Randomised controlled trials: still going for gold in 2012?

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The gold standard

‘The ‘gold-standard’ research method for addressing the question ‘what works?’ in evidence-informed policy-making and practice is the randomised controlled trial (RCT).’

(Torgerson & Torgerson, 2008, p.1)
## The randomised controlled trial

The classic experimental design:

<table>
<thead>
<tr>
<th></th>
<th>Pre-test</th>
<th>Intervention</th>
<th>Post-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental Group</strong></td>
<td>$O_1$</td>
<td>X</td>
<td>$O_2$</td>
</tr>
<tr>
<td><strong>Control Group</strong></td>
<td>$O_1$</td>
<td></td>
<td>$O_2$</td>
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Ahah but!

Experiments suited to lab work

You can’t evaluate a complex intervention to improve health in a lab

Hence - evaluations using randomised clinical trial methodology are controversial
Origins of the experimental method

The first randomised experiments were conducted in agriculture.

The 3 requirements of an RCT are:

- Application of an intervention
- Randomisation
- Control of all known & unknown variables

Easier to achieve in plants than in humans.
‘The RCT is a very beautiful technique of wide applicability, but as with everything else there are snags. When humans have to make observations there is always the possibility of bias’ (Cochrane, 1972, p.2)

Today I want to focus on some of the snags that can occur when investigating complex interventions
The plan

- Complex interventions
- Aspects of design in which snags can be expected:
  - The context in which research is conducted
  - Clearly defining the intervention
  - Gaining a representative randomised sample
  - The control group & placebos
- Reflections on CHOICE Study
- Internal v external validity: the trade off
What makes an intervention complex?

- Interventions that contain several interacting components

- Dimensions of complexity
  - Number of & interactions between components
  - Number and difficulty of behaviours to be delivered or received
  - Number of groups or organisational levels targeted
  - Number and variability of the outcomes
  - Degree of flexibility or tailoring of the intervention (MRC, 2008)
Interventions aimed at changing behaviour are complex. They have multiple related & inter-dependent components: Practitioner behaviour, Patient behaviour, Timing & frequency of behaviour, Organisational issues, The setting & location, Local culture.
In experiments contextual variables should be controlled

In the health service this is difficult

- Health service re-organisation
- Policy change
  - The new GMS contract
  - Focus on primary care for long term conditions
- Marketing campaigns
In the real world, there are no neat boxes or arrows:

- People, society and technologies co-evolve in complex ways over time
- There is no clean ‘policy-on’, ‘policy-off’ comparison

(Greenhalgh et al, 2011)
Health system dynamics

General Protection
- Safer Healthier People (Becoming safer and healthier)
  - Adverse Living Conditions

Targeted Protection
- Vulnerable People (Becoming vulnerable)
- Becoming safer and healthier

Primary Prevention
- Afflicted without Complications
  - Becoming afflicted

Secondary Prevention
- Afflicted with Complications
  - Developing complications

Tertiary Prevention
- Dying from complications

Public Work
- Demand for response

Milstein B, Homer J. (2003) CDC Futures Health Systems Workgroup; Atlanta, GA.
Does my educational intervention work?
3 Clarity of the focus of the research

- ‘A clear definition, the ability to control outside factors and standardisation of the intervention are cornerstones of the RCT’ (Blackwood, 2006, p612)
- The ability to clearly define what exactly is being investigated has proved a challenge
- The focus of the RCT
- The explicit nature of the intervention
Clarifying the focus of the intervention

- Self-care decision making
- Self-management
- Patient empowerment
- Depression & Anxiety
- Socio-economic position
- Nurse-led clinics
- The impact of diabetes nurse specialists
- Quality of life
Sounds obvious but overlooked

- Analysis of 47 RCTs of complex nursing interventions published over 2 year period
- America, Australia, Europe
  - None of the reports gave sufficient detail about the intervention to allow them to be replicated
- None of these studies adhered to the standard of reporting advised by CONSORT (Lyndsay, 2004, JAN)
Development - evaluation - implementation process

