Optimal design of cluster RCTs with unequal allocation

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Why consider unequal allocation?

- **Ethical** reasons
  e.g. less exposure to untested intervention

- **Logistical** reasons
  e.g. reduce cost from intervention

- **Implementation science**
  maximise learning about implementation of intervention

- **Statistical** reasons, difference between arms in
  outcome variance
  ICC
  cluster size

Why would ICCs or variance differ?

- Intervention might **reduce ICC** and/or variance if it standardizes practice e.g. use of a step-by-step checklist
- Intervention might **increase ICC** if it involves group activities or therapy

What is known?

- Given cluster sizes m_0, m_1 (1 intervention 0 control), ICCs ρ_0, ρ_1 variance ratio $\delta = \sigma_1^2/\sigma_o^2$ the optimal allocation ratio of individuals to the intervention arm is

$$\frac{p_{opt}}{1-p_{opt}} = \sqrt{\frac{\delta[1+(m_1-1)\rho_1]}{1+(m_0-1)\rho_0}}$$

- Equivalently as ratio for clusters

$$\frac{g_{opt}}{1-g_{opt}} = \frac{m_0}{m_1}\sqrt{\frac{\delta[1+(m_1-1)\rho_1]}{1+(m_0-1)\rho_0}}$$

Objective

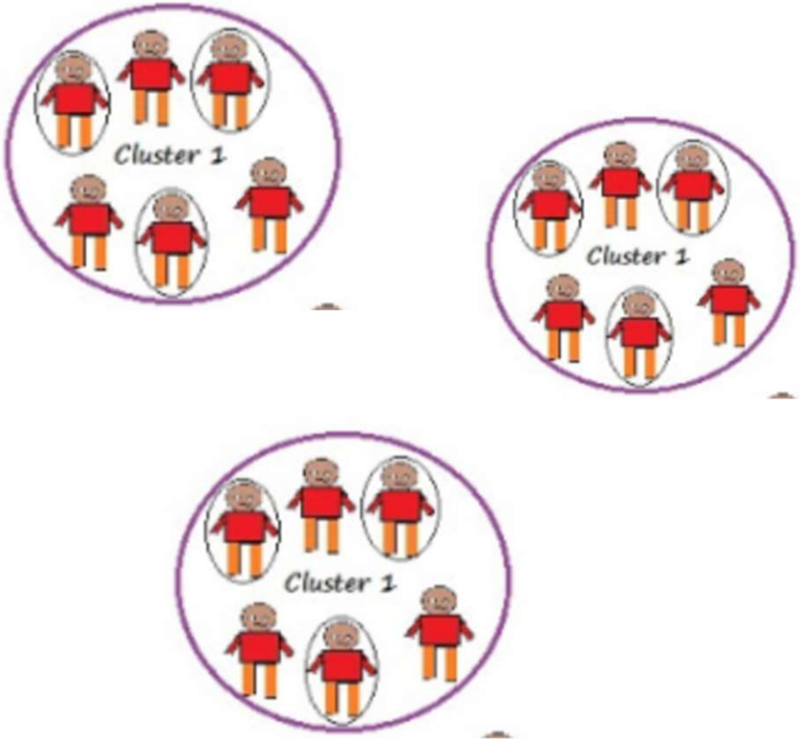
- Identify optimal allocations of clusters *g* and measurements *p* when ICCs (and variance) differ, when **cluster sizes can be chosen freely**

- When is this possible?
  - either ‘any’ number of individuals can be recruited to clusters, or
  - clusters are large (many exposed e.g. towns) but only a random sample measured

