Complex Interventions
Stage 1: Development of complex interventions
Professor David Richards

What types of research/data could inform a causal model of a complex intervention?

- Epidemiology
- Risk factors
- Barriers & facilitators (process)
- Theory
- Policy mapping ...

The Systematic Review 1

• “Systematic reviews locate, appraise, and synthesise evidence from scientific studies in order to provide informative empirical answers to scientific research questions.”
  CRD, 2001

The Systematic Review 2

- adhere to a strict scientific design
- search literature comprehensively
- attempt to minimise bias
- try to maximise reliability
- critically and concisely summarise the available evidence by applying uniform and rigorous standards of appraisal

Methods for Developing and Evaluating Complex Interventions

Feasibility/piloting
1. Testing procedures
2. Estimating recruitment/retention
3. Determining sample size

Development
1. Systematic Reviews
2. Defining Theory of Change
3. Theoretical/Economic Modelling

Medical Research Council Research Framework

Evaluation
1. Assessing effectiveness
2. Understanding change process
3. Assessing cost-effectiveness

Implementation
1. Dissemination
2. Surveillance and monitoring
3. Long term follow-up

MRC 2008 on intervention development ...

“You should begin by identifying the relevant, existing evidence base, ideally by carrying out a systematic review” MRC 2008

But,


see Table III of Hardeman et al. 2005 for full picture of which evidence informed which part of methods
Advantages of Systematic Reviews

- start with clear question
- strive to locate all relevant literature
- contain explicit study inclusion and exclusion criteria
- systematically examine primary study method quality for bias and heterogeneity
- base conclusions on studies which are most methodologically sound

Systematic reviews therefore....

- are examples of rigorous secondary research
- limit reviewers’ personal biases
- provide more accurate and reliable conclusions
- reduce large amounts of information to manageable and key findings
- identify best evidence for practice and gaps in the evidence base

Reviews of Effectiveness

- Oldest method
- What works?
- Narrative and statistical review
- Focused on interventions
- Interested in differences and heterogeneity

Qualitative Evidence Synthesis approaches

<table>
<thead>
<tr>
<th>QES approach</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis</td>
<td>Sandelowski &amp; Barrows (2003)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Forrest et al. (2000)</td>
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<td>Random effects meta-analysis</td>
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<td>Narrative synthesis</td>
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<td>Content analysis</td>
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<td>Case study</td>
<td>Forrest et al. (2000)</td>
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<td>Qualitative Comparative analysis</td>
<td>Forrest et al. (2000)</td>
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<td>Comparative case</td>
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Definition of MMRS

- ‘Mixed research synthesis’ (Sandelowski et al., 2006)
- ‘Mixed studies review’ (Pluye et al., 2000)
- ‘Mixed methods synthesis’ (Harden & Thomas, 2005)

A more integrative definition (Heysaert, Maes & Onghena, 2011):

- MMRS – A synthesis in which researchers combine primary qualitative, quantitative, and mixed methods studies, and apply a mixed methods approach in order to integrate these studies, for the broad purposes of breadth and depth of understanding and corroborating.
- Promising utility for research and practice: Combining strengths of qualitative and quantitative techniques and studies

Further sources for possible types of review to consider

  Realist review - a new method of systematic review designed for complex policy interventions. Journal

Systematic Effectiveness Reviews: Remember this…!

- Participants
- Interventions
- [Comparisons]
- Outcomes
- Design

Aims, Objectives and Research Questions

- Broad Aims
  - This study will look at the impact of steroids on chronic asthmatics
- Specific Objectives
  - To determine the impact of steroids on bone density in chronic asthmatics
- Clear Questions
  - Does the regular inhalation of steroids cause reduction in bone density in chronic asthmatics?

Aims and Objectives

- Write your own:
  - Aim
  - Objective
  - Question
- For a systematic review
  - PICOD!

Systematic Reviews: Summary

- Systematic reviews are rigorous reviews of the evidence base from numerous primary studies. They use a method which can be replicated and provide health care professionals with clear guidance for basing their practice on best evidence. They also identify where there are gaps in the evidence base and therefore generate future research questions.

Key Reference


Web Resources

- Database of Reviews of Effectiveness
  - http://www.york.ac.uk/inst/crd/darefaq.htm
- Cochrane Collaboration
  - www.cochrane.org/reviews/index.htm
- All European countries have evidence based sites, e.g.
  - www.cebam.be - Belgium
  - www.cbo.nl - Netherlands Cochrane Centre
- Joanna Briggs Institute and collaboration
  - www.joannabriggs.edu.au
A Systematic Review Protocol: What does it look like?

- Background
- Research question/hypotheses
- Study inclusion criteria (P-I-C-O-D)
- Search strategies
- Method of assessing study validity
- Data extraction sheet
- Method of data synthesis
- References

Searching

- Getting the most extensive coverage of primary research possible
- This is not the same as finding lots of journal articles

Inclusion Criteria Drive the Search

- Research question
- Concepts
  - Participants
  - Interventions
  - Comparisons
  - Outcomes
  - Design...
- Maximise concept identification
- Minimise concept combination
- Balance specificity with sensitivity

Where to Search?

