Trials in Primary Care: design, conduct and evaluation of complex interventions

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1. Introduction

- Research in Primary Care is time consuming and often challenging
- It requires extensive planning & prep
- Interventions are often complex and present a range of problems eg.
  - Working in health care setting
  - Sensitivity to local context
  - Logistics of applying experimental methods
What makes an intervention complex?

- Interactions between components in experimental and control arms
- Difficulty of behaviours required by those delivering or receiving the intervention
- Organisational levels targeted by the intervention
- Variability of outcomes
- Degree of flexibility/tailoring of intervention permitted
- Will it work in everyday practice?

NB. taken from MRC guidelines
Guidance

- MRC document
  ‘Developing and Evaluating Complex Interventions’
  [www.mrc.ac.uk/complexinterventionsguidance](http://www.mrc.ac.uk/complexinterventionsguidance)

- BMJ paper (Campbell NC et al. 2007, 334: 455-9)
  ‘Designing and Evaluating Complex Interventions to improve health care’

- Case studies
# Key statistical design issues

<table>
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<tr>
<th>Phases given in MRC guidance framework</th>
<th>Key elements in designing and evaluating complex interventions</th>
<th>General points to consider</th>
<th>Key statistical design issues addressed in our paper</th>
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<tr>
<td><strong>Development</strong></td>
<td>Background and context (For more information and examples see MRC and Campbell et al.)</td>
<td>Socio-economic background; Underlying cultural assumptions; Health service system; Government initiatives; Preventative policies</td>
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<tr>
<td></td>
<td>Defining and understanding the problem (See above docs)</td>
<td>Prevalence of condition; Population most affected; How condition is caused/sustained; Potential for intervention and improvement</td>
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<td></td>
<td>Conceptualising the problem (See above docs)</td>
<td>Levels of complexity of health problem and co-morbidity; Risk factors and factors influencing changes over time; Patient beliefs, symptoms and adherence to treatment</td>
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<tr>
<td></td>
<td>Gathering evidence</td>
<td>Systematic reviews; Epidemiological research; Qualitative research; Expert opinion</td>
<td>Using evidence from primary studies, systematic reviews and qualitative studies to inform study design</td>
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<td>Developing the intervention</td>
<td>Identify key processes and mechanisms for delivery; Potential beneficial effect; Define target group; Optimise best treatment combinations</td>
<td>Conducting primary care research in the UK: complying with research governance and assessing quality of care using the Quality and Outcomes Framework</td>
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## Key statistical design issues II

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<tr>
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<tr>
<td>Evaluation</td>
<td>Developing and optimising trial parameters</td>
<td>Testing the feasibility and integrity of the trial protocol; Consideration of appropriate primary/secondary endpoints; Recruitment and retention strategies; Method of randomisation to minimise imbalance; Sample size considerations</td>
<td>Pilot studies and pre-trial modelling; Selection of outcome measures for effectiveness and quality; Recruitment of practices and participants; Choosing the method of randomisation; Sample size and between trial variation</td>
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<td>Data collection forms; Design of database; Monitoring procedures; Awareness of issues of data analysis for different study designs</td>
<td>Choosing the method of analysis: cluster specific versus marginal models</td>
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<td>Implementation</td>
<td>Getting evidence into practice (See new MRC guidance document)</td>
<td>Publication and dissemination strategy; Stakeholder involvement; Benefits, harms, costs for decision making; Recommendations</td>
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</table>
2. Using evidence from primary studies, systematic reviews and qualitative studies in the design

- Much high quality research lacks generalisability (external validity)
- Intervention may not be easily implemented in practice (Who? How? Duration?)
- Strong argument for carrying out research in the most appropriate context and setting

Eg. Can we trust estimate of effect size when intervention studies to lower BP after stroke are mostly carried out in secondary care? (Mant et al BMJ 2006)
Systematic reviews of RCTs

- Useful because based on clearly formulated research questions and methodology
- Quality of included papers has been appraised
- Summary (pooled) estimate of effect size
- Feasibility, acceptability and uptake of intervention can be measured by level of attrition of participants

Eg. ‘Relative attrition’ has been used to compare levels of attrition across oral anticoagulation and Diabetes type II trials (Hennekens et al. BMC Res. Methods 2007)

- Systematic reviews of diagnostic test and method comparison studies also useful for selecting an appropriate measurement method or technique
Qualitative studies

- Especially useful when planning or evaluating a complex intervention

Can be used:

- **Before** the trial to explore issues of design eg. barriers to recruitment; acceptability of the randomisation from a patient’s perspective
- **During** the trial to understand and unpack the processes of implementation and change
- **After** the trial to explore reasons for the findings eg. are findings in line with underlying theory; acceptability to deliverers and receivers; comparisons with patient reported outcomes; the value of the intervention – as an evaluative assessment and to aid interpretation
3. Conducting primary care research in the UK

