





## Phase 2: Feasibility and piloting

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## Objectives

- Demonstrate a critical awareness of the role of a pilot study in addressing the main uncertainties that have been identified when developing complex interventions.
  - Testing procedures
  - Recruitment and retention
  - Determining sample size

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## Researching Complex Interventions

- A warning!
  - *“Developing, piloting, evaluating, reporting and implementing a complex intervention can be a lengthy process. All of the stages are important, and too strong a focus on the main evaluation, to the neglect of **adequate development and piloting work**, or proper consideration of the practical issues of implementation, will result in weaker interventions, that are harder to evaluate, less likely to be implemented and less likely to be worth implementing.” (MRC, 2008 p4)*

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## The Problem of Evaluating Complex Interventions

- All evaluations present practical and methodological difficulties
- Complex interventions present additional problems
  - the difficulty of standardising the design and delivery of the interventions
  - their sensitivity to features of the local context
  - the organisational and logistical difficulty of applying experimental methods to service or policy change
  - the length and complexity of the causal chains linking intervention with outcome




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## Elements of Complexity

- Number of and interactions between components within the experimental and control interventions
- Number and difficulty of behaviours required by those delivering or receiving the intervention
- Number of groups or organisational levels targeted by the intervention and inherent variation in the populations targeted by interventions (e.g. age; stage of disease)
- Number and variability of outcomes (e.g. possible levels of mobility)
- The degree to which researchers and clinicians are prepared to allow flexibility or tailoring in intervention fidelity




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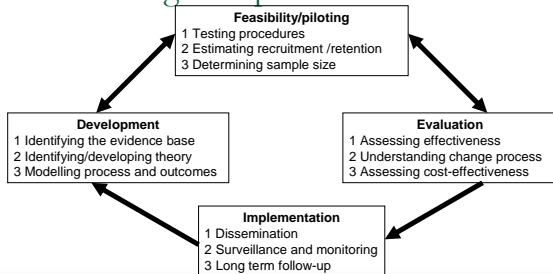
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## Methods for Developing and Evaluating Complex Interventions




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## Piloting the Intervention

- Evaluations are often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment and retention, and smaller than expected effect sizes that could have been predicted by thorough piloting



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## Remember this principle!

- A pilot study need not be a scale model of the planned evaluation but should examine the key clinical and methodological uncertainties that have been identified during development



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## Piloting the Intervention: Questions

- Is there enough piloting and feasibility work to be confident that the intervention can be delivered as intended?
- How acceptable to clinicians and patients is the intended intervention?
- Can safe assumptions be made about effect sizes and variability, and rates of recruitment and retention in a main evaluation study?



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## Group Work

- Divide into three small groups
- Take a scenario each
- Think about:
  - Methodological and clinical feasibility
  - Acceptability of the intervention to all involved
  - Likely effect size for an evaluation
  - Ability to recruit to an evaluation trial



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## Acceptability

- How acceptable to clinicians, patients and the public is the intended intervention?



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## Acceptability and feasibility

- Formal consensus development methods (Murphy et al, 1998, HTA, 2: 3, 1-88)
- 'Framework' guided qualitative methods (Pope et al, 2000, BMJ, 320, 114-16)
- Innovation in representing novelty (Richards et al, 2006, GenHospPsych, 28, 296-305)
- Public, patients, carers, clinicians
- Try it out and ask people about it afterwards and/or measure fidelity directly



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## Estimating recruitment/retention

- Can you make safe assumptions about rates of recruitment and retention in the main evaluation study?



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## Difficulties with recruitment

- 31% of trials achieve their original recruitment target (McDonald et al 2006)
  1. Unrepresentative sample = lack of external validity
  2. Poor recruitment reduces power, increasing the probability of type II error
  3. Inhibits the development of reliable evidence and lead to delays in the adoption of effective interventions.
  4. Raises ethical issues (Treweek et al, in press).
  5. Common approach is to apply for an extension to the length of the trial, which has significant cost implications.
- System related barriers, individual barriers and trial-design-related barriers



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RIS-SCH-4055. UK revised Protocol v2 Date: June 23, 2006

### INCLUSION CRITERIA

Subjects must satisfy the following criteria to be enrolled in the study:

1. Male or female inpatient or outpatient subjects, aged 18 – 65 years inclusive
2. Diagnosis of schizophrenia (subtypes include: Paranoid, Catatonic, Disorganized, Residual and Undifferentiated) as per Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text revision (DSM-IV TR)3e
3. Female subjects must be surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injection, intra-uterine device, double-barrier method, contraceptive patch, male partner sterilisation or abstinence) before entry and throughout the study, and have a negative urine pregnancy test at screening before study entry
4. Subjects who have had a minimum of 2 hospitalizations or 2 clinical exacerbations or 1 of each, over the past 2 years due to suspected deteriorating adherence
5. Within the last 5 years, patient must have demonstrated a satisfactory response (minimum of 6 weeks) to oral antipsychotics to confirm no treatment resistance. If the patient was previously treated with clozapine, the reason for initiation of clozapine must not be due to treatment resistance.
6. On monotherapy antipsychotic treatment as per local product label guidelines, at baseline.
7. Subjects (or their legally acceptable representatives) must have signed an informed consent document, indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study
8. Otherwise healthy as confirmed by physical exam, vital signs and laboratory testing.
9. Subject has an address and access to a telephone