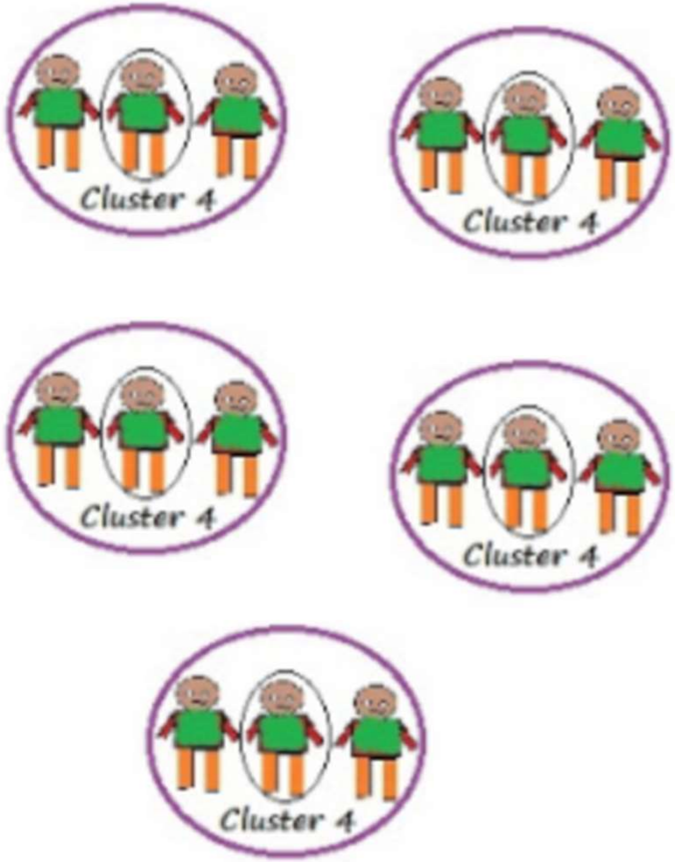
- In practice: choose range for number of clusters K, for each k identify optimal design giving smallest number of measurements N, **choose design ‘trading off’ K and N**

Optimal design 1 (intuitively)

Lower ICC



Higher ICC



Power function in *p* and *g*

- Continuous outcome, standardised effect size *d*

$$\Phi\left(\frac{d}{\sqrt{\frac{1+(m_0-1)\rho_0}{(1-p)N}+\frac{[1+(m_1-1)\rho_1]}{pN}}}-Z_{1-\frac{\alpha}{2}}\right)$$

- Can be written in terms of *g* because

$$m_1=\frac{pN}{gK};\ m_0=\frac{(1-p)N}{(1-g)K}$$

- Differentiate to identify p_{opt} and g_{opt}

Optimal design 2 (formulae)

$$\frac{g_{opt}}{1 - g_{opt}} = \sqrt{\frac{\rho_1}{\rho_0}}$$

$$p_{opt} = \frac{\sqrt{(1 - \rho_0)(1 - \rho_1)} - (1 - \rho_1)}{\rho_1 - \rho_0}$$