- Public generally trusts academic research
- **Research governance** ensures research integrity
  - to uphold the public’s confidence, to protect participants from abuse, and to protect researchers from accusations of misconduct
- **Wide range of legal requirements** eg.
  - European Clinical Trials Directive
  - Data Protection Act
- **Ethical approval**
  - NB. much debate about whether RECs should examine statistical issues & methodological rigour
Research governance

- GPs are usually self-employed or work within a limited company; contract to NHS
- NHS Primary Care Trusts (PCTs) commission GPs’ services within their given area
- PCTs facilitate research locally to ensure research integrity; research review committees
- Primary care research often involves several GP centres across multiple PCTs
  - very time-consuming to obtain approval; honorary contracts; CRB checks etc. (eg. 6 months)
- NIHR have recently introduced guidance and a Research Passport System to help the process
Research potential of QOF

- To monitor quality of care of patients, financial incentives (up to 30% of GP income) have been introduced through the Quality and Outcomes Framework (QOF)

- QOF has 5 domains of incentivisation
  - Clinical care
  - Organisation
  - Patient experience
  - Education and training
  - Other additional services

- Points are awarded according to the workload needed to achieve targets and prevalence of disease (age, sex, deprivation) in the area
Research potential of QOF

- To use QOF indicators in research eg. to assess differences in quality of care, there are certain problems to overcome:
  - Exclusions eg. failure to attend for assessment, frailty of condition, refuse treatment
  - Differences between GP Practices eg. how conditions are recorded, how interventions are assessed, composition and skills of practice staff
- QOF is primarily payment-driven and not created for research purposes
- Research databases have been created eg. GPRD, Qresearch, using samples of GP practices
4. Use of pilot studies

- Important pre-requisite for funding
- Often ad-hoc small stand-alone studies
- Subject to publication bias
- Is there a difference between a feasibility and a pilot study?
- Pilot studies address the integrity of the study protocol
- Need clear list of key objectives
Key objectives of a pilot study

- Test integrity of study protocol
- Sample size calculation
- Recruitment and consent rates
- Develop and test implementation and delivery of the intervention
- Acceptability of the intervention
- Train staff in delivery and assessment
- Selection of most appropriate outcome measures (endpoints)
- Randomisation procedure
- Pilot data collection forms/questionnaires
- Prepare and plan data collection and monitoring
Example – UK BEAM trial

- UK Back Pain, Exercise, Active management and Manipulation trial (Farrin et al. 2005)
- To test the integrity of the study protocol using a series of sub-studies
- Planned as cluster randomised trial
- 3 treatments – active management (practice level); spinal manipulation and exercise (patient level)

Findings:
- Majority of methods were successful
- Problem with differential recruitment between practices - changed to non-clustered design
Pre-trial modelling

Example - Falls prevention trial (Eldridge et al. 2005)

- To inform design and test likelihood of the intervention being viable and effective
- Cost-effectiveness model using pilot data
  - Used probability tree and Markov simulation

Findings:

- Intervention would reduce proportion falling by only 2.8% over 12 months
- If policy-makers were willing to spend £30,000 per QALY gained, there was still only a 40% chance the intervention would be cost effective
5. Selection of appropriate outcome measure(s)

- Distinguish between primary and secondary outcome measures
- **Valid and reliable** (repeatable & reproducible)
- Directly measured vs patient-reported
  - Include additional objective measures when self-reporting may be unreliable eg. self-assessed smoking cessation and biochemical measure
  - HRQL – use generic and disease-specific measure
- Select most appropriate outcome for evaluating the **effectiveness of the intervention**
  - eg. level of knee pain, knee function, ability to work, satisfaction with treatment
- Individual level vs group (cluster) level
6. Recruitment

- Successful recruitment requires a co-ordinated approach and good pilot work.
- Important to engage practices early-on:
  - Is research question important for Primary Care?
  - What is its priority compared to other issues?
  - How does it impact on patient-doctor relationship?
  - Is GP confident to raise research issue within a sensitive consultation?
- Time constraints are a major issue.
- Need to find efficient ways to identify the sample and gain consent.
- Complex interventions can have different levels of recruitment (practices & patients).
Principles of good recruitment

