When **NOT** to do an RCT: Considering Alternative Designs

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Hierarchy of Evidence

SYSTEMATIC REVIEWS OF RCTS

RANDOMISED CONTROLLED TRIALS

NON-RANDOMISED TRIALS

Cohort studies
Case-control studies
Cross-sectional surveys
Case series/reports
Editorials/expert opinion
When might an RCT may NOT be necessary?

• Example of treatments with dramatic effects that were largely accepted on basis of evidence from case series/ non-randomised cohorts

• Stable/progressive conditions- rapid effects of treatment are easy to demonstrate, ie. Removal of cataract ⇒ vision

• Very large treatment effect so that even if confounding factors have contributed to effect size, evidence suggests that treatment is effective

• Consider Bradford Hill criteria for causation
However...

- Be wary of inferring effects of treatments from evidence other than RCTs
- If condition is fluctuating/intermittent then case series may be misleading
- **Need randomisation and other measures to reduce bias**- so that we can distinguish treatment effects from effects of bias
Is an RCT the logical next step?

- Does an answer already exist to the question you are planning to study?
- Is the evidence-base sufficient so that an RCT is the natural “next step”? May need to consider extensive formative work plus pilot phase
- Is it ethical to randomise participants?
- Do you have enough resources and support to run an RCT?
Are RCTs the only gold that glitters?

- The important contribution of other study designs/methodologies in MH research & the limitations of RCTs
- Treatment protocols from RCT evidence focus clinicians upon diagnosis-based interventions rather than individualised interventions
- How generalisable are results to patients from other settings?
- Design lends itself particularly to pharmacological treatments
- “The challenge is to make he important measurable, not the measurable important”
- Researcher values and beliefs will lead them to investigate one intervention rather than another
Strengths of Observational Designs

• Investigating questions about the risk factors for disease
• Investigating questions about the course of a health state/disease
• Understanding mechanisms that underlie associations
• Understanding experiences and decision-making around health/illness/treatment
Strengths of Experimental Design

• Investigating questions about the efficacy/effectiveness of prevention and treatment interventions

• Not always feasible to randomise
• Opportunistic study designs
• Not always an RCT!
Introducing Quasi-Experimental Designs

**OBSERVATIONAL**
- Cohort studies
- Case-control studies
- Cross-sectional surveys

**QUASI-EXPERIMENTAL**
- Non-randomised, controlled trials
- Uncontrolled before and after studies
- Time series

**EXPERIMENTAL**
- Pragmatic RCTs
- Scientific RCTs
# Quasi-Experimental Designs

<table>
<thead>
<tr>
<th>Non-randomised controlled trials</th>
<th>Uncontrolled before and after studies</th>
<th>Time series</th>
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</thead>
<tbody>
<tr>
<td>• Control population identified which has similar characteristics/performance to the treatment group</td>
<td>• Measures performance before and after the introduction of an intervention</td>
<td>• Aim to detect whether an intervention has had an effect significantly greater than underlying trend</td>
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<td>• Data collected in both populations at the same time</td>
<td>• No comparison group</td>
<td>• Data collected at multiple time points before and after intervention</td>
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<td>• Similar data collection methods</td>
<td>• Observed differences presumed to be due to intervention</td>
<td>• Multiple time points before intervention → estimation of underlying trend</td>
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<tr>
<td>• Data collected before and after intervention is introduced in the treatment group</td>
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<td>• Multiple time points after intervention → estimate intervention effect, whilst accounting for underlying trend</td>
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<td>• “Between group” analysis</td>
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## Criteria for Cause and Effect

