A Trial By Any Other Name:

An Introduction to Complex Interventions, Pilot Trials and Cluster RCTs

Dr. Rosie Mayston, Centre for Global Mental Health,
Institute of Psychiatry, King's College London

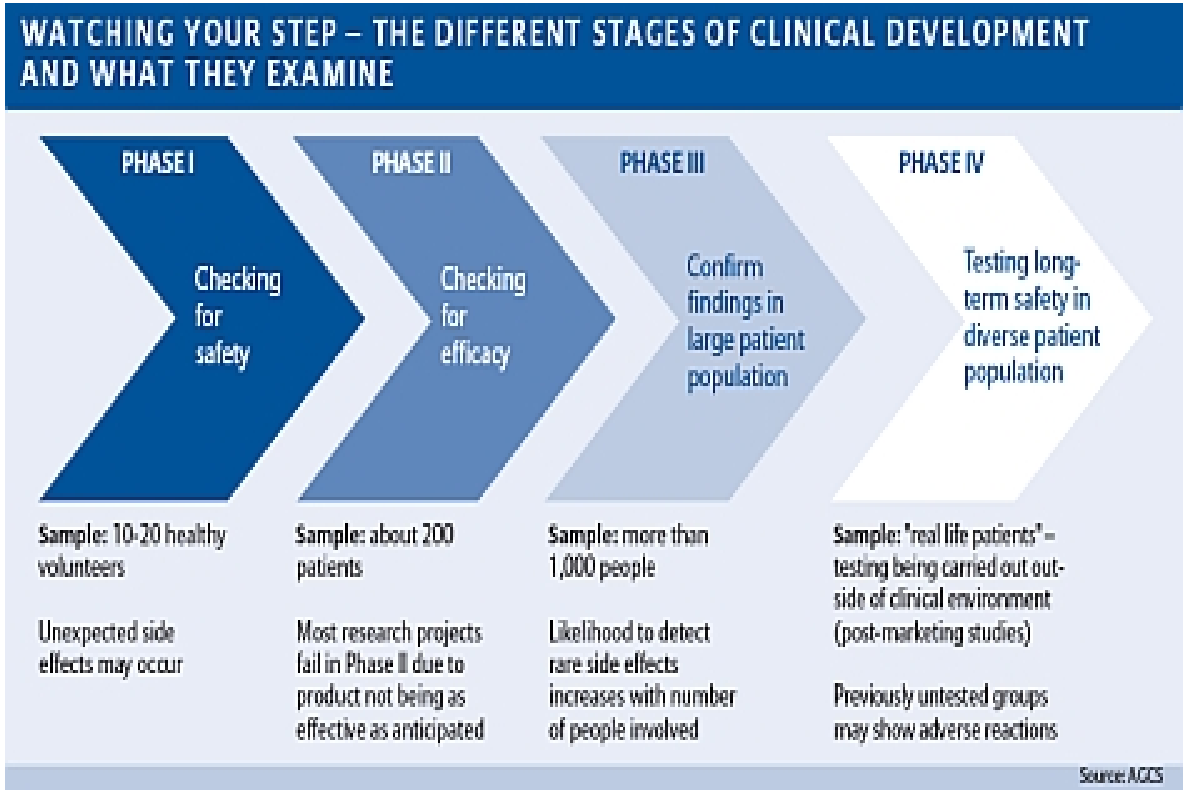
Alan J. Flisher Centre for Public Mental Health