- Computerised and manual searching
- Electronic databases
- Reference/footnote chasing
- Hand-searching journals
- Grey literature
- Research registers
- Researchers and manufacturers?

Electronic Search Principles

Start with individual broad concepts and combine them together, gradually narrowing your search down as you go.
Electronic Searching Stage 1
Searching for Each Concept in Turn

• Maximise hits with boolean operator ‘or’
• Use truncation ($) and wildcards
• Try ‘suggest’ button for exploding mesh terms
• Use keyword searches in absence of or as well as mesh
• BUT YOU DON’T NECESSARILY NEED TO SEARCH ALL CONCEPTS – TWO OR THREE IS USUALLY APPROPRIATE

Electronic Searching Stage 2: Combining Concepts

• Combine concepts with ‘and’
• Read results
• Mark results
• Output results
  – print, email, save

Developing a Search Strategy

Exercise
• Examine the search strategy provided
• Identify concept searches
  – how many?
• Identify concepts
  – what are they? which lines define concept?
• Identify concept combination
  – which text combines concepts?

Selecting Studies

• Read title
  – Reject or include? If include....
• Read abstract
  – Reject or include? If include....
• Read paper
  – Reject or include
• Always use specific criteria for inclusion or rejection and note reason for rejection (PIOD)

Appraisal

Determining relevance and quality of included studies
Data Extraction: Overview

- Extract on Scope:
  - Study Design
  - Participants and Setting
  - Interventions and Comparisons
  - Outcomes measured
- Quality
  - Specific factors
- Results of primary studies

Data Extraction

- Always allow space for:
  - Authors conclusions
    - space for brief synthesis from paper
  - Reviewers conclusions
    - overall view of interpretation of study quality and of results
  - The information extracted from primary studies is the raw data of the systematic review

Presenting the Extraction: Scope

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Participants</th>
<th>Interventions and Comparisons</th>
<th>Outcomes Measured</th>
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<tbody>
<tr>
<td>1</td>
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</tr>
</tbody>
</table>

Presenting the Extraction: Quality

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality A</th>
<th>Quality B</th>
<th>Quality C</th>
<th>Quality D</th>
<th>Overall Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tbody>
</table>

Presenting the Extraction: Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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</table>

Study Quality

- How do we know what is a good quality study?
- By methodological hierarchy
- By quality components within method
- Using checklists and scales
- By study conduct
Study Quality

- Apply study design hierarchies
- General quality/bias considerations
  - selection, performance, measurement, attrition
- Individual design quality checklists
- Quality scales (avoid average scores)
- Multiple Reviewers
- Managing Disagreement

Examples of Experimental Quality

- Randomisation
- Treatment allocation
- Group similarity
- Eligibility/exclusion criteria
- Blinding (assessor, patient, provider)
- Primary means and SDs
- Intention to treat analysis

Other criteria

- Sample representativeness
- Length of follow-up
- Similarity of health status
- Reliable identification of health status
- Matching for confounds
- Quality of outcome assessments

Synthesis

Putting it all together

Objectives of Data Synthesis

- Provide an estimate of the overall effectiveness of an intervention
- Review effectiveness in different studies, populations and settings
- Investigate differences
- Answers the review question!

Data Synthesis

- Narrative and/or statistical
  - i.e. Descriptive and/or meta-analysis
- Scope of combined studies
- Quality of combined studies
- Results of combined studies
- Weighting of studies by PICOD, size and quality
- Identification of themes to help explain the results
Method

• start broad
  – non-quantitative overview
• narrow down
  – quantitative synthesis (meta analysis)
  – in the framework of the non-quantitative overview
  – is an extension of the broad non-quantitative review

Non-Quantitative Overview - 1

• Always include this descriptive stage
  – people
  – interventions and comparisons
  – settings and environment (social etc.)
  – outcomes (domains and comparability of measures)
  – weight according to methodological rigour of studies (validity and sample size)

Examples (Ekers et al, 2007) I

• P: Twelve studies with a total of 459 patients contributed data to this analysis [1, 2, 4–7, 9, 11, 12, 14, 16, 17]. Participants were taken from adult community sources consisting of out-patients [2, 4, 6, 7, 11, 12, 16, 17], volunteers [5, 8, 14] and students [1], two studies used older adults [11, 12].
• I: Interventions ranged from supported bibliotherapy [12, 14], brief therapy with six 40-min sessions [1] to 24 50-min sessions [16]. Facilitators were advanced graduate psychology/therapy students in five studies [1, 5, 6, 7, 9], experienced psychotherapists in four studies [2, 11, 16, 17] and unclear in one study [4].

Examples (Ekers et al, 2007) II

• C: Control interventions consisted of delayed treatment [1, 3, 9, 11, 12, 14, 16, 17], treatment as usual [4, 5, 7] and relaxation [2, 5]. All comparisons were taken immediately after intervention.
• O: Depression symptom level was assessed using either BDI self-report measure [1, 2, 4, 5, 7, 9, 17] or the HAMD assessor rating scale [12], or both [6, 11, 14, 16]. Recovery was defined by clinical interview in one study [11] and by BDI score in two studies [2, 14].

