University, Sweden
Randomized Clinical Trials – RCT

**Strengths**
- Correctly designed studies with adequate power are gold standard
- Randomization extinguishes confounding

**Weaknesses**
- Highly selected populations due to exclusion criteria
- Often selected specialized study centers
- Often surrogate endpoints
- Long time to plan and complete
- Expensive
- Often sponsored by industry – only studies of economic interest will be performed
Big Cost Drivers in Traditional Clinical Trials

- Data collection – size of case report form
- Site monitoring - % source document verification
- Number of study-specific procedures and tests
- Number of study-specific contacts and visits
- Volume and complexity of safety reporting requirements
- Investigational drug storage and accountability
- Total trial timeline!!!!!
Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.
Sweden and clinical registries

• A system of national clinical registries has been established in the Swedish health and medical services during the last three decades.

• Six national competence centers for clinical registers and 96 national registries receive national funding in Sweden.

• UCR is the oldest and largest competence center for clinical registers hosting more than 20 national registers.

• Participation in clinical registers is voluntary. Based on the unique personal identification number given to each Swedish citizen (at birth or immigration) data from clinical registers can be combined with data from mandatory register such as cause of death, patient administrative (with discharge diagnoses), and drug prescription registers.
Clinical registers in Swedish health care

- **Clinical register**
  - Data entered:
    - Web interface
    - Electronic health records
    - Patient reported outcomes
  - Data from:
    - Clinical trials
    - Other registers

- **Research database**
  - Decision support tools
  - Reports to health care professionals and other stakeholders
  - Publications

**UCRO**
SWEDEHEART: Sweden’s new online cardiac registry, the first of its kind

Covering all hospitals in Sweden, SWEDEHEART is unique because it allows long-term follow-up and immediate feedback, says Ulf Stenestrand, MD, PhD, Associate Professor of cardiology and Senior consultant interventional cardiologist, Department of Cardiology, University Hospital, Linköping, Sweden, and President of SWEDEHEART.
Number of cases annually: 80 000

<table>
<thead>
<tr>
<th>Service</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIKS-HIA</td>
<td>73 CCU hospitals, 100%</td>
</tr>
<tr>
<td>SCAAR</td>
<td>30 PCI hospitals, 100%</td>
</tr>
<tr>
<td>Percutaneous valves</td>
<td>7 hospitals, 100%</td>
</tr>
<tr>
<td>Heart surgery</td>
<td>7 hospitals, 100%</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>65 hospitals, 85%</td>
</tr>
<tr>
<td>Cardiogenetic registry</td>
<td>New</td>
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</table>

>200 variables

(Baseline data, procedural and outcome measures)

At monitoring: 95-96% agreement between files and registry.
Data entry on line by the operator

Automatic linkage with population registry to provide name, sex

Automated data checks

Auto populated fields from previous registrations

Calculated variables
Thrombus aspiration in ST-elevation myocardial infarction (STEMI)

RCT vs registry data
Thrombus aspiration in STEMI
Thrombus aspiration in Sweden
TAPAS / Swedish registry data

HR (95% CI): 1.21 (1.08-1.35)

Number at risk
<table>
<thead>
<tr>
<th></th>
<th>Conventional PCI</th>
<th>Thrombus aspiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1071</td>
<td>1025</td>
</tr>
<tr>
<td></td>
<td>536</td>
<td>519</td>
</tr>
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<td></td>
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<td>506</td>
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<tr>
<td></td>
<td>489</td>
<td>505</td>
</tr>
</tbody>
</table>

Randomized Controlled/Clinical Trials - RCT

Randomized Studies (RCT)

Non randomized Observational studies
Utilizing clinical registers for randomized clinical trials
Register-based Randomized Clinical trials (R-RCT)

A prospective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting.
How can a registry be utilized in a RCT?

