Experimental Study

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James Lind

- Born Edinburgh 1716
- On HMS Salisbury in 1747 he allocated 12 men with scurvy
  - Cider
  - Seawater
  - Horseradish, mustard, garlic
  - Nutmeg
  - Elixir Vitriol
  - Oranges and Limes
Evaluation process

- Define research question
- What is already known?
- Identify appropriate study design
- Define population, intervention and criteria for evaluation
- How large a study?
- Consider measurement of evaluation criteria ("outcomes")
  - How often?
  - Timing? Length of follow up?
  - To whom? Who collects the data? What format?
- Analysis of data
- Dissemination and implementation
The need to evaluate health care

- Variations in health care
- Unproven treatments
- Inadequacies in care
- Inaccurate medical models
- Limitation of resources
- New innovations
- ...
Define research question and what is already known

- Research question (PICOT)
  - Population
  - Intervention
  - Control/comparator
  - Outcome
  - Target
- Has the question already been answered?
  - Conduct review to assess what is know about intervention
Definition of population, intervention and "outcomes"

- Population
  - Strict definition (explanatory) or flexible (pragmatic)
- Intervention
  - Dose of drug, timing etc
- "Outcomes"
  - Health related Quality of Life
  - Biochemical outcomes
  - Symptoms
  - Physical assessment
  - Patient satisfaction
  - Acceptability
  - Cost-effectiveness
Measuring “outcome”

- Questionnaires, interview, medical notes etc
- Timing of questionnaires?
  - Baseline (prior to treatment)
  - Short term outcomes
  - Long term outcomes
- Who collects the data?
Study design

Experimental studies
(intervention of the researcher, observation of what happens)

- Randomised Controlled trials (RCTs)
- Non-Randomised Controlled trials

Observational studies
(subjects are observed, no action from the researcher)

- Cohort studies
- Case-control studies
- Cross sectional studies
- Ecological studies
Study Designs

- Observational
  - Cross-sectional surveys
  - Cohort
- Case-control studies
- Experimental
  - RCT
  - Quasi-experiments

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Quick; can cover whole population, giving representative information whether or not people are seeking care</td>
<td>Based mainly on self-report (biases?); diagnostic information usually inaccurate; can't establish causal sequence</td>
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<tr>
<td>Prospective, so can establish causal sequence; can estimate incidence</td>
<td>Time-consuming; costly; attrition of cohort?</td>
</tr>
<tr>
<td>Relatively cheap way of focusing on causal factors</td>
<td>Requires recall of past events (inaccurate?); controls not equivalent to cases</td>
</tr>
<tr>
<td>Controls for all main forms of bias; good for both etiological and evaluative research</td>
<td>Ethical concerns in etiological applications; Often uses selected populations: issue of generalizability?</td>
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<tr>
<td>May be more practical than RCT: can use &quot;natural experiments&quot;</td>
<td>Allocation bias often significant (exp'tal and control groups not equivalent)</td>
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What is a randomised controlled trial?

**Simple Definition**

- A study in which people are allocated at random to receive one of several interventions

(simple but powerful research tool)
Simple RCT model

Trial participants

RANDOMLY allocated to experimental or CONTROL group

EXPERIMENT

CONTROL
What is a randomised controlled trial?

- Random allocation to intervention groups
- All participants have equal chance of being allocated to each intervention group

Why RCTs are referred to as randomised controlled trials.
Terminology

- **Interventions** are comparative regimes within a trial

- Prophylactic, diagnostic, therapeutic e.g.
  - preventative strategies
  - screening programmes
  - diagnostic tests
  - drugs
  - surgical techniques
Patients → RANDOMISATION → Control, Treatment A, Treatment B
Patients → Randomisation