Meta analysis

The statistical combining of data
Meta analysis is possible when:
• data available
• enough data available
• studies not too heterogeneous for combination
  – no differences in patient characteristics, variable interventions, study design and quality

Effect of low salt diet on Syst. blood pressure (13-60 mo)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number, change in SBP (sd)</th>
<th>WMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low salt</td>
<td>Control</td>
<td>Low salt - Control</td>
</tr>
<tr>
<td>TOHP II</td>
<td>594</td>
<td>-0.7 (8.2)</td>
</tr>
</tbody>
</table>

'dif' equals mean change in low salt group minus mean change in control group:
dif = -0.7 – 0.3 = -1.0
### Showing uncertainty

- The result for each study (shown by the ‘blob’) has a level of uncertainty attached.
- This is expressed as a 95% confidence interval.
- For the TOHP phase II study the difference in BP is –1.0 mmHg.
- The 95% confidence interval is -2.03 to 0.03.

### Effect of low salt diet on Syst. blood pressure (13-60 mo)

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<th>WMD Low salt</th>
<th>Control</th>
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<th>Dif, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOHP II 1997</td>
<td>594 -0.7</td>
<td>596 0.3</td>
<td></td>
<td>-1.0 (-2.03 to 0.03)</td>
<td></td>
</tr>
<tr>
<td>Morgan 1978</td>
<td>31 -5.5</td>
<td>31 -4.0</td>
<td></td>
<td>-1.5 (-12.60 to 9.60)</td>
<td></td>
</tr>
<tr>
<td>TOHP I 1992</td>
<td>327 -4.9</td>
<td>417 -3.2</td>
<td></td>
<td>-1.7 (-2.85 to –0.55)</td>
<td></td>
</tr>
<tr>
<td>HPT 1990</td>
<td>174 -2.8</td>
<td>177 -2.9</td>
<td></td>
<td>0.1 (-1.85 to 2.03)</td>
<td></td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>1126</td>
<td>1221</td>
<td></td>
<td>-1.12 (-1.83 to –0.41)</td>
<td></td>
</tr>
</tbody>
</table>

### A real example

![A real example](image1.png)

### When to pool...

- We only combine the numbers from studies that we believe to be asking the same questions.
- Sometimes, though, studies can appear similar but give very different answers – we need to look out for this when performing a meta-analysis.

### The Systematic Review (reminder)

- “Systematic reviews locate, appraise, and synthesise evidence from scientific studies in order to provide informative empirical answers to scientific research questions.”
  
  CRD, 2001

### But...

- “The goal of a synthesis is not simply to compute a summary effect, but rather to make sense of the pattern of effects.”
  
  Borenstein et al, 2009

- One way to do this is to explore and explain variance in synthesis results.
**Heterogeneity**

- Another example of heterogeneity

**Population, design, intervention?**

**Substantial and genuine heterogeneity**

- Many statistical terms used to describe heterogeneity
- All driven by ‘Q’ statistic
  - a summated measure of the deviation of all studies’ effect sizes from the overall meta-analysis mean
  - provides an assessment of the statistical significance of heterogeneity
  - ‘genuine’ heterogeneity

- $I^2$ derived from $Q$
  - the proportion of observed dispersion that is real, rather than spurious
  - expressed as a ratio from 0% to 100%
  - 25% low, 50% moderate, 75%+ high
  - ‘magnitude’ of heterogeneity

- Older Chi-squared test of heterogeneity
  - $p<0.10$ demonstrates statistically significant heterogeneity

**Effect of low salt diet on Syst. blood pressure (13-60 mo)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number, change in SBP</th>
<th>WMD</th>
<th>Dif, 95% CI</th>
<th>Test for heterogeneity chi-square=2.54 df=3 $p=0.28$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Low salt</td>
<td>Control</td>
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</table>

- Favours low salt
**Meta-analysis 2**

- **Meta-analysis**
  - Overall, the effect of self-help interventions was 'indeterminate' according to current convention. With a pooled standardized mean difference of 0.43 and 95% CI 0.09–0.77 (Cohen, 1988).
  - The variation in effect size attributable to heterogeneity was 73.3%. When the analysis was restricted to those studies using 'graduated self-help', the pooled standardized mean difference was 'large' according to current convention (0.80, 95% CI 0.58–1.01), and the variation in effect size attributable to heterogeneity was 68.3%.

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**The Correct Order of Things**

- Meta-analysis precedes meta-regression
- Systematic review precedes meta-analysis

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**PRISMA**

- Reporting standards for Systematic reviews
- Development of ‘QUORUM’ standards

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**Systematic Reviews: Summary**

- Systematic reviews are rigorous reviews of the evidence base from numerous primary studies. They use a method which can be replicated and provide health care professionals with clear guidance for basing their practice on best evidence. They also identify where there are gaps in the evidence base and therefore generate future research questions.