For some or all parts of trial

- Identify patients
- Randomize
- Collect baseline and procedure characteristics (CRF)
- Assist with and collect consent forms
- Identify clinical endpoints (endpoint detection)
- Collect clinical outcome events (adjudication, CEC)
Two questions need to be answered:

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

## TASTE

**Did the patient consent?**
- [ ] Yes
- [ ] No

**Are inclusion and exclusion criteria met?**
- [ ] Yes
- [ ] No

### PCI

**Operator**
- [ ] Yes

### Segment

**Segmentnummer**
- [ ] 0 Nej

**Graft**
- [ ] Nej

**Nummer på stenosis i samma segment**
- [ ] Första

**Ocklusion**
- [ ] Nej

**Stenotyp**
- [ ] Nej

**Stenosklass**
- [ ] Nej

**Procedurtyp**
- [ ] Nej

**Lokal framgång**
- [ ] Nej

### Randomisera & Spara

### Spara
<table>
<thead>
<tr>
<th>Randomize and store data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the patient consent?</td>
</tr>
<tr>
<td>Are inclusion and exclusion criteria met?</td>
</tr>
</tbody>
</table>

**TASTE**

- Did the patient consent?
- Are inclusion and exclusion criteria met?
TASTE inclusion rate

Patients vs Date

- All primary PCI:s
- Randomized
- 7244 patients
All patients with STEMI in Sweden and Iceland undergoing primary or rescue PCI. N=11,709.

Enrolled in TASTE N=7,259

- Enrolled in TASTE N=7,244
  - Randomized in TASTE N=7,244
    - N=3,621 assigned to thrombus aspiration
    - N=3,623 assigned to conventional PCI
      - N=3,445 underwent conventional PCI
        - N=1162 underwent thrombus aspiration
        - N=3,535 underwent conventional PCI
          - N=1,162 were followed up
          - N=3,535 were followed up
    - N=1162 underwent thrombus aspiration
      - N=1162 were followed up
  - N=1,162 were lost to follow-up of the primary outcome!
All-cause mortality up to 1 year

HR up to 30 days 0.94 (0.72 – 1.22), P=0.63
All-cause mortality up to 1 year

HR up to 1 year 0.94 (0.78 – 1.15), P=0.57

Outcomes 1 Year after Thoracic Endarterectomy for Myocardial Infarction: The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Thórarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Jonas Andersson, M.D., Ph.D., Fredrik Calais, M.D., Olov Collste, M.D., Matthias Göteborg, M.D., Ph.D., Dan Ioanes, M.D., Anders Kallryd, M.D., Ralf Anders Lundin, M.D., Jacob Odenstedt, M.D., Verner Puskar, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D., Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.
Thrombus aspiration pre/post Taste

Mean use during trial

Län (folkbokföring)
- Stockholms län
- Uppsalal län
- Södermanlands län
- Östergötlands län
- Jönköpings län
- Kronobergs län
- Kalmar län
- Gotlands län
- Blekinge län
- Skåne län
- Hallands län
- Västra Götalands län
- Värmlands län
- Örebro län
- Västmanlands län
- Dalarnas län
- Gävleborgs län
- Västernorrlands län
- Jämtlands län
- Västerbottens län
- Norrbottens län
R-RCT vs. RCT

STEMI Thrombectomy Story

TASTE (R-RCT)

1st patient: June 2010
30 centers
33 months to full enrollment
7,244 patients

500,000 €

TOTAL (traditionell RCT)

1st patient: August 2010
87 centers
48 months to full enrollment
10,732 patients

15,000,000 €

## Guidelines

<table>
<thead>
<tr>
<th>Title</th>
<th>Citation</th>
<th>Class</th>
<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>2014 ESC/EACTS guidelines on myocardial revascularization</td>
<td>Eur Heart J. 2014 Oct 1;35(37):2541-619</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>2017 ESC Guidelines ST-segment elevation myocardial infarction</td>
<td>European Heart Journal 2017</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
DETermination of the role of Oxygen in suspected Acute Myocardial Infarction