Development
1. Identifying the evidence base
2. Identifying/developing theory
3. Modelling process and outcomes

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

Evaluation
1. Assessing effectiveness
2. Understanding change process
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Implementation
1. Dissemination
2. Surveillance and monitoring
3. Long term follow-up

(MRC, 2008)
4 Recruiting a representative sample

- Inclusion/exclusion criteria
- Tend to recruit people who are:
  - Not too young not too old
  - English speaking
  - Preferably have no other health care problems
- The sample tends to:
  - Comprise well-educated (at least literate)
  - Include those with desire & ability to attend series of educational classes
  - Under-represent ethnic minorities
Randomisation

- ‘the process of assigning participants to groups such that each participant has a known and usually an equal chance of being assigned to a given group’ (Altman et al., 2001, p 688)

- Randomisation can be a difficult concept for potential participants to understand (Snowdon et al., 1997)

- Nature of the trial often poorly understood

- The random basis of allocation & rationale for it often problematic

- Need better understanding of patients views of participation

- Who should do the randomisation?
According to Schulz

‘Researchers need to realise that, given the opportunity, trial implementers will frequently subvert the intended aims of random assignment’ (Schulz, 1995)

‘If you think from the start that people aren’t really going to stay the course, and aren’t going to stick to treatments, then we try to steer away from those a little bit’ (Lawton et al 2012)
HCPs and RCT recruitment

- Agenda for hosting RCTs:
  - Research intrinsically good
  - Getting ‘ahead of the game’
  - Income generation

- Recruitment
  - Psychologically grooming patients

- A competitive and egotistical element
  - “And I would sort of think ‘Ha ha got more than Oxford!’”

- Cherry picking for good outcomes
Retention: Inducements

- ‘... They did get a lot of attention and they did get ruined (laughter). If they had anything, they got an ingrown toenail, I just put them straight on to the podiatrist. You know, they got very good attention, and they liked that, and it kept them motivated’

- ‘Coffee mornings to foster commitment’

- ‘Offered patients far more telephone contact than was prescribed for the study’

(Lawton et al 2012)
5 The control group

- In drugs trials a placebo drug is used for those people not in the intervention group
- The placebo can be made to look like the trial drug
- Neither the patient nor the staff know who is in the intervention/control groups
- In complex interventions compare with ‘usual treatment’
In trials we often see the outcomes for both the intervention and the control groups improving.

Placebos produce real and substantial effects.

Mechanisms behind placebo effects:
- Conditioning
- The manipulating of expectancies
- Influencing patients affective state and stress level
The use of placebos

Invitation to participate

Randomisation

Expensive pills $2.50

Cheap pills $0.10

Electric shocks to wrists

(Waber et al, 2008, JAMA, 299, 1016-7)
IBS and sham acupuncture trial

- Invitation to participate
- Randomisation
- Baseline Data
  - Observation of acupuncture
    - IBS symptoms improved: 3%
  - Sham acupuncture
    - IBS symptoms improved: 20%
  - Sham acupuncture & enriched relationship with clinician
    - IBS symptoms improved: 37%

(Kaptchuk et al, 2008, BMJ)
The control group in complex interventions

- Usual care?
- Equivalent other intervention of similar duration to trial intervention?

Editorial: ‘What does make the difference?’ following publication of RCTs on patient education; ‘when enthusiastic and motivated health-care professionals invest more time with patients in a structured way to help them manage their diabetes, we see improved biomedical outcomes’ (Skinner, 2006, Diabetic Medicine 23, 933)
Reflections on CHOICE Study
Evaluation of the Carbohydrate, Insulin, Collaborative Education (CHOICE) programme for young people with Type 1 diabetes
CHOICE Study

- **Design:** A multi-centre RCT using pre and post intervention measurements
- **Purpose:** To evaluate the effectiveness of a structured education programme (CHOICE) about diet and insulin management for adolescents between 13 – 19 yrs diagnosed with type 1 diabetes
Inclusion & exclusion criteria

