Fit for the Future: The Digital Revolution
- The Rewards
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University of Oxford, UK

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We live in a data-rich world
Individual decisions from collective experience
The value of multiple dimensions

**Scale:** Number of people (cases & controls)

**Breadth:** Range of exposures & outcomes

**Length:** Frequency & duration of observations

**Depth:** Level of detail

Using the power of data to understand disease, develop treatments, and improve healthcare
The power of large numbers: Ischaemic heart disease vs. Systolic BP

Prof Sarah Lewington on behalf of the Prospective Studies Collaboration
Big Data for Cardiovascular Research

- Increased use of routine data
  - primary & secondary care, national registries, environmental

- Advances in technology & analytic methods
  - sensors, smartphones, imaging, machine learning/artificial intelligence

- Expanded opportunities for cardiovascular research
  - scale, breadth, depth, and duration of investigation
  - causes & consequences, prevention & treatment of disease

- Fundamental scientific principles remain
  - consideration of bias & confounding in observational studies
  - critical role of randomization to assess moderate treatment effects
Comprehensive assessment of phenotype
(plus 70M imputed genetic variants)

Consent / Questionnaire
Cognition
Diet
Respiratory function
Routine healthcare data
Multi-modal imaging
Physical activity
Retinal imaging
Comprehensive assessment of phenotype
(plus 70M imputed genetic variants)

Data are available for health-related research that is in the public interest:
www.ukbiobank.ac.uk
Data-driven approaches to understanding activity

[Images of a smartwatch and graph showing accelerometer data over the course of a day, with different activities labeled: Asleep, Jog to work, Working Day, Jog home, Asleep.]

[Graphs showing accelerometer and self-report data with horizontal bars representing different activities and a vertical axis showing the hour of the day.]
Robust assessment of treatment effects

• **Rising cost & complexity of late-phase trials**
  – 2 recent trials of PCSK9 inhibitors cost >$1Bn each
  – 85% commercial trials fail to recruit on time and to target
  – temptation to abandon randomization for lure of observational methods

• **Distorted treatment development priorities**
  – early decisions to continue treatment development based on limited data
  – away from preventive and long-term treatments for common diseases
  – focus on very expensive drugs for rare conditions
Robust assessment of health interventions

How can we take advantage of technological advances in healthcare, engineering & communications to facilitate randomized assessments of treatment efficacy & safety?
Opportunities for data-driven trials

• **Efficient recruitment** using routine clinical data

• **Effective assessment of safety & efficacy** using routine data (clinical events) & digital technology (symptoms & function)

• **Excellent study quality** through protocol design, software engineering & statistical monitoring

• **Enhanced engagement** for participants & their doctors through integrated communication & consent approaches
Re-imagining the recruitment pathway

- Key inclusion criteria
- Re-usable algorithms for identifying the right patients
- Innovative methods of pre-screening

Research question → Protocol design → Feasibility → Identify patients → Invite patients → Pre-screening → Consent

- Easy analysis of de-identified data
- Accessible methods for large-scale invitation
- Digital tools for consent & engagement
A national, digitally-enabled trial feasibility platform

Target: 12,000 pts with prior MI, ischaemic stroke or peripheral revascularization

<table>
<thead>
<tr>
<th>Patients/hospital</th>
<th>Hospitals</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10,000</td>
<td>96</td>
<td>~1.5M</td>
</tr>
<tr>
<td>&gt;15,000</td>
<td>54</td>
<td>~0.8M</td>
</tr>
<tr>
<td>&gt;20,000</td>
<td>26</td>
<td>~0.5M</td>
</tr>
</tbody>
</table>
## 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><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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><strong>Omega-3 fatty acids</strong></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>

- **Adjudicated follow-up (N Engl J Med 2018)**
- **Electronic health record follow-up only (unpublished)**

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

*NEJM 2018*
Multi-source outcome ascertainment:
Use of routine data to assess safety & efficacy of immunosuppressive strategies in the 3C trial among 800 kidney transplant patients

Graft function, graft survival

Graft rejection, graft function, graft survival

Bespoke web-based case report forms (for 1 yr post-transplant)

Hospitalisation data

Annual postal questionnaire (adverse events, compliance, HRQoL, healthcare usage)

Haynes et al. Lancet 2014
Multi-source outcome ascertainment:
Use of routine data to assess safety & efficacy of immunosuppressive strategies in the 3C trial among 800 kidney transplant patients

No significant improvement kidney function at 18 months:
eGFR 53.7 mL/min/1.73 m² vs. 54.6 mL/min/1.73 m² (P = 0.50)

Greater risk of transplant rejection and serious infection

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus</th>
<th>Tacrolimus</th>
<th>Rate ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic</td>
<td>11%</td>
<td>11%</td>
<td>1.00 (0.56-1.81)</td>
<td>0.9</td>
</tr>
<tr>
<td>Non-opportunistic</td>
<td>42%</td>
<td>31%</td>
<td>1.54 (1.11-2.15)</td>
<td>0.01</td>
</tr>
<tr>
<td>Any serious infection</td>
<td>48%</td>
<td>35%</td>
<td>1.51 (1.11-2.06)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Haynes et al. Lancet 2014
Careful evaluation of new technologies – A cautionary tale

RCT: electronic alerts among 2300 inpatients with acute kidney injury

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert group (n=1201)</td>
<td>Usual care group (n=1192)</td>
<td></td>
</tr>
<tr>
<td>Renal consult</td>
<td>24 (17%)</td>
<td>18 (13%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>27 (19%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>Death</td>
<td>40 (29%)</td>
<td>44 (32%)</td>
</tr>
<tr>
<td>Death or dialysis</td>
<td>58 (41%)</td>
<td>55 (40%)</td>
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Medical intensive care unit (n=278)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
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<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal consult</td>
<td>41 (8%)</td>
<td>58 (11%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>29 (6%)</td>
<td>30 (6%)</td>
</tr>
<tr>
<td>Death</td>
<td>28 (5%)</td>
<td>29 (6%)</td>
</tr>
<tr>
<td>Death or dialysis</td>
<td>50 (10%)</td>
<td>52 (10%)</td>
</tr>
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Medical ward (n=1044)

<table>
<thead>
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<th>Events, n (%)</th>
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<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal consult</td>
<td>38 (17%)</td>
<td>32 (15%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>30 (13%)</td>
<td>32 (15%)</td>
</tr>
<tr>
<td>Death</td>
<td>36 (16%)</td>
<td>32 (15%)</td>
</tr>
<tr>
<td>Death or dialysis</td>
<td>49 (22%)</td>
<td>50 (23%)</td>
</tr>
</tbody>
</table>

Surgical intensive care unit (n=444)

<table>
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<th>Events, n (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal consult</td>
<td>36 (12%)</td>
<td>17 (5%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>19 (6%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Death</td>
<td>14 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Death or dialysis</td>
<td>26 (8%)</td>
<td>11 (4%)</td>
</tr>
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</table>

Surgical ward (n=627)
Implications for cardiovascular community

• New collaborations & partnerships
  – across academic disciplines and organizational & sector boundaries

• New methods & IT infrastructure
  – data acquisition, management, analysis & access
  – advanced computing + controlled management of large sensitive datasets

• New cadre of scientists
  – fellowships, doctoral training, continuing professional development

• New regulatory & governance approaches

• Maintain trust of patients, public, & clinical community
Benefits & trustworthiness

- Patients & public
- Science & academia
- Health service
- Industry & economy

European Society of Cardiology