Registers and observational studies to improve provisions for personalised medicine and clinical trials

The Nordic Rheumatology Register Pilot

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Registers throughout the life cycle of drugs

- Basic research
- Discovery
- Pre-clinical
- Phases I and II
- Phase III
- Approval
- Risk Management Plan
- Uptake and reimbursement
- Comparative effectiveness
- Cost effectiveness
- Biomarker development
- New Indications / users
1. RCTs need registers for contextualisation
Crude and standardised cancer incidence in 5 RA cohorts

<table>
<thead>
<tr>
<th>Registry</th>
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**RCTs need registers for contextualisation**

Askling et al, ARD 2015
2. Registers monitor drug safety
TNF inhibitors, cancer risk and survival

Relative Risk = 1.1 (0.8-1.6)

Askling et al, Arthritis & Rheumatism, 2009  Raaschou et al, Arthritis & Rheumatism, 2010
3. Clinical registers for studies of uptake, effectiveness, and cost-effectiveness
Uptake of biosimilars, and of new biologics
Therapeutic strategies?

Switching from one biologic to another?

Results  Half of all patients starting infliximab, adalimumab or etanercept during the period 2005–2012 discontinued treatment for various reasons. Of these patients, a third switched within 2 months to a second TNFi (infliximab, etanercept or adalimumab). Around 35% of all patients achieved low disease activity or remission at 6 months. Regarding the switching strategy, best results were observed among patients who switched from infliximab to etanercept because of (secondary) inefficacy. Etanercept as second TNFi was associated with longer drug survival compared with infliximab.

Chatzidinonysiou et al, ARD 2014
4. Registers move state of the art of the art of trials
Registers move state of the art of trials

A. From explanatory to pragmatic trials
B. Trials in the framework of clinical registers
   A. Explanatory trials in the era of Precision Medicine
   B. Pragmatic trials in registers (R-RCTs)
C. Enriching trials with external register data
Registers move state of the art of trials

A. From explanatory to pragmatic trials

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C. Enriching trials with external register data
From explanatory to pragmatic trials

Explanatory trials

- Aim at understanding *how and why an intervention works* (efficacy), *under optimal conditions*

- Designed to control for all known biases and confounders, so that the intervention's effect is maximized

- Focus towards *homogeneity*, so that the errors and biases will influence the results as little as possible

- E.g., a **double-blind placebo-controlled trial** (*Biologic X+MTX vs. placebo+MTX*)
From explanatory to pragmatic trials

Pragmatic trials

- Aim at informing clinical decision making, performed in real world setting
- Comparison against a realistic alternative treatment
- Comparative effectiveness (effectiveness, safety, and costs) rather than efficacy, in a clinically relevant study population
- Allows for heterogeneity in all aspects
- Large enough yet simple in design
- e.g., strategy trials (*BeSt* study), head-to-head RCTs (*Biologic X vs. Biologic Y*)
From explanatory to pragmatic trials
From explanatory to pragmatic trials

When there is equipoise: Replace clinicians’ uncertainty with randomization
From explanatory to pragmatic trials

The SWEFOT trial

Rheumatoid arthritis symptoms < 1 year
No previous DMARD use
DAS28 > 3.2
(n=487)

Methotrexate monotherapy
20 mg per week
3-4 months

Methotrexate + sulfasalazine + hydroxychloroquine (→ ciclosporin A) (n=130)

Methotrexate + infliximab (→ etanercept) (n=128)

3 months
Screening and inclusion
Randomisation of patients with DAS28 > 3.2

12 months
Primary endpoint: proportion of patients with a good response according to EULAR criteria

24 months
Re-randomisation of patients with low disease activity or in remission

van Vollenhoven et al, Lancet 2009 & 2012
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C. Enriching trials with external register data
Trials in the framework of registers

1. *Explanatory* trials in the era of Precision Medicine

- The aim: focus on *homogeneity* and *maximal effect of intervention* (targeted therapies for targeted patients)
- Where do we find the target population?
  - Search the clinical register for eligible patients, then do the trial "as usual", outside the register
- Increases efficacy, and improves risk/benefit
Trials in the framework of registers

2. Pragmatic trials within registers (R-RCTs)

- Rapid (automated?) recruitment
- Run the trial within the register
- The one difference: randomized instead of physician’s treatment allocation
- Standard of care follow-up
- Assessment of representativity
Registers move state of the art of trials

A. From explanatory to pragmatic trials
B. Trials in the framework of clinical registers
   A. Explanatory trials in the era of Precision Medicine
   B. Pragmatic trials in registers (R-RCTs)
C. Enriching trials with external register data
Enriching trials with external data