Table 2: Definitions of Hill's Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1  Strength</td>
<td>The size of the risk as measured by appropriate tests.</td>
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<td>2  Consistency</td>
<td>The association is consistent when results are replicated in studies in different settings using different methods.</td>
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<td>3  Specificity</td>
<td>When a single putative cause produces a specific effect.</td>
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<td>4  Temporal sequence</td>
<td>Exposure always precedes the outcome.</td>
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<td>5  Dose response</td>
<td>An increasing level of exposure (in amount and/or time) increases the risk.</td>
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<td>6  Experimental evidence</td>
<td>The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen</td>
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<td>7  Biologic plausibility</td>
<td>The association agrees with currently accepted understanding of pathobiological processes.</td>
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<tr>
<td>8  Coherence</td>
<td>The association should be compatible with existing theory and knowledge.</td>
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<td>9  Analogy</td>
<td>A finding of analogous associations between similar factors and similar diseases.</td>
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Non-randomised controlled Trials

- Control population identified which has similar characteristics/performance to treatment group
- Data collected in both populations at the same time, similar data collection methods
- “Between group” analysis
- Observed differences presumed to be due to the intervention
Strengths & Limitations

• Can be used where randomisation not possible
• Well-designed studies should protect against secular trends/sudden changes
• Difficult to identify comparable control group
• Even in well-watched control/treatment groups, baseline differences
• “Within group” analyses sometimes carried out - not appropriate
• Difficult to attribute effect to intervention with confidence
Example: PRiSM (Thornicroft et al 1998)

• Non-randomised controlled trial investigating impact of introduction of community-based MH care upon people with psychosis
• Comparing intro of two different types of community-based care (intensive v. generic)
• Measures at t0 and t1 (2yrs later)
• 2 geographical areas in South London- well-matched in terms of population characteristics
• **Reason for NOT randomising**- intervention was at geographical area, resources did not allow inclusion of enough areas to allow randomisation
Uncontrolled before-after study

• Measures performance before and after the introduction of an intervention
• No comparison group
• Observed difference presumed to be due to intervention
Strengths & Limitations

- Sudden changes/secular trends make it difficult to be sure if observed changes are due to the intervention
- Intervention = confounded by Hawthorne effect - non-specific benefit of taking part in research
- Evidence to suggest that uncontrolled trials over-estimate treatment effects (Lipsey & Wilson 1993)
- Caution when interpreting results!
Example: Guided self-help (Farrand et al 2008)

• Guided self-help clinics with graduate MH workers for people with anxiety and/or depression

• Initial assessment → 2 x weekly 20min sessions → 3m progress meeting

• 62% of those with depression experienced clinically significant and reliable change in 3m follow-up
Uncontrolled before-after Study

Patient progress through Graduate Mental Health Worker clinic
Uncontrolled before-after Study

Mean score on Hospital Anxiety & Depression Scale (HADS) Anxiety (HADS-A) and Depression (HADS-D)
Strengths & Limitations

- Useful as proof of concept study
- Results justify and recommend subsequent RCT?
- Problems with interpretation - spontaneous remission?
Time Series Analysis

• Aims to detect whether an intervention has had an effect that is significantly greater than the underlying trend
• Data collected at multiple time points before and after intervention
• Multiple time points before intervention $\rightarrow$ estimation of underlying trend
• Multiple time points after intervention $\rightarrow$ estimation of intervention effect, whilst accounting for underlying trend
Example: Cannabis Classification (Hamilton et al 2013)

- Cannabis= Class B (1999-2004); moved to Class C (2004-2009); Class B (2009-?)
- Class C would free up police time for more serious offences, credibility of drugs education
- Concern in media (2004 onwards) re. MH effects
- 141 measurement points
- Decline in trends for admissions for cannabis-related psychosis from 2004-2009
- Due to reclassification?!
Time Series Analysis

Trend in the number of admissions for cannabis psychosis
Strengths & Limitations

• Opportunistic study- using routinely collected data
• Causal chain? Reclassification → changes in cannabis use → levels of cannabis psychosis → levels of admissions for cannabis psychosis
• Difficult to estimate error- particularly around diagnosis
• No data on whether/how proportion of cases admitted varied over study period
• Time lag? If reclassification was expected to have impact, could expect time lag
Key Messages

Is an RCT the right design/right next step?

• Ethics
• Evidence-base
• Resources/logistics
• Consider alternative study designs