
Selection Bias in Cluster Randomised Trials

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Background

- In most RCTs people are randomised as individuals to treatment. Whilst this method is appropriate for many interventions (e.g. drug trials), in some types of intervention individuals cannot be randomised.
- An alternative approach is randomise groups of individuals or 'clusters'.

History

- Cluster trials originated from educational research. Intact classes or schools were randomised to an intervention or no intervention.
- Lindquist in 1940 argued that Fisher's Book "Design of experiments" was not appropriate in an educational context, where the natural unit of allocation was not the student or pupil but the class or the school.
- Consequently he amended Fisher's work, by for example, arguing that the class randomised trials should be analysed using group means not individual data.

Rationale For Cluster Randomisation

- Some interventions have to be delivered at a group level.
- Guidelines for clinicians
- Curriculum interventions aimed at schools or classes.
- Institutional interventions (e.g., changes in prison regimes).
- Interventions where there may be contamination or spill over (e.g., health promotion campaigns).

Clusters

- A cluster can take many forms:
 - » GP practice or patients belonging to an individual practitioner;
 - » School, class, prison, hospital;
 - » A period of time (week; day; month);
 - » Geographical area (village; town; postal district).

Problems with Cluster Randomisation

- **Possible Selection Bias;**
- Inadequate uptake of intervention by either group reduces study power;
- Sample size needs to be increased (typically between 50% to 100%), which will often increase the cost and complexity of a trial.

Good randomisation practice

- Randomisation must be generated by an independent person to avoid predictable sequences.
- Sequence must be kept secret until participant has consented and been enrolled into the trial.
- Allocation is revealed and recorded at the same time to avoid manipulation of assignment.
- Funding agencies are unlikely to fund *individually* randomised trials if this is not the case.
- What about cluster trials?

Selection Bias in Cluster Trials

- Properly randomised cluster trials should not be biased at baseline.
- **HOWEVER**, the clusters are balanced at the individual level **ONLY** if all eligible people, or a random sample, within the cluster are included in the trial.

Recruitment Bias

- A key issue is individual participant recruitment into cluster trials.
- There are a number of ways where biased participant recruitment can occur, which can lead to baseline imbalances in important prognostic factors.
- In an individually randomised trial we avoid recruitment bias by concealing the random allocation from the potential participant and researcher until AFTER they have consented to be in the trial and have been recruited.
- In cluster trials sometimes this is not possible.

Identification Problems

- For example, in a cluster trial of back pain treatments equal number of patients with same severity of back pain will be present in both clusters. The problem lies in how to identify such patients to include them in the interventions. Unless one is very careful different numbers and types of patient can be selected.