Follow-up

Treatment X

Treatment Y
Enriching trials with external data

Follow-up

Treatment X

Treatment Y

External outcome data
Enriching trials with external data

Follow-up

Treatment X

External outcome data

Treatment Y

Extended follow-up through linkage to external register
Enriching trials with external data

Follow-up

Treatment X

Treatment Y

External

Benchmark data

Extended follow-up through linkage to external register
Enriching trials with external data

The SWEFOT trial

**Biological vs Conventional Combination Treatment and Work Loss in Early Rheumatoid Arthritis A Randomized Trial**

**Research**

**Original Investigation**

**Biological vs Conventional Combination Treatment and Work Loss in Early Rheumatoid Arthritis A Randomized Trial**

**Jöran K. Ericsson, MSc; Martin Nexo, PhD; Johan Bratt, MD, PhD; Ingemar F. Petersson, MD, PhD; Ronald F. van Vollenhoven, MD, PhD; Per-Ingvar Jeppsson, MD, PhD; Sofia Emestam, MD, PhD**

**Importance** The introduction of biological tumor necrosis factor inhibitors has improved the treatment of rheumatoid arthritis (RA) but at a substantial cost. These drugs have been shown to lead to superior radiological outcomes compared with a combination of conventional disease-modifying antirheumatic drugs over 2 years.

**Objective** To investigate whether radiological superiority translates into better work loss outcomes.

**Design, Setting, and Participants** Multicenter, 2-arm, parallel, randomized, active-controlled, open-label trial. Patients with early RA (symptom duration <1 year) were recruited from 15 rheumatology clinics in Sweden from October 1, 2002, through December 31, 2005. The study population was restricted to working-age patients (aged < 63 years).

**Interventions** Patients who did not achieve low disease activity after 3 to 4 months of methotrexate therapy were randomized to receive additional biological treatment with infliximab or conventional combination treatment with sulfasalazine plus hydroxychloroquine.

**Main Outcomes and Measures** Monthly sick leave and disability pension days 21 months after randomization retrieved from the nationwide Swedish Social Insurance Office register. Main analyses were by intention to treat, including all patients, and adjusted for baseline sick leave and disability pension.
Enriching trials with external data

Lost work days per month (max 30 days/month), from external register

Months in Relation to Randomization

Eriksson, Neovius, Bratt, Petersson, Van Vollenhoven, Geborek & Ernestam
JAMA Internal Medicine 2013
Enriching trials with external data

Lost work days per month (max 30 days/month), from external register

- Biologic treatment (n=105)
- Conventional treatment (n=99)

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- Controls (n=1 020)

Matched general population comparator subjects, from external register

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The five investments for a better future!
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I. Smarter trials and personalised medicine require investment in clinical registers
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II. Investments in clinical registers require investment in *clinical infrastructures*
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The five investments for a better future!

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IV. Use of registers require investment in *clinical epidemiology*
The five investments for a better future!

I. Smarter trials and personalised medicine require investment in *clinical registers*

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III. Investments in registers and clinical infrastructures can only be made in collaboration with the *clinical profession*

IV. Use of registers require investment in *clinical epidemiology*

V. Cutting-edge research require investment in Nordic *collaboration*
The Nordic Rheumatology Registers Pilot

- Nordic setting: similar health registers, existence of national registers on societal outcomes, possibility to link information together
- Similar health care and treatment strategies for patients with chronic inflammatory diseases
- Nordic Rheumatology at the forefront in population-based longitudinal clinical patient registers
- Collaboration between the applicants, including the ongoing pragmatic NORD-STAR trial
The Nordic Rheumatology Registers Pilot
The Nordic Rheumatology Registers Pilot
Enriching trials with external data

Pragmatic trials linked to registers can take us from...

- High quality data on small number of surrogate endpoints...
- in selected patients...
- followed for a limited time...
- in a strictly controlled setting...
- comparing active intervention with placebo...
- at a very high cost
Enriching trials with external data

Pragmatic trials linked to registers can take us from...

- High quality data on small number of surrogate endpoints...
- in selected patients...
- followed for a limited time...
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- comparing active intervention with placebo...
- at a very high cost

...to...

