When NOT to do an RCT: Considering Alternative Designs

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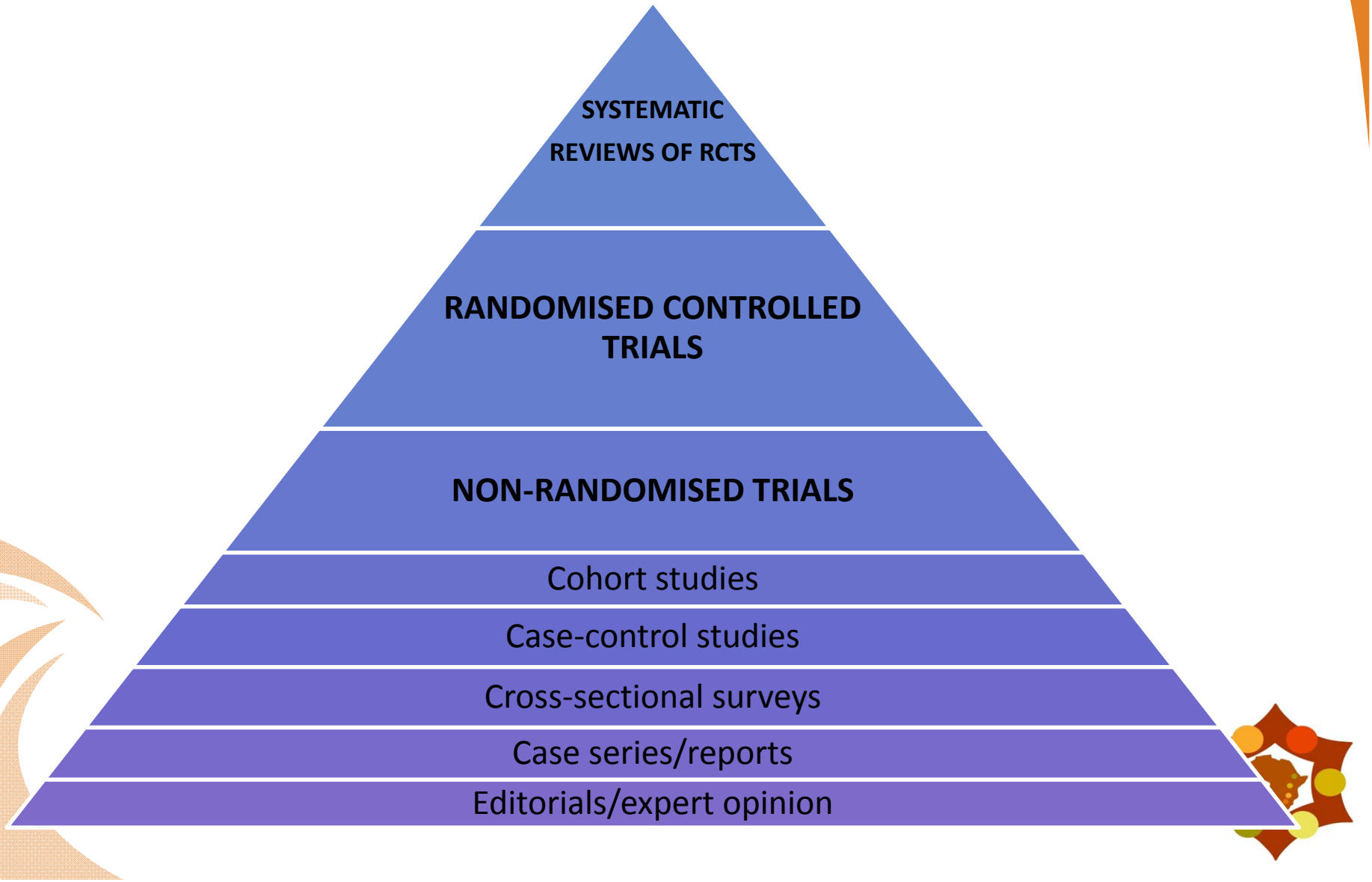
Hierarchy of Evidence



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	QUASI-EXPERIMENTAL	EXPERIMENTAL
• Cohort studies • Case-control studies • Cross-sectional surveys	• Non-randomised, controlled trials • Uncontrolled before and after studies • Time series	• Pragmatic RCTs • Scientific RCTs