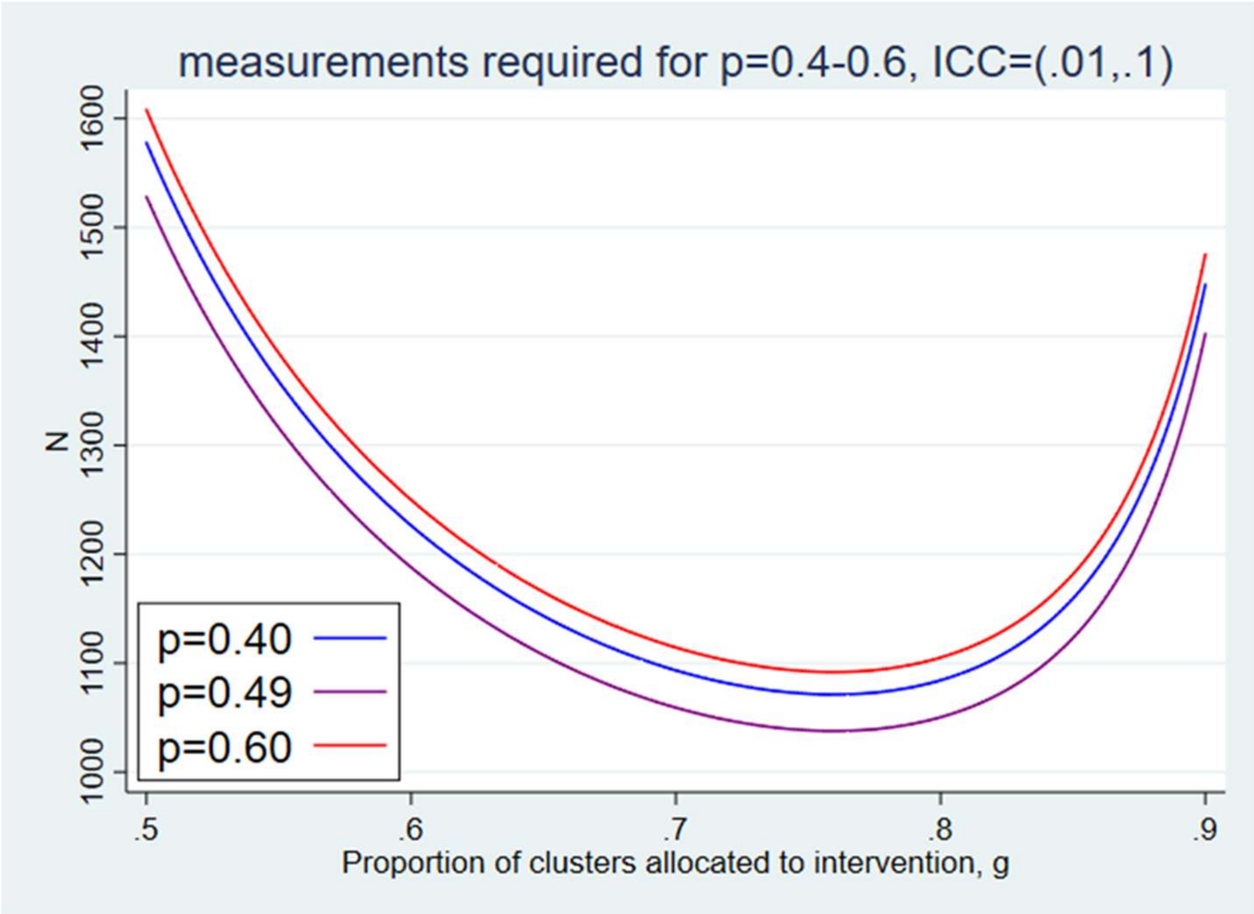
- Higher ICC in an arm means more clusters, but slightly less than half the measurements (smaller cluster size)
- p_{opt} and g_{opt} depend only on ICCs!
- If *p* or *g* fixed, doesn't affect optimal value of the other

Example

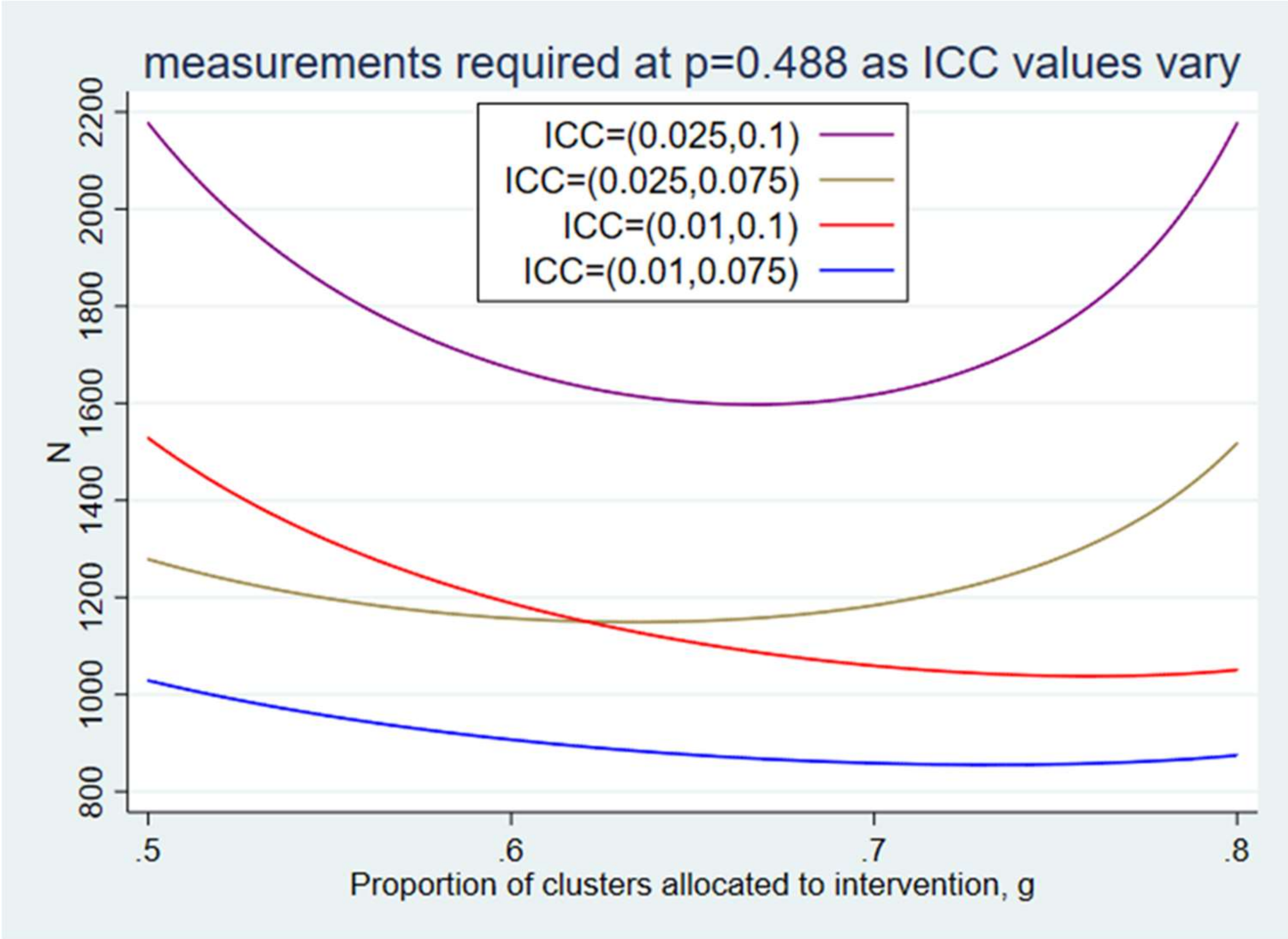
- Consider group intervention trial that increases ICC from 0.01 to 0.1
- $p_{opt} = 0.488$ and $g_{opt} = 0.760$
- Consider K from 40 to 50, identify optimal design and compare to $p = 0.5$ and $g = 0.5$, calculate sample size 80% power, effect size 0.25