Period 1:
- Treatment A
- Treatment B

Period 2:
- Treatment A
- Treatment B

Wash out period
<table>
<thead>
<tr>
<th>Treatment B</th>
<th>Treatment A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (placebo)</td>
<td>NO</td>
<td>Neither A nor B</td>
</tr>
<tr>
<td>NO (placebo)</td>
<td>YES</td>
<td>A only</td>
</tr>
<tr>
<td>YES</td>
<td>B only</td>
<td>Both A and B</td>
</tr>
<tr>
<td>Type of randomisation</td>
<td>Description</td>
<td>Cons</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td><strong>Simple randomisation: For large RCTs</strong></td>
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</table>
| **Simple** | - Basic concept of tossing a coin commonly used for large sample size  
- Tables of random numbers can be used | Can be unbalanced over treatments if small RCTs |
| **Restricted randomisation: To balance group sizes in smaller RCTs** | | |
| **Blocked** | - A "block size" and "allocation ratio" (number of subjects in one group versus the other group) are specified, and subjects are allocated randomly within each block  
- Ensure equal treatment numbers | Small blocks may be decoded and may not preserve double blinding |
| **Stratified** | Ensure good balance of participant characteristics in each group | Can require small blocks |
| **Adaptive randomisation: For many factors and small RCTs** | | |
| **Covariate-Adaptive randomization** (e.g Minimisation) | The probability of being assigned to a group varies in order to minimize "covariate imbalance." | Lessens randomness because only the first subject's group assignment is truly chosen at random |
"Normal" Randomization

100 Participants
50 Get Drug
50 Get Placebo

Unknown mix of gender in each group

Stratification, then Randomization

100 Participants
50 Men
50 Women
25 Men Get Drug
25 Men Get Placebo
25 Women Get Drug
25 Women Get Placebo
Minimising bias in RCTs

- **Blinding**
  - Single blind – participants are unaware of treatment allocation
  - Double blind – both participants and investigators are unaware of treatment allocation
  - Requires use of placebos in drug trials
Blinding, placebos

- RCTs should use the maximum degree of blinding that is possible
- Placebo is a ‘dummy’ treatment given when there is no obvious standard treatment
  - needed as the act of taking a treatment may have some effect - need to attribute
  - double blind treatments must be indistinguishable to those affected
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<thead>
<tr>
<th></th>
<th><strong>Explanatory</strong></th>
<th><strong>Pragmatic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question</strong></td>
<td>efficacy</td>
<td>effectiveness</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>‘laboratory’</td>
<td>normal practice</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>strictly defined</td>
<td>broader, clinically indicated (uncertainty)</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>strictly defined</td>
<td>as clinical practice</td>
</tr>
<tr>
<td></td>
<td>Explanatory</td>
<td>Pragmatic</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>short-term surrogates</td>
<td>long-term, patient-centered and resource orientated</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>small (usually single centre)</td>
<td>larger (often multi-centre)</td>
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<tr>
<td><strong>Analysis</strong></td>
<td>treatment received</td>
<td>intention to treat</td>
</tr>
<tr>
<td><strong>Relevance to practice</strong></td>
<td>indirect</td>
<td>direct</td>
</tr>
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Patients with cerebrovascular disease

Surgery + ASA

ASA

1 month 1 year

Surgery

Stroke

Per protocol 10/90 = 0.11
Intention-to-treat 20/100 = 0.20

RRR = 0.45
RRR = 0

20/100 = 0.20
20/100 = 0.20
RCT strengths

- Confounding variables minimised
- Only research design which can in principle yield causal *relationships*
  - can clarify the direction of cause and effect
- Accepted by EBM school
- Don’t have to know everything about the participants
RCT limitations

- Contamination of intervention groups
- Comparable controls
- Problems with blinding
- What to do about attrition?
- Are patients/professionals willing to be in trial different from ‘refusers’? - external validity
- Cost!
Classical Design of Randomized Experiments

Randomization:
- Intervention group
- Control group

A1, B1 = Pre-intervention data collection points
A2, B2 = Post-intervention data collection points

Classical Quasi-Experimental Design

Non-random assignment to groups:
- Intervention group
- Control group

A1, B1 = Pre-intervention data collection points
A2, B2 = Post-intervention data collection points
Post-Test Only Quasi-Experimental Design

- Intervention group
- Non-random assignment to groups
- Control group

Non-Experimental Pre-Test/Post-Test Design

A1 = Pre-intervention data collection points
A2 = Post-intervention data collection points
Non-Experimental Time Series Design

A1, A2, A3 = Pre-intervention data collection points
A4, A5, A6 = Post-intervention data collection points
Efficacy of Single-Dose and Triple-Dose Albendazole and Mebendazole against Soil-Transmitted Helminths and *Taenia* spp.: A Randomized Controlled Trial

Peter Steinmann¹,²,³*, Jürg Utzinger¹,², Zun-Wei Du⁴, Jin-Yong Jiang⁴, Jia-Xu Chen³, Jan Hattendorf¹,², Hui Zhou³, Xiao-Nong Zhou³

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Community-directed educational intervention for malaria elimination in Bhutan: quasi-experimental study in malaria endemic areas of Sarpang district

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