A Trial By Any Other Name:

An Introduction to Complex Interventions, Pilot Trials and Cluster RCTs

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Overview

1. Trial phases
2. Complex interventions and the MRC Frameworks
3. Exploratory v. definitive RCTs
4. Individual v. cluster randomisation
Phases of Trials

**PHASE I**
- Checking for safety
- Sample: 10-20 healthy volunteers
- Unexpected side effects may occur

**PHASE II**
- Checking for efficacy
- Sample: about 200 patients
- Most research projects fail in Phase II due to product not being as effective as anticipated

**PHASE III**
- Confirm findings in large patient population
- Sample: more than 1,000 people
- Likelihood to detect rare side effects increases with number of people involved
- Previously untested groups may show adverse reactions

**PHASE IV**
- Testing long-term safety in diverse patient population
- Sample: “real life patients” – testing being carried out outside of clinical environment (post-marketing studies)

*Source: AGCS*
MRC Framework (2000)

- **Pre-clinical**
  - Explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues.

- **Phase I**
  - Identify the components of the intervention, and the underlying mechanisms by which they will influence outcomes to provide evidence that you can predict how they relate to and interact with each other.

- **Phase II**
  - Describe the constant and variable components of a replicable intervention AND a feasible protocol for comparing the intervention to an appropriate alternative.

- **Phase III**
  - Compare a fully-defined intervention to an appropriate alternative using a protocol that is theoretically-defensible, reproducible and adequately controlled, in a study with appropriate statistical power.

- **Phase IV**
  - Determine whether others can reliably replicate your intervention and results in uncontrolled settings over the long term.

**Continuum of increasing evidence**
What Makes An Intervention Complex?

- Number of interacting components within the experimental and control interventions
- Number and difficulty of behaviours required by those delivering and receiving interventions
- Number of groups/organisational levels targeted by the intervention
- Number and variability of outcomes
- Degree of flexibility of tailoring of the intervention permitted
Limitations of the Original MRC Framework

- Too closely tied to phases of drug development
- Needed greater attention paid to early phase piloting and development work
- Integration of process and outcome evaluation
- Greater tailoring to local context - not complete standardisation
- Need more guidance on development, reporting, implementation
- Consideration of alternatives to RCTs
Revised MRC Framework - 2008

**Development**
- Identifying the evidence base
- Identifying or developing theory
- Modelling process and outcomes

**Feasibility and piloting**
- Testing procedures
- Estimating recruitment and retention
- Determining sample size

**Implementation**
- Dissemination
- Surveillance and monitoring
- Long term follow-up

**Evaluation**
- Assessing effectiveness
- Understanding change process
- Assessing cost effectiveness
Developing a Complex Intervention

- Identifying existing evidence
- Identifying and developing theory
- Modelling process and outcomes
Example: UPBEAT

- Depression and coronary heart disease programme
Identifying Existing Evidence

Systematic review

• Qualitative and quantitative studies carried out in the UK
• Published after 2000
• Containing GP/Practice Nurse generated data concerning attitudes towards and experience of managing depression
Identifying and Developing Theory

- Interviews with practice nurses (n=12) and GPs (n=10) to determine preferences for future intervention
- Purposive sample - diversity in terms of ethnicity, age, practice setting from 4 x SE London boroughs
- Interviews with patients with CHD & depression
- Recruited from UPBEAT cohort study
- 30 patients with a positive PHQ-2, sampled consecutively
- Findings from systematic review and qualitative interviews discussed at multidisciplinary project group and steering group
Modelling Processes and Outcomes

• **Focus Group Study** - to determine potential acceptability of the intervention, identify any potential changes to content

• Participants were patients with a positive PHQ-2 score

• Provided with a short presentation describing the intervention as well as draft intervention materials
Conclusions

• Formative work led to change of plan
• Originally had planned to carry out definitive RCT of nurse-led stepped care intervention
• However, formative work demonstrated need for flexible intervention that could be tailored to individual needs
• Practice nurses stated that they would need support to deliver the intervention
• Therefore supporting need for an exploratory trial
Pilot/Feasibility/Exploratory Trials