### EXCLUSION CRITERIA

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. Primary DSM-IV TR Axis I diagnosis other than schizophrenia
2. Confirmed hypersensitivity or intolerance to risperidone
3. Contraindications for use as listed in the product monographs for risperidone, olanzapine, quetiapine, and where commercially available aripiprazole and amisulpride
4. Female subjects who are currently pregnant or breastfeeding or planning a pregnancy within 2 years of trial start
5. Long acting formulations of neuroleptic medications within 1 treatment cycle of screening
6. Subjects who have failed to respond to 2 or more adequate treatment trials of antipsychotics (an adequate trial is defined as 6 weeks of treatment on the maximum local label dose of the monotherapy antipsychotic) or 1 adequate trial with oral risperidone.
7. Laboratory abnormality that is deemed clinically significant by the investigator
8. Serious, unstable and untreated medical illnesses: vascular or cardiovascular disease, history of liver or renal insufficiency, significant cardiac, pulmonary, gastrointestinal, endocrine, neurological or metabolic disturbances
9. Subjects at significant risk of suicide or violence at study start
10. Evidence of substance dependence (except for nicotine and caffeine dependence) according to DSM-IV TR criteria diagnosed in the last month prior to entry
11. Treatment with electroconvulsive therapy (ECT) within 2 years of screening
12. Have received an experimental medication or used an experimental medical device within 30 days before screening.
13. Employees of the investigator or study centre, with direct involvement in the proposed study or other studies under the direct control of investigator or study centre, or as family members of the employees of the investigator or study centre.



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Multi-centre Randomised Controlled Trial  
of Collaborative Care for Depression



**INCLUSION CRITERIA**

1. Patients aged 18 years and above with moderate or severe depression in primary care. This includes patients with new and recurrent/ongoing episodes of depression. Patients may or may not be on antidepressants

**EXCLUSION CRITERIA**

1. Patients who are actively suicidal
2. Current co-morbid diagnosis or history of Bipolar disorder, Schizophrenia or other psychotic disorders
3. Patients currently being treated by secondary care mental health services
4. Current bereavement reaction as a primary diagnosis
5. Current and clinically significant drug or alcohol dependence



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Which recruitment methods have evidence of effectiveness?

1. Telephone reminders to non-responders (Nystuen 2004)
2. Opt-out procedures requiring potential participants to contact the trial team if they do not want to be contacted about a trial (Trevena 2006)
3. Open label trials rather than blinded (Avenell 2004; Hemminki 2004)



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Determining sample size

- Can you make safe assumptions about effect sizes, variability and the numbers of participants required in your study to be able to reject the null hypothesis safely



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## Calculating Sample sizes

- Calculations for sample size can be conducted using computer programs
- Clinstat is open source
  - carries out calculations for the comparison of means and proportions and for testing correlation
  - Available via Martin Bland's web directory of randomisation software and services  
<http://www-users.york.ac.uk/~mb55/guide/randsery.htm>
- Commercial package, [nQuery advisor](#), Elashoff (2000).



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## Sample size calculation is dependent on a variety of factors...

- The variables of interest in your study, including the type of data
- The desired power
- The desired significance level
- The effect size of clinical importance
- The standard deviation of continuous outcome variables
- Whether analysis will involve one- or two-sided tests
- Aspects of the design of your study



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## Case Example: Collaborative Care for Depression in the UK: Developing

- Systematic review and meta-analysis of existing literature
  - Gilbody, S, Bower, P, Fletcher, J, Richards, DA, Sutton, A. (2006). Collaborative care for depression: a systematic review and cumulative meta-analysis. *Archives of Internal Medicine*, 166:2314-2321.
- Meta-regression of above data to determine predictors of effect and core elements of a collaborative care clinical protocol
  - Bower, P, Gilbody, S, Richards, DA, Fletcher, J, Sutton, A. (2006). Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta regression. *British Journal of Psychiatry*, 189, 484-493
- Mixed methods qualitative study of proposed clinical protocol to determine feasibility, acceptability and barriers to collaborative care in the UK
  - Richards, DA, Lankshear, AJ, Fletcher, J, Rogers, A, Barkham, M, Bower, P, Gask, L, Gilbody, S, Lovell, K. (2006). Developing a UK Protocol for Collaborative Care: A Qualitative Study. *General Hospital Psychiatry*, 28: 296-305



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## Case Example: Collaborative Care for Depression in the UK: Piloting

- Small scale (n=114) randomised controlled trial of collaborative care to:
  - estimate sample size for proposed large trial;
  - clarify choice of cluster or patient randomisation for proposed trial;
  - test recruitment procedures for proposed trial;
  - test intervention
    - Richards, DA, Lovell K, Gilbody S, Gask L, Torgerson D, Barkham M, Bower P, Bland JM, Lankshear A, Simpson A, Fletcher J, Escott D, Hennessy S, Richardson R. (2008). Collaborative Care for Depression in UK Primary Care: A Randomised Controlled Trial. *Psychological Medicine*, 38: 279-288
- Qualitative study of patients' experiences receiving collaborative care to determine acceptability of implemented protocol and identify any changes prior to large trial
  - Simpson, A., Richards, D., Gask, L., Hennessy, S. and Escott, D. (2008). Patients' experiences of receiving collaborative care for the treatment of depression in the UK: a qualitative investigation. *Mental Health in Family Medicine*, 5, 95-104



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## Conclusion: Pilots can do it all!

- Addressing all the unknown acceptability, feasibility, recruitment and effect size factors is essential for a successful and fair test of a complex intervention
- Pilot and feasibility stages should address these uncertainties head on
- Remember, a pilot is not a scale model.



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