Choosing Your Study Design

Research Development Workshop

Auburn Clinical School

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Outline

Principles
• types of study design
• minimising bias
• study phases

Practical points
• choosing your study design
• example
### Study design elements

<table>
<thead>
<tr>
<th>Descriptive</th>
<th>Analytic</th>
<th>Timeframe</th>
<th>Outcomes</th>
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<td>Population</td>
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<td>Risk factors</td>
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<td></td>
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<tr>
<td>Incidence</td>
<td>Treatment - benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>Treatment - harm</td>
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**Descriptive:** describe health status or outcomes

**Analytic:** measure relationship between E, I and outcomes

Includes comparator
Taxonomy of study designs

Descriptive
- qualitative
  - survey
  - registry
  - case series
- quantitative

Analytic
- observational
  - cohort study
  - case-control
  - cross-sectional
- experimental
  - randomised controlled trial
  - non-randomised controlled trial

Centre for Evidence Based Medicine (CEBM)
Oxford University
Principle - minimise bias

- Choose the optimal design for question, data, resources
- Design the optimal protocol to ↓bias, ↑efficiency

**Ideal study design**
- Randomise
- Conceal allocation
- Blind
- Blind
- Register protocol

**Population**
- Exposure (+) Intervention
- Exposure (-) Comparator

**Outcomes**
- Outcomes A
- Outcomes B

*Test null hypothesis A=B*
# Observational study designs

<table>
<thead>
<tr>
<th>Study design</th>
<th>Feature</th>
<th>Example</th>
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<tr>
<td>Cohort</td>
<td>$E \rightarrow 0$</td>
<td><strong>Do mobiles increase risk of brain cancer?</strong>&lt;br&gt;Measure mobile phone use $\rightarrow$ brain cancer&lt;br&gt;Need large population (rare events), can get accurate real-time exposure history, expensive, potential confounding+</td>
</tr>
<tr>
<td>Case-control</td>
<td>$E \leftarrow 0$</td>
<td><strong>Do mobiles increase risk of brain cancer?</strong>&lt;br&gt;Population = Brain cancer cases, matched controls&lt;br&gt;Efficient use of controls, rely on recalled history of mobile use, time &amp; resource efficient, potential confounding+</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>$E &amp; 0$</td>
<td><strong>Does having a mobile phone improve kids verbal skills?</strong>&lt;br&gt;Measure mobile phone use and verbal skills at same time.&lt;br&gt;Causality? ? Confounding factors++</td>
</tr>
<tr>
<td>Case series</td>
<td>$E+ \rightarrow 0$</td>
<td><strong>What is the risk of brain cancer in kids attending primary school near a mobile phone tower?</strong>&lt;br&gt;No direct comparison group. Confounding factors ++</td>
</tr>
</tbody>
</table>
Principle – establish feasibility

PHASE I → PHASE II → PHASE III

First in human
Maximum tolerated dose

Safety/Toxicity/Activity
Single arm study

Effectiveness
Randomised controlled trial

Pilot study
Feasibility
Acceptability

Proof of concept
Safety

Pivotal
Example: new MRI sign

Interesting phenomenon! .....clinical value?

Potential value to classify lumbar spine stenosis (LSS) and inform treatment decision for surgery versus conservative management

**Negative** Sedimentation Sign: Normal nerve root sedimentation

**Positive** Sedimentation Sign: Absent nerve root sedimentation

A  Negative Sedimentation Sign  B  Positive Sedimentation Sign
Phase I Proof of concept

Nerve Root Sedimentation Sign
Evaluation of a New Radiological Sign in Lumbar Spinal Stenosis

Thomas Barz, MD,* Markus Melloh, MD, MPH,† Lukas P. Staub, MD,‡ Sarah J. Lord, MBBS,§ Jörn Lange, MD,¶ Christoph P. Röder, MD,‖ Jean-Claude Theis, MD,¶ and Harry R. Merk, MD**

Preliminary data: efficient, set critical performance criteria

Diagnostic case-control study

• N=200 (100 LSS, 100 low back pain, No LSS)
• Validity: is sign associated with LSS? No reference standard
• Reliability: intra-observer and interobserver reliability?