AFFIRM
AFrica Focus on Intervention Research for Mental Health

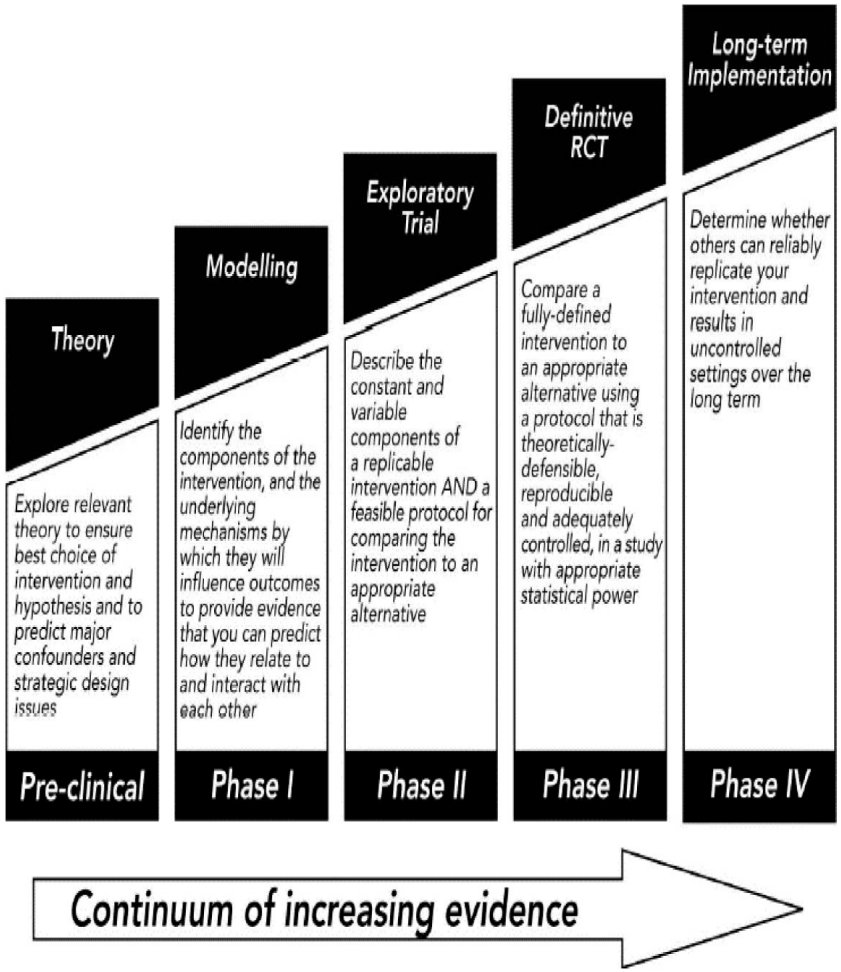
Overview

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

Phases of Trials



MRC Framework (2000)



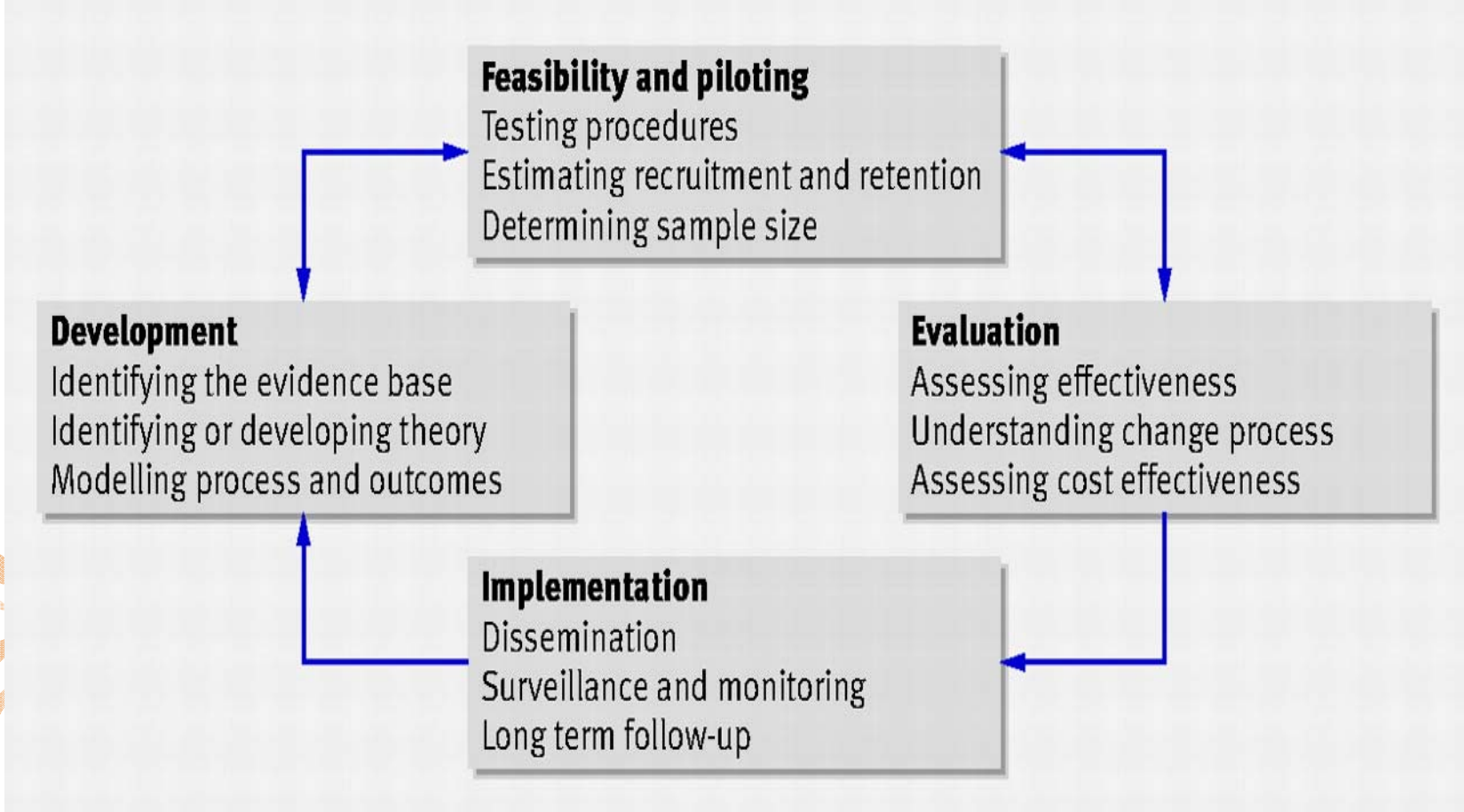
What Makes An Intervention Complex?

- 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



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 samples ize 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**