K	K_1	K_0	m_1	m_0	N	N_{equal}
40	30	10	17	54	1050	1560
42	32	10	15	51	990	1386
44	33	11	14	44	946	1276
46	35	11	13	42	904	1196
48	36	12	12	37	876	1152
50	38	12	11	36	850	1100

Investigating ‘suboptimal’ choices



Design under uncertainty in ICCs



Optimal design given constraints

- Effect size 0.32, **ICC=0.05 both arms**, consider K 40-50
- $p_{opt} = g_{opt} = 0.5$

- Constrain $K_1 \geq 30$ for implementation learning, optimal design vs. design with equal cluster sizes

K	K_1	K_0	m_1	m_0	N	N_{equal}
40	30	10	10	30	600	800
42	30	12	9	22	534	672
44	30	14	9	18	522	572
46	30	16	8	15	480	552
48	30	18	8	13	474	480
50	30	20	8	11	460	450

Optimal design: only one arm clustered

- Extend to individually randomised trials where one arm is clustered, e.g. group therapy vs. medication

- Already known, for given cluster size m_1, p_{opt}>0.5

$$\frac{p_{opt}}{1-p_{opt}} = \sqrt{[1 + (m_1 - 1)\rho_1]}$$

- But if cluster size chosen freely, p_{opt} <0.5

$$p_{opt} = \frac{\sqrt{(1-\rho_1)} - (1-\rho_1)}{\rho_1}$$

- Why so different?

Further work

- Clearly cluster size (measurements) can never be entirely unrestricted – extend to a ‘feasible maximum’
- Investigate optimal design for other outcome types
- Develop software, Stata ‘power’ cannot calculate sample size with different ICCs by arm
- Investigate what sorts of trials may have different ICC or variance between arms – should we recommend reporting their values by arm?

Conclusions

- Identifying optimal designs feasible because simple expressions for p_{opt} and g_{opt} only depending on the ICCs (and variance ratio)
- Furthermore p_{opt} generally very close to 0.5. Can first identify g_{opt} which will then be ratio of cluster sizes m_0/m_1
- Easy to constrain on number or proportion of clusters (measurements) in one or both arms
- Practical use depends on whether outcome data are routinely collected or not, and feasibility / efficiency of recruiting or measuring a proportion of available individuals

For further discussion, or for references, please get in touch:

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