| Table 2. Cross Tabulation of Results of Sedimentation Sign in LSS and LBP Study Groups |
|---------------------------------|-----|-----|
| Positive sedimentation sign     | 94  | 0   |
| Negative sedimentation sign     | 6   | 100 |
| Total                           | 100 | 100 |
| Total                           | 200 |

LSS indicates lumbar spinal stenosis; LBP, low back pain.
Phase II validation study

Clinical validation study to measure the performance of the Nerve Root Sedimentation Sign for the diagnosis of lumbar spinal stenosis

Lukas P. Staub\textsuperscript{a,*}, Thomas Barz\textsuperscript{b}, Markus Melloh\textsuperscript{c}, Sarah J. Lord\textsuperscript{a,d}, Mark Chatfield\textsuperscript{a}, Patrick M. Bossuyt\textsuperscript{e}

**Best data available to address clinically relevant question**

- Retrospective cohort study, N= 118, representative population
- No reference standard to define LSS, or eligibility for surgery
- Is the sign associated with treatment outcomes?

No established treatment criteria

1. comparison of patient outcomes by sedimentation sign (within treatment groups)
2. 2x2 cross-classification of treatment selection (based on existing tests) with sedimentation sign
Methods study

Improve research methods...

Target practice: choosing target conditions for test accuracy studies that are relevant to clinical practice

S J Lord research fellow¹², L P Staub PhD candidate¹, P M M Bossuyt professor of clinical epidemiology³, L M Irwig professor of epidemiology²

Summary points

Studies of test accuracy traditionally measure how well the test distinguishes between the presence and absence of disease

Such studies may underestimate or overestimate a test’s clinical value if a narrower spectrum of disease is relevant for diagnosis and management decisions

Accuracy studies should use clinically relevant disease as the target condition

Definition of the target condition should be based on evidence from prognostic studies and treatment trials

*BMJ* 2011;343:d4684
Phase III prospective validation

Accessible protocol – expedite validation, dissemination

• Independent validation: sign validity and reliability
  – US (SPORT trial), Canada, Korea

• Editorials

that it reported on an imaging finding that meets many of the criteria we all look for when evaluating a new diagnostic method or modality (such as guide for treatment, simplicity of use, cost-effectiveness, and so forth). Most importantly, this study shows (and I believe) that a positive or negative sedimentation sign can be used to guide the treatment of patients with LSS. As with any imaging, his-


John Hopkins University, Baltimore
Next phase

- Grant applications...

Spine surgery registry data
- classify test results
- identify risk factors

Develop risk models to improve treatment selection
Sum-Up

• Preliminary evidence – critical seed
  – Pilot study
  – Proof of concept study
  – Demonstrate feasibility

• Build evidence – seek highest quality achievable design
  – Minimise bias
  – Optimise applicability

...don’t get distracted from the important question for practice

• Limited data – can still provide best available evidence to inform practice, and will have high impact if important neglected clinical problem

***robust design***
Resources

• EQUATOR  Enhancing the QUAlity and Transparency Of health Research

http://www.equator-network.org/

- Comprehensive lists of the available reporting guidelines, listed by study type:
  - Experimental studies
  - Observational studies
  - Diagnostic accuracy studies
  - Biospecimen reporting
  - Reliability and agreement studies
  - Systematic reviews
  - Qualitative research
  - Mixed methods studies
  - Economic evaluations
  - Quality improvement studies
  - Other reporting guidelines
  - Reporting data
  - Statistical methods and analyses
  - Sections of research reports
  - Specific conditions or procedures.

Quick links to reporting guidelines:
- CONSORT checklist and flow diagram
- CONSORT extensions
- TRED checklist
- STARD checklist & flow diagram
- STROBE checklists
- PRISMA checklist and flow diagram
- COREQ checklist
Non-randomised comparisons

- Flawed: different risk groups, test criteria, treatment protocols, supportive care

**Historical cross-trial comparisons for competing treatments in advanced breast cancer – An empirical analysis of bias**

C.K. Lee a,*,d, S.J. Lord a,d, M.R. Stockler b,d, A.S. Coates c,d, V. Gebski a,d, R.J. Simes b,d

![Adjusted analysis chart](image)

- Individual patient data meta-analysis

*(Eur J Cancer (2009))