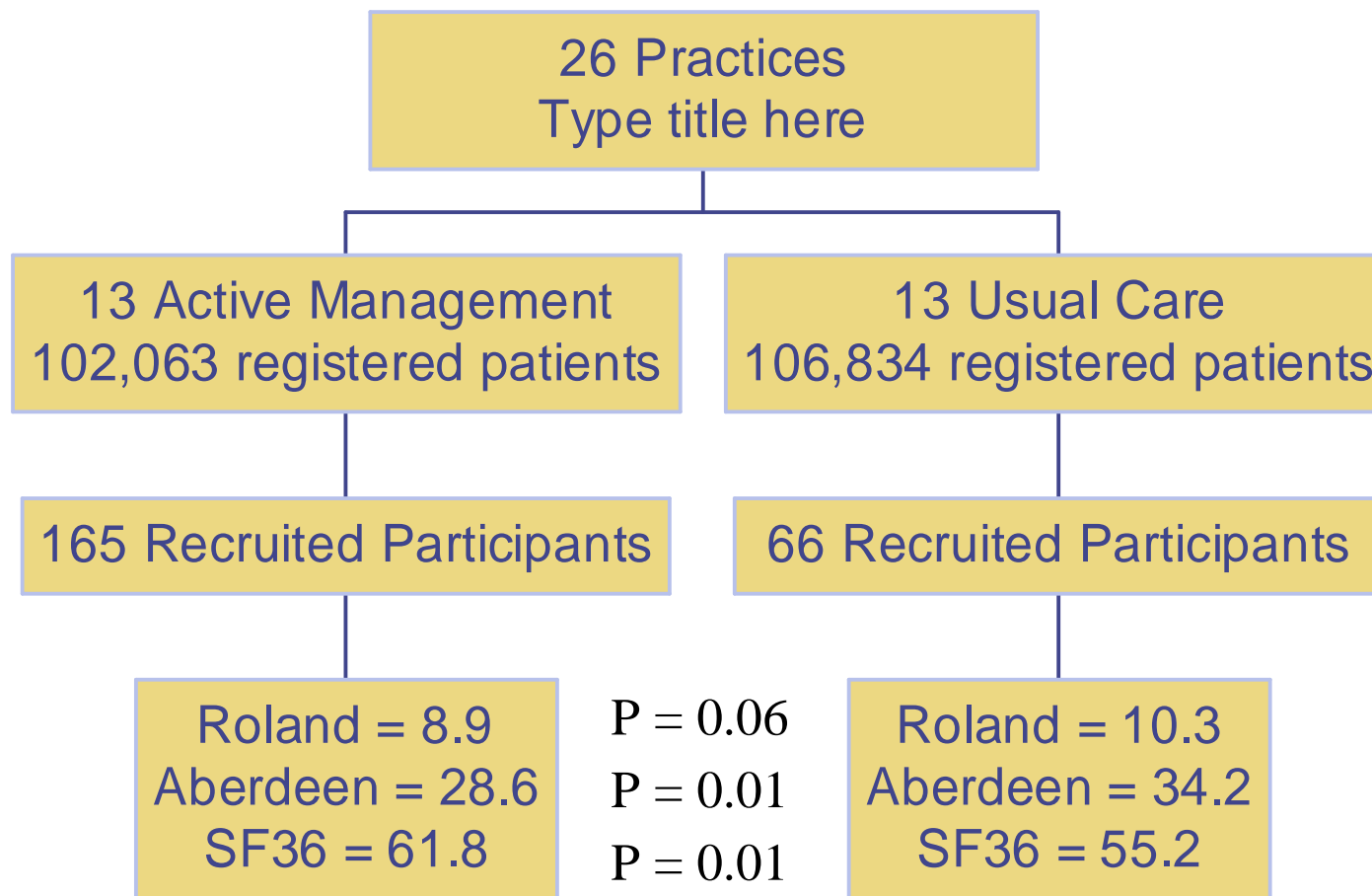
UK BEAM Trial

- The UKBEAM pilot study used a cluster design. Eligible patients were identified by GPs for trial inclusion.
- GP practices were randomised to usual care or extra training.
- The 'primary care team' were trained to deliver 'active' management of backpain.

UK BEAM Selection bias

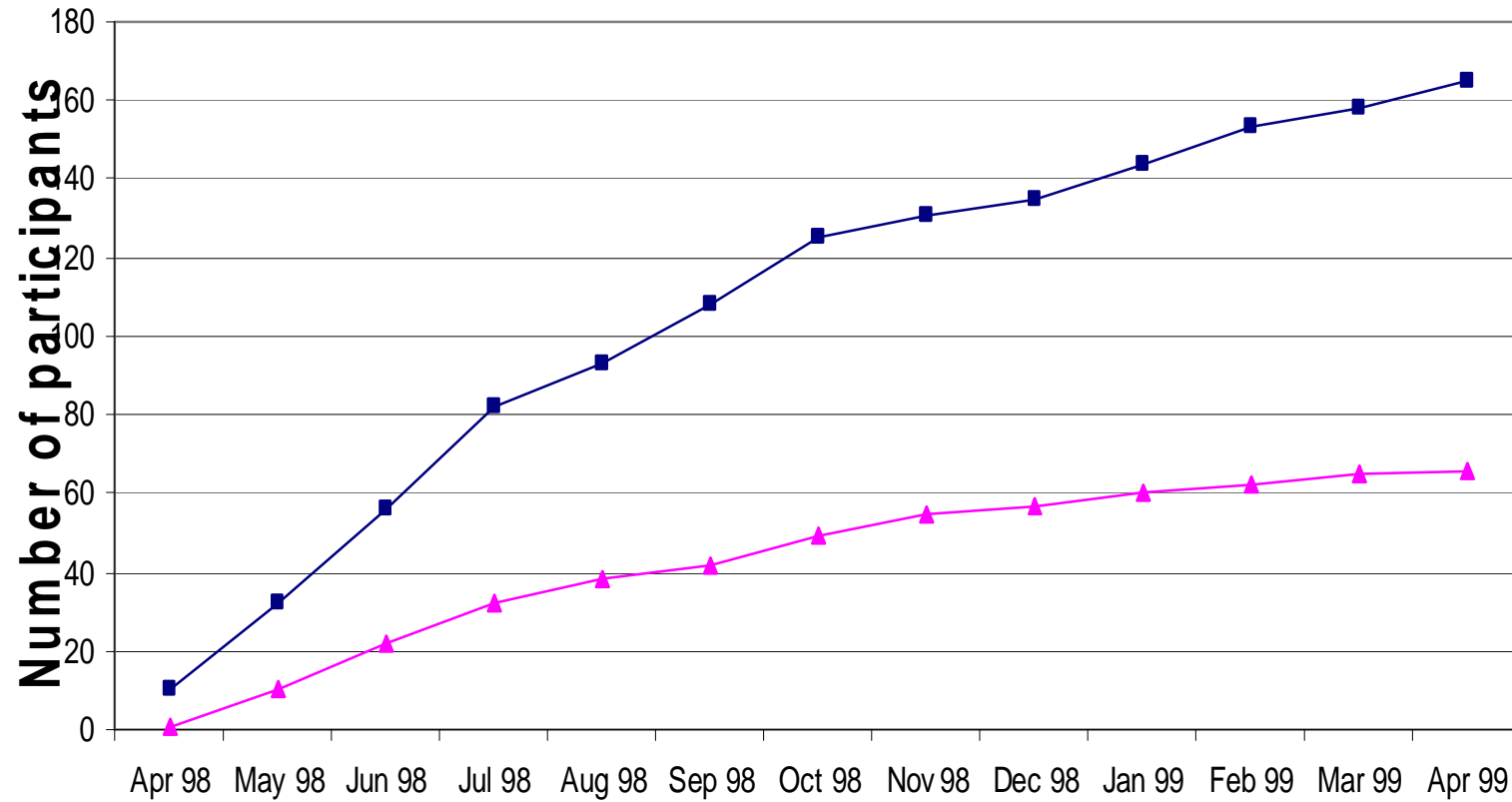
- The pilot showed that practices allocated to 'active management' were more adept at identifying patients with low back pain and including them in the trial.
- Patients had different characteristics in one arm than the other.