• Pilot studies may lead to changes in study design
• May be required before large amounts of funding may be allocated for a definitive RCT
• External= stand-alone pieces of work planned and carried out prior to main study
• Internal= incorporated into the main study design of the RCT
Objectives of External Pilot Studies

1. To determine initial data for the primary outcome measure- in order to carry out **sample size calculation for main trial**
2. “Dummy run” of main trial- procedures, inclusion/exclusion criteria, storage and testing of equipment/materials, training of staff in admin and assessment of intervention
3. Testing data collection **forms/questionnaires**- comprehensibility, appropriateness
4. **Randomisation** procedure
5. **Recruitment and consent**
6. **Selection of most appropriate outcome measure**
7. **Follow-up**
8. **Adherence/compliance to intervention**
Internal Pilot Studies

• Carried out among the first pre-specified number of participants entering the trial
• Sample size estimates for main trial calculated from estimates obtained in pilot phase
• Does not allow pre-testing the feasibility etc. of other factors relating to trial
• Advantage= allows more accurate sample size estimates without lengthening main trial
Example- UPBEAT Exploratory Trial

Aims:
• To examine the feasibility and acceptability of telephone-delivered personalised care with treatment as usual for patients with comorbid CHD & depression
• To explore the types of needs and problems identified by patients in collaboration with case manager

**Primary outcome**= depressive symptom severity (HADS) at 1, 6 and 12m

**Secondary outcomes**= CHD symptoms, wellbeing, health service utilisation
Methods

- Individual randomisation
- Primary care v. primary care + personalised care involving regular follow-up by nurses
- Estimation of definitive effect size is NOT an aim of this study
- However, assuming a mean difference of >3 on HADS, a pooled SD around mean scores of 4, 30 participants would be needed per group (90% power, 5% significant level). Allowing LTFU of 25% → recruitment of 80 (40 per arm)
- Patients on case register for CHD sent info, those who provided consent assessed for depression, those who scored >8 were eligible, randomly allocated
Intervention

• Tailored face-to-face assessment and telephone-delivered follow-up provided by clinically qualified case managers
• Case managers were members of the research team
• Development of shared plan of care- copy to participant, case manager and GP
• Focus= identification of problems that are contributing to depression; health advice but aim to develop patient’s confidence in dealing with problems
• Researcher blinded to group allocation
Analysis

• Descriptive- summary estimates of outcome measures, focussing upon drop-out rate at each time-point
• Linear mixed effect model- between treatment arms difference in HADS scores at 1, 6 and 12m
Individual Randomisation

• Simple randomised trials may be less robust
• Danger that treatment offered to control patients will be contaminated by HCW’s experiences of applying intervention to patients receiving experimental intervention
• Therefore, evaluation may under-estimate effects
Cluster Randomisation

- Randomisation of groups of professionals rather than individual patients
- Data collected about process and outcome of care at the individual level
- **Randomise at one level and collect data at another= cluster RCT**
- Can overcome contamination but has implications- planning, conduct and analysis
Challenges of Conducting Cluster RCTs

- Assumption of independence is violated in cluster RCTs - patients within cluster more likely to respond in a similar manner
- Eg. The management of patients in a single hospital is more likely to be consistent that management across a number of hospitals
- Not statistically efficient - lower statistical power than patient-randomised trial
- Lack of independence → inflated sample sizes to adjust for clustering effect
- If few clusters randomised → increased danger of difference in performance due to chance
Example: MANAS trial

- **Sampling frame for phase 1**= PHCs with minimum space available for the intervention team; >350 attendees per month
- Facilities divided into 3 x strata- urban with visiting psychiatrist; rural with visiting psychiatrist; rural without visiting psychiatrist
- Two intervention and two control PHCs selected at random from each stratum
- **Sampling frame for phase 2**= all GPs with adequate clinical space and who consent to participate; similar stratification
- Consent required from clusters and individual participants