Robin Hofmann, MD
Karolinska Institutet
Department of Clinical Science and Education
Division of Cardiology, Södersjukhuset
Stockholm, Sweden
Background (1)

- Oxygen therapy has been used for more than a century and is widely recommended by guidelines despite limited evidence*

- Rationale: Increased oxygen delivery to the ischemic myocardium reduces infarct size and subsequent complications

Background (2)
• No high quality data from large RCTs available

• The clinical effect of routine oxygen therapy in normoxemic patients with suspected AMI remains uncertain
Study Enrollment

Patient contact with EMS, ED, CCU or cath lab

Eligible patient
Initial oral informed consent (written confirmation within 24h)

Oxygen
Delivered by open face mask at 6L/min for 6-12 hours

Ambient Air

Data analysis through the Swedish Population Registry and SWEDEHEART
DETO2X-AMI compared to other studies

Number of randomized patients with suspected AMI
0 1000 2000 3000 4000 5000 6000 7000

Hofmann, DETO2X-AMI (2017)
COCHRANE Meta-analysis (2016)
Stub, AVOID (2015)
Ranchord (2012)
Ukholkina (2005)
Rawles (1976)
Primary Endpoint up to 365 days

Oxygen treatment 5.0%
Ambient air 5.1%

HR 0.97
95% CI, 0.79 – 1.21
P=0.8

Hofmann, et al.
Myocardial injury by Troponin T

Cumulative distribution of hs-Cardiac Troponin T according to treatment group

<table>
<thead>
<tr>
<th>hs-cardiac Troponin T (ng/L)</th>
<th>Oxygen (N=1998)</th>
<th>Ambient air (N=1978)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ng/L* - median** (IQR)</td>
<td>946.5 (243-2884)</td>
<td>983.0 (225-2931)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

* Confirmed AMI
**Highest measured value during hospitalization

Hofmann, et al.
Oxygen Therapy in Suspected Acute Myocardial Infarction

Robin Hofmann, M.D., Stefan K. James, M.D., Ph.D.,
Tomas Jernberg, M.D., Ph.D., Bertil Lindahl, M.D., Ph.D.,
David Erlinge, M.D., Ph.D., Nils Witt, M.D., Ph.D., Gabriel Arefalk, M.D.,
Mats Frick, M.D., Ph.D., Joakim Alfredsson, M.D., Ph.D.,
Lennart Nilsson, M.D., Ph.D., Annica Ravn-Fischer, M.D., Ph.D.,
Elmir Omerovic, M.D., Ph.D., Thomas Kellerth, M.D., David Sparv, B.Sc.,
Ulf Ekelund, M.D., Ph.D., Rickard Linder, M.D., Ph.D.,
Mattias Ekström, M.D., Ph.D., Jörg Lauermann, M.D., Urban Haaga, B.Sc.,
John Pernow, M.D., Ph.D., Ollie Östlund, Ph.D., Johan Herlitz, M.D., Ph.D.,
and Leif Svensson, M.D., Ph.D., for the DETO2X–SWEDEHEART Investigators*
Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

Patients enrolled from ~11,018 eligible patients in registry
N=3500 (SWE 2700, US 800)

Primary Endpoint: All cause death,
Secondary efficacy endpoints: HF hospitalization and other cardiovascular outcomes
Safety endpoints related to renal function and potassium

Spirinolactone

Standard of care

Event driven 1073 events

Funded by
Swedish Heart Lung foundation
National Institute of Health, US

Planned start
Q4 2017

- Stable chronic HF
- Age ≥ 50 years
- EF ≥ 40%
- NT-proBNP
  - > 300 (sinus rhythm); > 750 (AF)
Prospectively designed registries and cohort studies in the context of clinical practice are highly valuable, and randomized trials conducted in the context of clinical practice, often called a pragmatic clinical trial, may be the most important source of knowledge in the future.
Part of Uppsala University and Uppsala University Hospital.