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# Cluster randomised trials in palliative care

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# Introduction

- *Randomised controlled trial (RCT)* randomises individual patients between intervention to be evaluated & control, often 'treatment as usual.
- *Cluster randomised trial (CRT)* randomises 'clusters' of patients, eg groups from same general practice, ward, hospice.
- Ideally those clusters should be the subject of the intervention to be evaluated.
- However unit of analysis should be patients; otherwise important information will be lost.

# The need for CRTs

- Primary – if simple RCT violates assumption that members of each allocated group are independent eg through natural clustering (eg within family – CHARISMA) or staff training (eg in self-care for back pain – UK BEAM).
- Secondary – if entry into RCT (including info sheet, reflection, consent & randomisation) is so complex that few potential participants have the capacity to enrol (eg care of dementia, emergency care, palliative care).

# Ethical basis of CRTs

- 'Cluster guardian' is responsible for giving informed consent to allocate cluster at random between intervention & control.
- 'Cluster gatekeeper' is responsible for assessing eligibility of individual members of cluster to receive intervention or else control; if so to get their consent to provide data to CRT; & if so to register them in the CRT.
- Potential participants are responsible only for consenting to provide data to CRT.

# **Dangers of CRTs: eg UK Back pain Exercise And Manipulation (UK BEAM) Trial**

- Interventions piloted (1) Spinal manipulation (2) Graded exercise (3) Train GP reception staff in use of Back Book for self-management
- Design piloted = 2 x 2 (individual) x 2 (CRT)
- Problem: trained practices recruited 2.5 times as many patients as untrained practices!
- Specific solution: update review; train all GP staff in Back Book; & adapt to 2 x 2 RCT.

# Good practice in CRTs

- CRT size = Equivalent RCT size x  $[1 + \rho \times (\text{average cluster size} - 1)]$  where  $\rho$  (intra-cluster correlation coefficient) lies between 0 & 0.03 for PROMs, but 0.01 & 0.2 for process outcomes.
- Stratify randomisation by cluster prognostic variables, eg pathway for condition in question.
- Prospective ConSORT flowchart of eligible clusters & patients in each cluster.
- Analyse by multi-level modelling viz. patients within clusters within groups.

# Randomised consent trials – alternative to CRTs?

- Zelen (N Engl J Med 1979; 300: 1242-5) proposed ‘new design for trials’ which randomises patients to treatments ***before consent***.
- Patients allocated to ‘current best practice’ do not need to consent because their care is as expected.
- Patients allocated to experimental treatment choose between accepting that & ‘current best practice’.
- This design provides unbiased response to issue of patient preference IF analysis is by intention to treat.
- But it generates other problems – ethical (increasing in UK) & practical (eg consent to data collection).

# Zelen's design – examples

- In 1990s Aberdeen Neonatal Screening Trial (NEST) compared 1 (experimental) screening exam / child with 2 / child, by allocating ward-months at random & giving all parents allocated to 1 exam the right to ask for 2.
- In 2000s Multi-Institution Nurse Endoscopy Trial (MINuET) compared nurse & doctor endoscopists by allocating endoscopists at random & giving all patients allocated a nurse the right to a doctor.

# Best design for palliative care?

- Feasibility study in NW Wales in 2004-5.
- Compared CRT with Zelen's design as means of evaluating 2 terminal care pathways – with or without anti-emetic in syringe driver.
- DGH oncology ward ran CRT for 1 quarter chosen at random; & Zelen's for the other.
- Palliative care unit in community hospital reversed this random sequence.

# Feasibility study – population

<b>Location Quarter</b>	<b>Unit A</b>	<b>Unit B</b>
<b><i>1st</i></b>	CRT: 7 dying	Zelen's: 22 dying
<b><i>2nd</i></b>	Zelen's: 7 dying	CRT: 17 dying
<b><i>Total</i></b>	14 dying	39 dying

# Feasibility study – eligibility

<b>Design Quarter</b>	<b>CRT</b>	<b>Zelen's design</b>
<b>1st</b>	3 consent / 7 2 'eligible' / 7	1 consent / 22 1 'eligible' / 22
<b>2nd</b>	10 consent / 17 4 'eligible' / 17	6 consent / 7 1 'eligible' / 7
Mantel- } P=0.06 Haenszel } P=0.09 tests }	13 consent / 24 6 'eligible' / 24	7 consent / 29 2 'eligible' / 29

# Feasibility study – recruitment

<b>Design</b> <i>Quarter</i>	<b>CRT</b>	<b>Zelen's design</b>
<i>1st</i>	2 'eligible' / 7 2 recruits / 7	1 'eligible' / 22 0 recruits / 22
<i>2nd</i>	4 'eligible' / 17 4 recruits / 17	1 'eligible' / 7 0 recruits / 7
Mantel- } P=0.09 Haenszel } P=0.02 tests }	6 'eligible' / 24 6 recruits / 24	2 'eligible' / 29 0 recruits / 29

# Simulation of all-Wales CRT

- Source of data = all-Wales survey of compliance with palliative care pathway
- Simulated CRT in 10 PCUs x 40 patients
- Analyse reported incidence of 4 indicants – agitation, N or V, pain, rattle
- Intra-PCU Correlation Coefficient = 0.07
- Variance inflation factor = 3.7
- Effective sample size = 108!!

# Simulation of 'crossover' CRT

- Source of data = same survey with 2003 data as control, 2005 data as intervention
- Simulated Xover CRT in same 10 PCUs
- Analyse incidence of same 4 indicants
- Intra-PCU-phase Corr. Coeff. = 0.015
- Variance inflation factor = 1.3
- Effective sample size =  $303\sqrt{\phantom{x}}$

# Conclusions

- Beware feasibility studies in 2 units with 53 patients!
- Cluster randomisation may be more effective than Zelen's design in palliative care research.
- To overcome resulting problems of intra-cluster correlation & variance inflation may need crossover, even switchback, designs.
- Cluster randomised trials have many other practical problems; CRT extension to ConSORT is helpful.
- Time to tackle next step in MRC framework for developing evaluating complex interventions, namely 'definitive' crossover CRT?

# Acknowledgements

- Patients for contributing to research.
- Palliative care staff in Gwynedd.
- (previous) NW Wales NHS Trust for funds.
- NWW LREC for sympathetic consideration!
- My co-authors in:  
Andy Fowell et al. Design of trials with dying patients. *Palliative Medicine* 2006;**20**:799-804.