- **Inclusion:** Aged between 13 – 19 years, diagnosed Type 1 for 12 months +

- **Exclusion criteria:**
  - Adolescents who have been diagnosed for < 12 months
  - Other medical conditions affecting diabetes management
  - Adolescents with a registered learning disability
  - Intensive involvement of social services with the family (verified in medical notes)
  - Psychiatric admission in past 6 months
  - Diagnosis of psychosis
  - Documented behavioural difficulties/disorder in the adolescent’s medical notes where a referral has been made for further specialist help
  - Major depression managed by anyone other than the adolescent’s GP, e.g. Psychiatry
  - Documented substance abuse disorder
  - Documented eating disorder or suspected eating disorder in adolescent’s medical notes
  - History of self-harm documented in the adolescent’s medical notes
Boundary between research and clinical practice

- ‘Working as a DSN and a research nurse, that is a bit of an issue for me... I sometimes found myself in a bit of a dilemma where I think, well off trial, I wouldn’t be doing this’
Confounding variables

- The maths!
- Dose adjustment requires some ability to do the sums
- Dynamics in the group
- A typical example would be Peter a 13 year old boy who came to CHOICE under pressure from his mother having been allocated to the intervention group
- Obvious from start that Peter did not want to engage with the programme and he made no effort to hide this. His actions exerted influence on the remaining participants of the group resulting in poor engagement all round
Financing an RCT

- ESMON Study
  - £120K (R&D Office, Belfast)

- CHOICE Study
  - £275K (Diabetes UK & ROCHE & R&D Office NI)

- Fleet Study relating to bowel prep
  - Action Cancer £10K – not enough
Internal v external validity: The trade off
External validity

- ‘It cannot be overemphasised that unless an experiment can be generalised at least a bit, time and resources have been wasted. One does not really care about the results of a study unless its conclusions can be used to guide future decisions’ (Berk, 2005, 76)

- A study has high external validity if the results can be generalised to other people

- An RCT needs high internal validity to control bias
The current dominant paradigm of reductionist studies focused predominantly on internal validity using highly homogenous patients and academic settings is not and will not produce the desired translation to real world practice and policy.

We need to realise that the world is complex and embrace and study this complexity to produce further progress.

(Glasgow, 2008)
Practical effectiveness: a key question

- Will the intervention work in everyday life?
- Need to understand the whole range of effects
- How they vary among
  - the recipients of the intervention
  - between sites, over time, causes of variation
- Then to implementation

(MRC, 2008)
External validity: Sampling

- There are several threats to external validity but sampling and intervention support will be mentioned as examples.
- Inclusion and exclusion criteria. Useful purpose as they exclude other confounding variables.
- There may be a tension between excluding many variables yet still having a sample that can be generalised to the study population in question.

(Yusuf, Held and Teo, 1990)
The nature of the intervention and the amount of support it requires is also very important.

It may be possible to apply an intervention that requires intensive support in a research setting while staff or resources have been funded but such interventions are less likely to be translated to general health care.

Only conducted in ‘centres of excellence’

The artificial environment centred around the RCT may not mirror everyday reality.
‘If we’d stuck strictly to the contact schedule then I think we’d have struggled to get most of our patients down to target… the nurses rang these patients more often than they were supposed to, to make sure that objectives were achieved’

‘There’s such a lot of contact for some patients that, well that’s not going to happen to them in the real world. I know we’re not alone: I know other centres were doing the same’

(Lawton et al 2012)
Conclusions - developing and evaluating complex interventions

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Conclusion

- RCTs: best research method for answering ‘what works?’
- ‘Arguably the most significant contribution to health care research in the last century was the development of the methodology and methods of the randomised controlled trial’  
  (Torgerson & Torgerson, 2008)

BUT

- The quality of the preparatory work on the intervention and the design of the evaluation will dictate whether ‘gold‘ is possible
Acknowledgements

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