Embedding pragmatic trials within databases of electronic health records / disease registries

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Utrecht University
The big-data revolution in health care [McKinsey]

Exhibit 4: Applying early successes at scale could reduce US healthcare costs by $300 billion to $450 billion.

<table>
<thead>
<tr>
<th>Value at stake</th>
<th>Value</th>
<th>Key drivers of value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right living</td>
<td>70–100</td>
<td>Targeted disease prevention, Data-enabled adherence programs</td>
</tr>
<tr>
<td>Right care</td>
<td>90–110</td>
<td>Alignment around proven pathways, Coordinated care across providers</td>
</tr>
<tr>
<td>Right provider</td>
<td>50–70</td>
<td>Shifting volume to right care setting, Reducing ER¹/readmit rates</td>
</tr>
<tr>
<td>Right value</td>
<td>50–100</td>
<td>Payment innovation and alignment, Provider-performance transparency</td>
</tr>
<tr>
<td>Right innovation</td>
<td>40–70</td>
<td>Accelerating discovery in R&amp;D, Improving trial operations</td>
</tr>
</tbody>
</table>

¹ Emergency room.

Source: American Diabetes Association; American Hospital Association; HealthPartners Research Foundation; McKinsey Global Institute; National Bureau of Economic Research; US Census Bureau
Phases of drug development
Explanatory and pragmatic trials
(Schwartz and Lellouch 1967)

• Explanatory trials
  • To verify a biological hypothesis: study population well adapted to the problem at hand, homogeneous and low withdrawal rate
  • To assess causal effects of e.g. molecule

• Pragmatic trials
  • To choose between treatments. Usually complex interventions; no external validity beyond class of patients studied
  • For decision making of e.g. a policy

=> Different interventions, exposures and patients!
Differences in interventions, exposures and patients in explanatory trials versus real life

Confounding: RRs of cancer in first 3 months after start exposure [van Staa Diabetologia 2012]

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Age-, sex-, calendar year-adjusted RR (95% CI)</th>
<th>Fully adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td>0.64 (0.51, 0.81)</td>
<td>0.70 (0.55, 0.90)</td>
</tr>
<tr>
<td>Metformin and no thiazolidinediones</td>
<td>reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.87 (1.58, 2.22)</td>
<td>1.93 (1.56, 2.39)</td>
</tr>
<tr>
<td>Metformin and no insulin</td>
<td>reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>1.43 (1.23, 1.65)</td>
<td>1.40 (1.19, 1.63)</td>
</tr>
<tr>
<td>Metformin and no sulphonylureas</td>
<td>reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>
Epidemiological methods: statin use and lower limb revision surgery

<table>
<thead>
<tr>
<th>Rate ratio (95% confidence interval)</th>
<th>Cohort design</th>
<th>Case-control design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time fixed</td>
<td>Time dependent</td>
</tr>
<tr>
<td>Method 1 (a)</td>
<td>Method 2 (b)</td>
<td>(d)</td>
</tr>
</tbody>
</table>

Unadjusted (c)

<table>
<thead>
<tr>
<th></th>
<th>Method 1 (a)</th>
<th>Method 2 (b)</th>
<th>Time fixed</th>
<th>Time dependent</th>
<th>Unadjusted (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.51 (0.47-0.55)</td>
<td>0.72 (0.67-0.78)</td>
<td>0.90 (0.84-0.97)</td>
<td>0.89 (0.82-0.95)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for:

- Age and sex
- + Diseases / drug use (d)
- + Lifestyle (e)
- + Calendar time
- + Time dependent adj.
- Propensity score (i)
- Propensity matched (i)

<table>
<thead>
<tr>
<th></th>
<th>Method 1 (a)</th>
<th>Method 2 (b)</th>
<th>Time fixed</th>
<th>Time dependent</th>
<th>Adjusted (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>0.50 (0.46-0.54)</td>
<td>0.73 (0.67-0.78)</td>
<td>0.93 (0.86-1.00)</td>
<td>0.89 (0.83-0.96)</td>
<td></td>
</tr>
<tr>
<td>+ Diseases / drug use (d)</td>
<td>0.42 (0.39-0.46)</td>
<td>0.67 (0.61-0.73)</td>
<td>0.90 (0.83-0.98)</td>
<td>0.88 (0.81-0.97)</td>
<td></td>
</tr>
<tr>
<td>+ Lifestyle (e)</td>
<td>0.42 (0.38-0.45)</td>
<td>0.65 (0.60-0.71)</td>
<td>0.90 (0.82-0.97)</td>
<td>0.88 (0.80-0.96)</td>
<td></td>
</tr>
<tr>
<td>+ Calendar time</td>
<td>0.42 (0.38-0.45)</td>
<td>0.66 (0.61-0.72)</td>
<td>0.91 (0.84-0.99)</td>
<td>0.87 (0.79-0.95)</td>
<td></td>
</tr>
<tr>
<td>+ Time dependent adj.</td>
<td>0.36 (0.33-0.39)</td>
<td>0.64 (0.58-0.71)</td>
<td>0.92 (0.84-1.01)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Propensity score (i)</td>
<td>0.44 (0.40-0.47)</td>
<td>0.67 (0.61-0.73)</td>
<td>0.96 (0.88-1.04)</td>
<td>0.85 (0.78-0.94)</td>
<td></td>
</tr>
<tr>
<td>Propensity matched (i)</td>
<td>0.41 (0.37-0.45)</td>
<td>0.65 (0.59-0.71)</td>
<td>0.96 (0.87-1.05)</td>
<td>0.85 (0.77-0.95)</td>
<td></td>
</tr>
</tbody>
</table>
Pragmatic randomised trials using routine electronic health records