Quasi-Experimental Designs

Non-randomised controlled trials

- Control population identified which has similar characteristics/performance to the treatment group
- Data collected in both populations at the same time
- Similar data collection methods
- Data collected before and after intervention is introduced in the treatment group
- "Between group" analysis
- Observed differences presumed to be due to the intervention

Uncontrolled before and after studies

- Measures performance before and after the introduction of an intervention
- No comparison group
- Observed differences presumed to be due to intervention

Time series

- Aim to detect whether an intervention has had an effect significantly greater than underlying trend
- Data collected at multiple time points before and after intervention
- Multiple time points before intervention→ estimation of underlying trend
- Multiple time points after intervention→ estimate intervention effect, whilst accounting for underlying trend

Criteria for Cause and Effect

Table 2: Definitions of Hill's Criteria

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

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

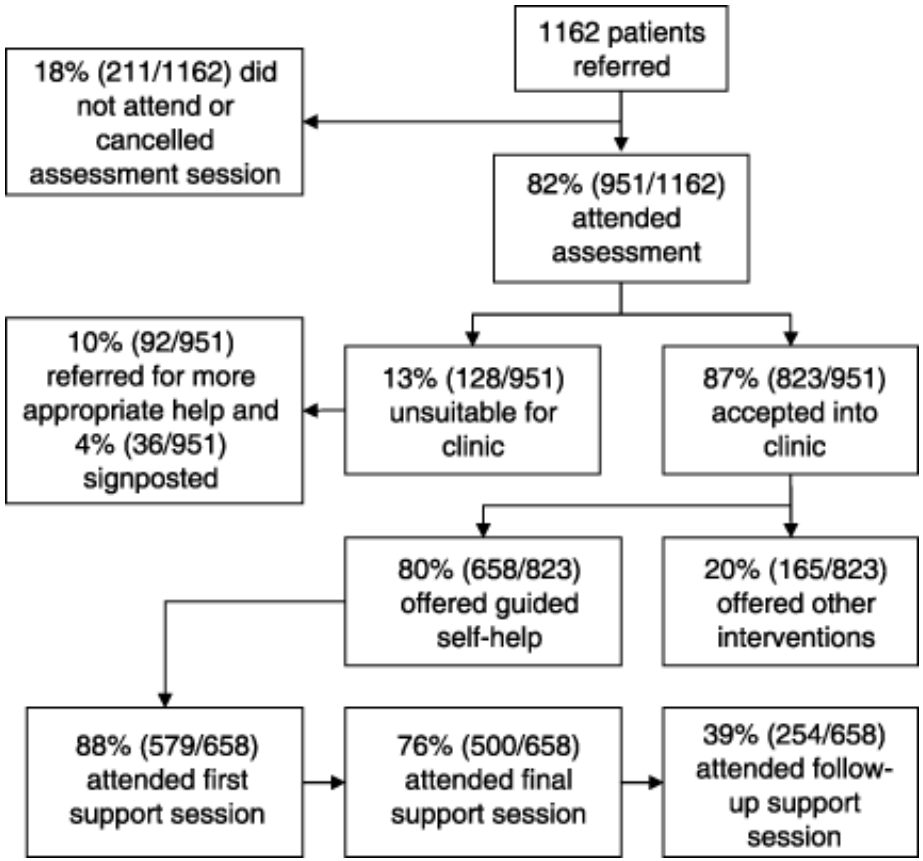
Strengths & Limitations

- 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)