- Engage with all stakeholders (GPs, practice staff and participants)
  - Brand for trial (eg. BEAM, PANDA, SCAMPS)
  - Well-developed marketing strategy, good PR
    eg. Bell’s Palsy trial used local celebrity in media
  - Well-written patient information documents
- Invitation to take part coming from own GP
- Use trained staff other than GPs to identify and consent participants eg. practice nurses
- Provide staff training in disease topic and research
- Get support from local PCRN infrastructure
  - ‘Research Ready’ accreditation scheme
  - ePCRN (www.ePCRN.org)
- Reimburse practices for taking part
- NB. Participants are allowed to opt-out
7. Method of randomisation

- By individual or by cluster eg. GP practices, households, nursing homes
  - relative costs and justification
- Relatively fewer clusters than individuals are usually available ➔ higher prob. of imbalance
  - in the size of each treatment arm
  - in baseline covariate distributions at individual level
- Complex interventions in primary care may have multiple components
  eg. simple parallel design vs factorial design
Imbalance in size of tr’t groups

- To **optimise power** need to ensure
  - an equal number of clusters in each treatment arm
  - an equal number of people in each treatment arm
- To **ensure balance** in numbers of people in each arm can use blocking
  - interventions are assigned randomly within each block
  - varying block sizes reduces predictability of next assignment
- **Allocation concealment** is harder in cluster trials
  - each cluster gets same allocation
  - use of placebos is not usually feasible
Imbalance in baseline covariates

- Imbalance may affect **face validity of comparisons** and overall conclusions

Ways to minimise imbalance:

- **Adjustment by analysis** - may result in different unadjusted and adjusted estimates of treatment effects
  - by effect size and significance
  - difficulties in interpretation

- **At the design stage** - by identifying selected covariates which may be important predictors of outcome
  - Randomise using stratification – prepare a separate randomisation schedule for each strata
  - Use minimisation – handles larger number of selected variables
8. Between practice variation and sample size

- Variation between practices in treatment and referral patterns is well-established
  - has implications for generalisability of a study
- It is an important consideration in planning cluster randomised trials eg. sample size
- How do we accurately measure this variation?
  - Need good quality data from large datasets eg. GPRD, Mediplus, MIQUEST, ?QOF
  - Primary research
- Trade off between bias and precision
Sample size

- Identify primary outcome measure and calculate sample size for individual trial
- Find estimate of *Intra-cluster Correlation Coefficient (ICC)*
  - For trials randomising general practices with patient-level outcomes, ICCs usually around 0.05.
  - Papers have been published providing lists of ICCs
- Multiply (inflate) sample size by design effect
  - $1 + (m-1) \times \text{ICC}$ where $m$ is cluster size assuming all cluster sizes are equal
- Pre-2000 many CRTs were underpowered
9. Method of analysis

Individually randomised RCTs
- Well-documented standard methods

Cluster-randomised trials
- Individuals within clusters
  eg. GP practices, nursing homes
- Summary measures approach
  o Simple - uses means or proportions for each cluster
  o Gives equal weight to each cluster (wts can be used)
  o Cannot adjust for individual level covariates
- Population averaged (marginal) models
  o Uses GEEs, minimum of 20 clusters per group
- Cluster-specific models
  o Uses ML, better for smaller numbers of clusters
Example – DESMOND trial

Comparison of 4 methods of analysis: outcome is the proportion of patients with an HbA1c below 7%, intervention is structured educ’n

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio</th>
<th>Standard Error</th>
<th>z</th>
<th>P &gt;</th>
<th>z</th>
<th>(95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster specific</td>
<td>1.085539</td>
<td>0.166037</td>
<td>0.54</td>
<td>0.592</td>
<td>(0.804362, 1.465007)</td>
<td></td>
</tr>
<tr>
<td>Population averaged:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robust</td>
<td>1.161681</td>
<td>0.271156</td>
<td>0.64</td>
<td>0.521</td>
<td>(0.735194, 1.835573)</td>
<td></td>
</tr>
<tr>
<td>Independent errors</td>
<td>1.161681</td>
<td>0.162818</td>
<td>1.07</td>
<td>0.285</td>
<td>(0.882643, 1.528933)</td>
<td></td>
</tr>
<tr>
<td>Exchangable errors</td>
<td>1.079769</td>
<td>0.160086</td>
<td>0.52</td>
<td>0.605</td>
<td>(0.807480, 1.443876)</td>
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</table>
10. Conclusion

- Presented main statistical issues for conducting complex interventions
- Provides a flavour of the issues covered in our PHCSG meetings over past 8 years
- Balance between methodological issues and more practical issues of ‘real-life’ research
  - many issues not unique to primary care setting
- Challenge remains of maintaining and expanding the capacity of both methodological and applied expertise in primary care
Reference

- Faculty of 1000 publication.
- Primstat data archive
  - www.jiscmail.ac.uk/primstat
  - presentations and summaries of discussions from meetings of PHCSG