What to prescribe for a patient in general practice when the choice of treatments has a limited evidence base? Tjeerd-Pieter van Staa and colleagues argue that using electronic health records to enter patients into randomised trials of treatments in real time could provide the answer.
Examples of pragmatic trials

• RETROPRO: the effectiveness of simvastatin compared to atorvastatin—a feasibility study (ISRCTN33113202)

• eLUNG: the effectiveness of antibiotics compared to no antibiotics for exacerbations of chronic obstructive pulmonary disease: a feasibility study (ISRCTN72035428)

=> Aim to conduct simple trials without site visits etc
Hospital based large simple trial

- The TASTE trial
- Sweden
- Comparison of two different approaches for percutaneous coronary intervention
- Based on a national registry of myocardial infarction
- Recruitment at the time of registry entry
- Follow-up through national data systems
Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (TASTE TRIAL NEJM 2013)

**Diagram A**
- Cumulative Risk of Death from Any Cause (%)
- Days

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>PCI</th>
<th>PCI+TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>3623</td>
<td>3567</td>
</tr>
<tr>
<td>PCI+TA</td>
<td>3621</td>
<td>3568</td>
</tr>
</tbody>
</table>

**Diagram B**
- Cumulative Risk of Readmission Due to Reinfarction (%)
- Days

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>PCI</th>
<th>PCI+TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>3623</td>
<td>3562</td>
</tr>
<tr>
<td>PCI+TA</td>
<td>3621</td>
<td>3533</td>
</tr>
</tbody>
</table>

[Notes:](#)
Ideal pragmatic trial

- **Simple to conduct:**
  - Only difference with non-RCT is ‘flip-of-the-coin’
- Patients, clinicians and interventions are similar to those outside the trial; consent consistent with usual practice
- Endpoints: patient-oriented and simple to collect (e.g. mortality / hospital admissions / major clinical outcomes)
- Randomisation with usual care / standard intervention
  - No placebo / clinicians not blinded

=> *Point-of-care* trials, done as part of routine clinical care
⇒ Electronic health records / routinely collected data can help to keep data collection simple – data quality / completeness!
⇒ e.g. Statin+lifestyle+nurse monitoring versus nothing
Data flow in pragmatic trials [van Staa BMJ]
Data Quality of routinely collected data – different views

- Only prospectively collected data are valid: site visits / study-specific CRFs / central adjudication of outcomes
- Gold-standard approach + validation
- ‘Pragmatic’ approach: mixture of statistical techniques, clinical review of potential cases and confirmation of known associations
- Big Data: lots of data with application of statistical models

⇒ Simple outcomes!
⇒ Duration of follow-up / statistical power / costs also affect data quality
⇒ High quality of data recording may be reached when the conclusion is no different than if all of these elements had been recorded without error [innovative approaches to clinical trials IOM]
Number and percentage of records recorded in primary care (Clinical Practice Research Datalink), hospital care (Hospital Episode Statistics), and disease registry (Myocardial across the three sources (n=17 964 patients).
Challenges in pragmatic trials

• Blinding of outcomes: major clinical outcomes
• Placebo effect: nuisance factor in explanatory trial while you want to maximise in actual clinical practice
  • Example use of statin:
    – Trial: choice between statin versus placebo with diet – lifestyle advice - monitoring etc offered to all
    – Actual practice: choice between statin + diet-lifestyle advice – monitoring etc versus nothing
• Simple trials do not yet exist
  – Consent requirements
  – Paperwork for approval
Cluster randomised trial in the General Practice Research Database: 1. Electronic decision support to reduce antibiotic prescribing in primary care (eCRT study)

Martin C Gulliford, Tjeerd van Staa, Lisa McDermott, Alex Dregan, Gerard McCann, Mark Ashworth, Judith Charlton, Andrew P Grieve, Paul Little, Michael V Moore, Lucy Yardley and for electronic Cluster Randomised Trial Research Team eCRT Research Team.
Discussion

• Major need for simple trials testing the effects of clinical decisions in routine clinical practice

• Randomisation as a matter of routine – learning healthcare system
  – Complex research governance procedures
  – Paternalistic consent procedures

• Disease registries linked to EHR databases can play an important role in conducting simple trials
  – Engagement of clinicians
  – Engagement of patients

• A cultural shift: randomisation as part of normal health service provision