- Data on several (hard) endpoints using objective data
- Long follow-up in large number of patients
- Patient groups reflecting the ones actually treated in the real world
- Clinical reality = real world
- Head-to-head-comparisons of the most relevant treatments
- At an affordable cost
Pragmatic trials in registers (R-RCTs)

Two questions need to be answered:
Are the patient informed verbally and accepts participation?
Are inclusion and no exclusion criteria met?
The aim

To *pilot three infrastructure approaches* to enable collaborative studies, on the Nordic level, based on the *combination of existing socio-economic and health registers in the Nordic countries with clinical Rheumatology registers*, and *trial data*
The project

Phase I. Data assembly at the national level
- SRQ
  - Register 1
  - Register 2
  - Register 3
  - Register ...
  - Linkage Database
  - Curated Database
- DANBIO
  - Register 1
  - Register 2
  - Register 3
  - Register ...
  - Linkage Database
  - Curated Database
- NORDMARD
  - Register 1
  - Register 2
  - Register 3
  - Register ...
  - Linkage Database
  - Curated Database
- ROB-FIN
  - Register 1
  - Register 2
  - Register 3
  - Register ...
  - Linkage Database
  - Curated Database
- ICEBIO
  - Register 1
  - Register 2
  - Register 3
  - Register ...
  - Linkage Database
  - Curated Database

Phase II. Piloting analytic platforms on a Nordic level
- (i) Federated analysis; data remaining in country of origin
- (ii) Analysis based on export of curated data into pan-Nordic database
- (iii) Common analysis protocol but separate analysis in each country

Phase III
Using the infrastructure to perform demonstrator projects
- Enriched pragmatic trials (NORD-STAR)
- RA drug safety and co-morbidity
- SpA outcomes research

Phase IV. Evaluation of the different approaches, including bottlenecks and measures needed to address those
Pragmatic trials in registers (R-RCTs)

Still a trial...

”Clinicians who admit there is uncertainty in a choice between two interventions, and wish to address the uncertainty by offering treatment in the context of a randomized evaluation, are subject to intense regulatory scrutiny.”

van Staa, BMJ 2012
Pragmatic trials in registers (R-RCTs)

Still a trial...

"Yet, during routine clinical care, in situations where there is no comparative effectiveness research to guide treatment choice,..., no such constraints apply"

van Staa, BMJ 2012
Still a trial...

“Yet, during routine clinical care, in situations where there is no comparative effectiveness research to guide treatment choice, ..., no such constraints apply”

“Experimentation by politicians on the delivery of health services also does not suffer from this intense regulatory scrutiny”

van Staa, BMJ 2012
The project

- **Phase I** assemble register-based Rheumatology research infrastructures in each of the Nordic countries, through linkages of clinical and other registers
- **Phase II** pilot different technical and analytical approaches to make the resultant data linkages available for joint analyses on a Nordic level
- **Phase III** use of the resultant Nordic platform to address issues in an enriched pragmatic RA trial, and observational studies in RA and in SpA.
- **Phase IV** identify and address hurdles and bottlenecks
The project

- **Phase I.** Data assembly at the national level
  - Sweden: Clinical data, Register 1, Register 2, Register 3, etc.
  - Norway: Clinical data, Register 1, Register 2, Register 3, etc.
  - Denmark: Clinical data, Register 1, Register 2, Register 3, etc.
  - Finland: Clinical data, Register 1, Register 2, Register 3, etc.
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- **Phase IV**
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The partners

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<thead>
<tr>
<th>Country</th>
<th>Lead</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Sweden</td>
<td>Sofia Ernestam</td>
<td>Karolinska Institutet</td>
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<tr>
<td>Denmark</td>
<td>Lars-Erik Kristensen</td>
<td>Univ of Copenhagen</td>
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<tr>
<td>Norway</td>
<td>Karin Fagerli</td>
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<td>Iceland</td>
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Impact

A Nordic research infrastructure based on register-linkages and IT solutions for collaborative analyses:

*ground-breaking research and Nordic competitiveness in sectors of medical research in which the Nordic countries have traditionally had a strong position but in which new development is needed in order to remain in lead: clinical trials, post-marketing safety studies, and in outcomes research*
Our data landscape

National Registers

Clinical Registers

Research Databases

Medical Files

Biobanks
Our data landscape: SRQ

- 1997-
- 60+ centres
- > 45000 visits / år
- Patient ID
- Demography
- Diagnosis
- Disease activity
- Treatment
- PROMs

New-onset RA n=15000

Biological treatment n=25000
Our data landscape: a multi-purpose tool
- Where does epidemiology fit into the bigger picture?
- Our data landscape and approach
- **Is Sweden alone in universe?**
- Some examples
European RA biologics registers

- NOR-DMARD
- ROB-FIN
- ARTIS
- DANBIO
- BSRBR
- DREAM
- RABBIT
- ATTRA
- HU-REGAR
- SCQM
- BioRx.si
- GISEA
- BIOBADASER
- BioR.x.sI
- Reuma.pt
- BSRBR
- DANBIO
- ARTIS
- HU-REGAR
- SCQM
- BioRx.si
- GISEA
- BIOBADASER
- Reuma.pt
1. Disease area knowledge

How many patients are there?