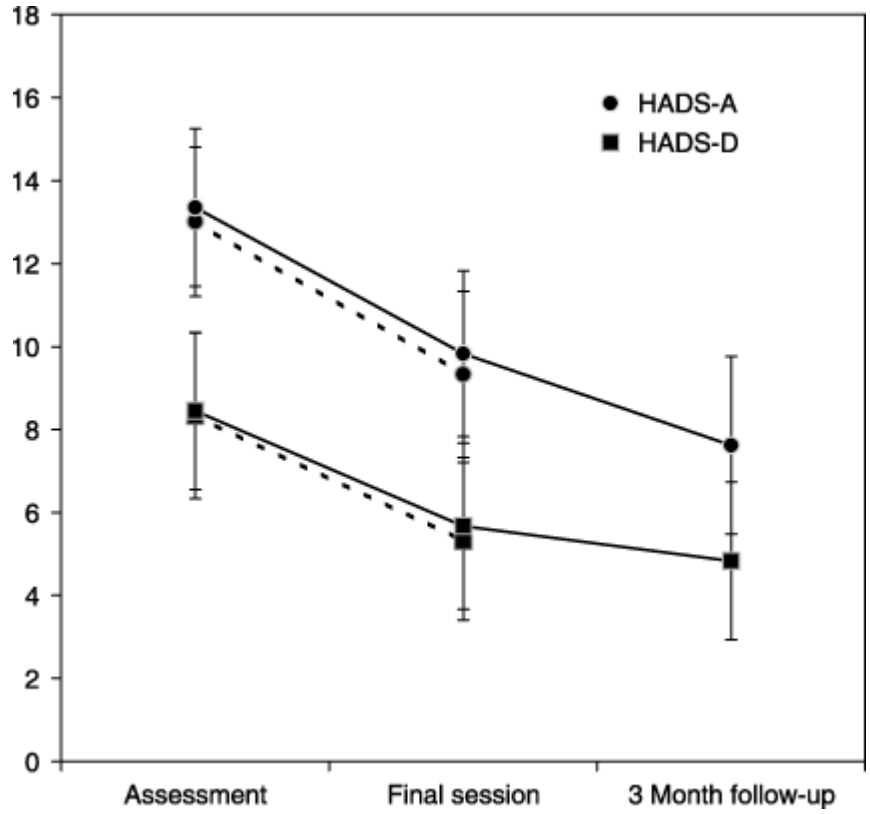
- Guided self-help clinics with graduate MH workers for people with anxiety and/or depression
- Initial assessment→ 2 x weekly 20min sessions→ 3m progress meeting
- 62% of those with depression experienced clinically significant and reliable change in 3m follow-up

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?**

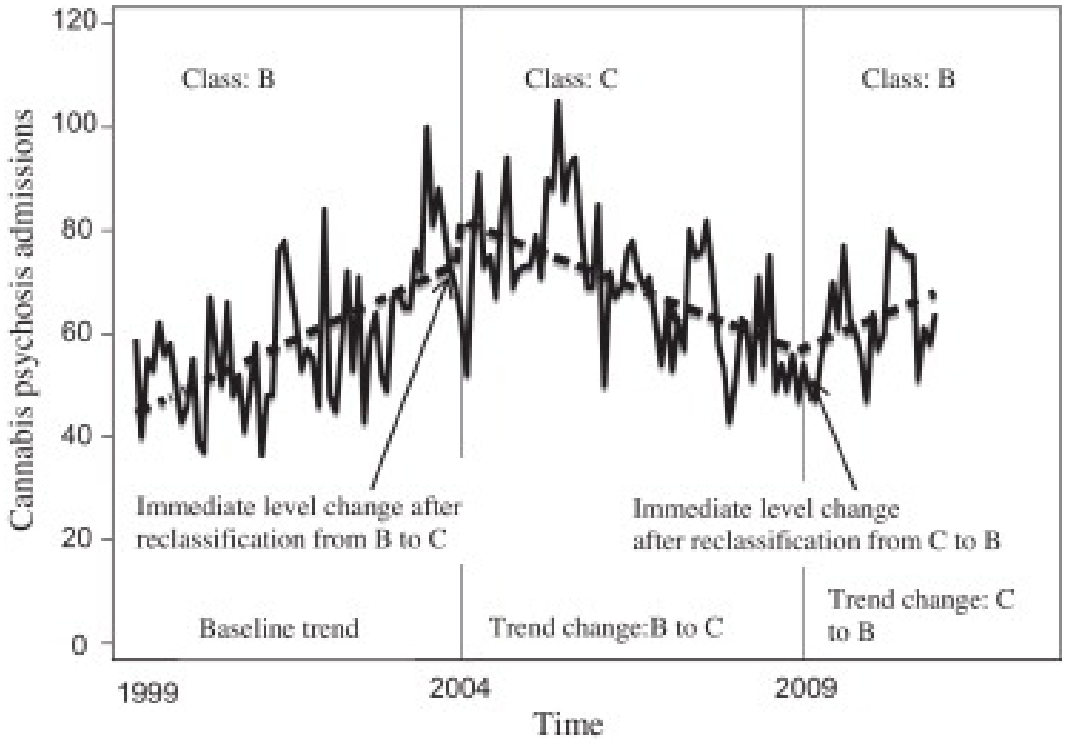
Time Series Analysis

- 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→ estimation of underlying trend
- Multiple time points after intervention→ 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