Neovius, Simard & Asling for the ARTIS Study Group
ARD 2011
2. Safety

Real world data to inform on drug safety, already pre-approval

Crude and standardised cancer incidence in 5 RA cohorts

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Askling et al, ACR 2013
2. Safety

Have increased clinical vigilance had any impact on TB risks with TNF inhibitors?

Arkema et al, ARD, in revision
3. Effectiveness

Combination of a TNF inhibitor and a DMARD is good, but does it matter which DMARD you choose?

<table>
<thead>
<tr>
<th></th>
<th>No response</th>
<th>Moderate response</th>
<th>Good response</th>
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<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ETA/MTX n = 305</td>
<td>21</td>
<td>45</td>
<td>34</td>
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<td>ETA/LEF n = 78</td>
<td>19</td>
<td>50</td>
<td>31</td>
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<tr>
<td>ADA/MTX n = 274</td>
<td>26</td>
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<tr>
<td>ADA/LEF n = 80</td>
<td>28</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>INF/MTX n = 249</td>
<td>19</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>INF/LEF n = 54</td>
<td>24</td>
<td>56</td>
<td>20</td>
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*Strangfeld et al, ARD, 2009*
4. Therapeutic strategy

Drug survival on abatacept across Europe

Graphics stolen from Axel Finckh, SCQM, ACR 2013
5. Effects on other outcomes

Does effective disease control in RA reduce the risk of acute heart attacks?

Swedish population (reference)

- Good response: 0.74 (0.27-2.06)
- Moderate: 2.25 (1.27-4.01)
- No: 3.15 (1.74-5.68)

Ljung et al, ACR 2013
6. Health-economy

Annual cost for RA, and its distribution

- **€31,000** for RA exposed to biologics (n=4476)
- **€22,000** for RA (n=22896)
- **€8,000** for GenPop (n=114480)

Legend:
- Orange: Biologic drugs
- Blue: Non-biologic drugs
- Purple: Non-primary outpatient care
- Green: Inpatient care
- Red: Sick leave
- Blue: Disability pension

Eriksson et al, ARD 2013
Pragmatic trials in registers (R-RCTs)

The TASTE study included 50% of ALL primary PCIs in the country...
Adaptive licencing

Basic research
Discovery
Pre-clinical
Phases I and II
Phase III
Approval
Risk Management Plan
Reimbursement
Comparative effectiveness
Cost effectiveness
Biomarker development
New Indications / users
From explanatory to pragmatic trials

Equipoise
Clinical equipoise occurs if there is genuine uncertainty within the expert medical community about the preferred treatment (X vs. no X, or X vs. Y)
Pragmatic trials in registers (R-RCTs)

Pro’s
- Leverage information already gathered in clinical practice
- Rapid identification of large samples
- Little additional cost
- High risk patients not excluded
- Quantifiable generalisability to real world population
- Still a trial!

Lauer et al, NEJM, 2013
Pragmatic trials in registers (R-RCTs)

**Con’s**
- Registry data of high enough quality to suffice as outcome measures?
- Missing data?
- Good enough representativity?
- Still a trial (admin hurdle)!

*Lauer et al, NEJM, 2013*
Placebo-controlled double-blind RCTs vs. observational studies
Placebo-controlled double-blind RCTs vs. observational studies
Placebo-controlled double-blind RCTs vs. observational studies

RCTs

Randomization

Outcome
Placebo-controlled double-blind RCTs vs. observational studies

RCTs

Outcome

Randomization

Blinding
Placebo-controlled double-blind RCTs vs. observational studies

RCTs

Observational
Placebo-controlled double-blind RCTs vs. observational studies

Confounding (by indication)

Observational
Placebo-controlled double-blind RCTs vs. observational studies

Confounding (by indication) vs. Bias

Observational
Placebo-controlled double-blind RCTs vs. observational studies

- **Placebo-controlled blinded RCTs**
  - (-) External generalizability?
  - (+) Causality
  - (-) Costly

- **Observational Data**
  - (+) External generalizability
  - (-) Causality?
  - (+) Affordable

- (-) Lack of required data?
- (-) Data quality?