UK BEAM participant recruitment



UKBEAM pilot study.

Recruitment by Practice Status



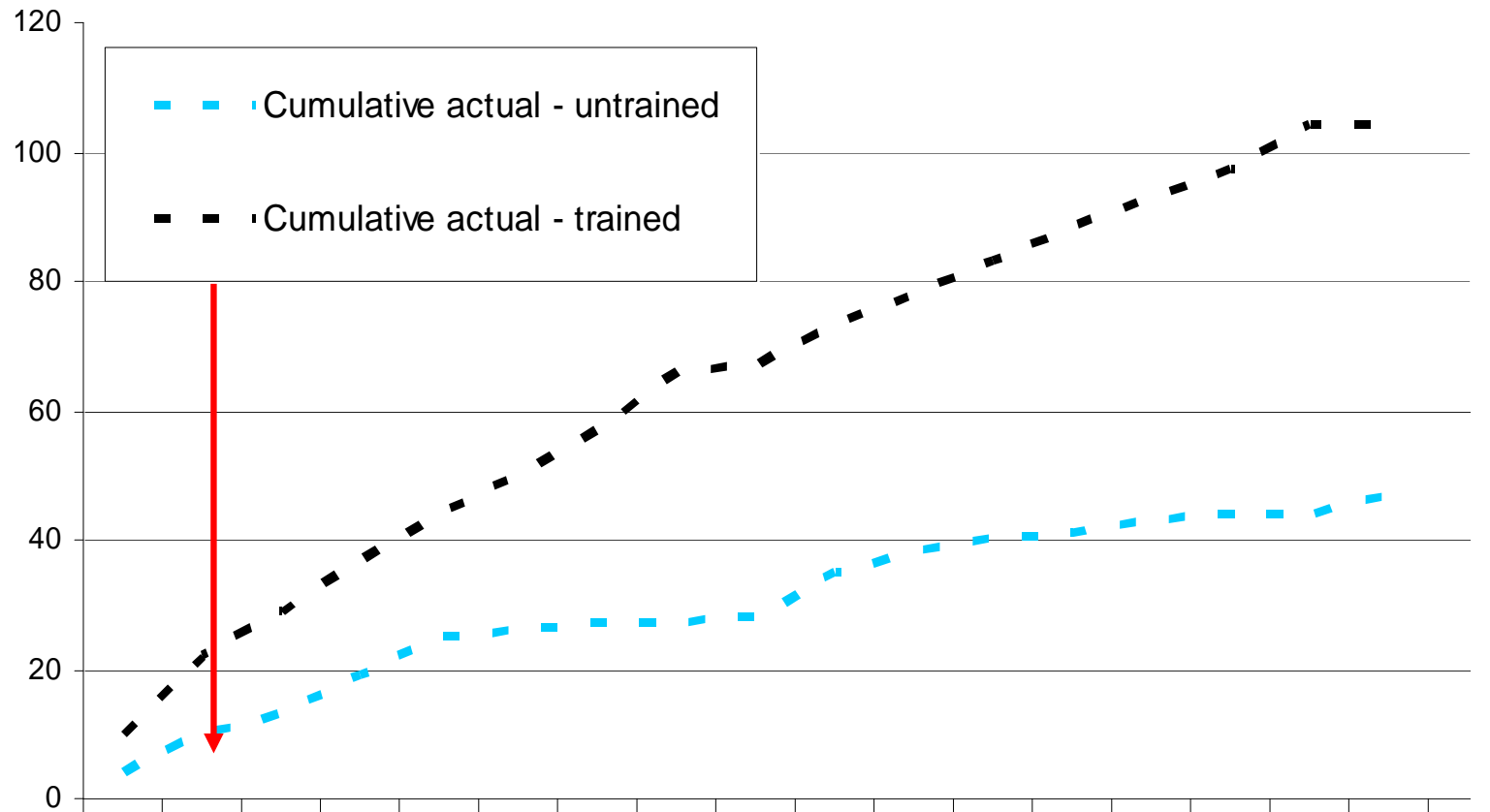
UK BEAM

- Because of the selection bias in the cluster design that element of the trial was abandoned and the trial reverted to completely individual allocation.

Another musculoskeletal trial

- In 2002 I joined a steering group for a trial of training GPs to identify and treat a common musculoskeletal condition.
- GPs were to recruit the participants.
- With the BEAM experience we KNOW what WILL happen.
- GPs WILL recruit more patients if they are trained.
- Did they?

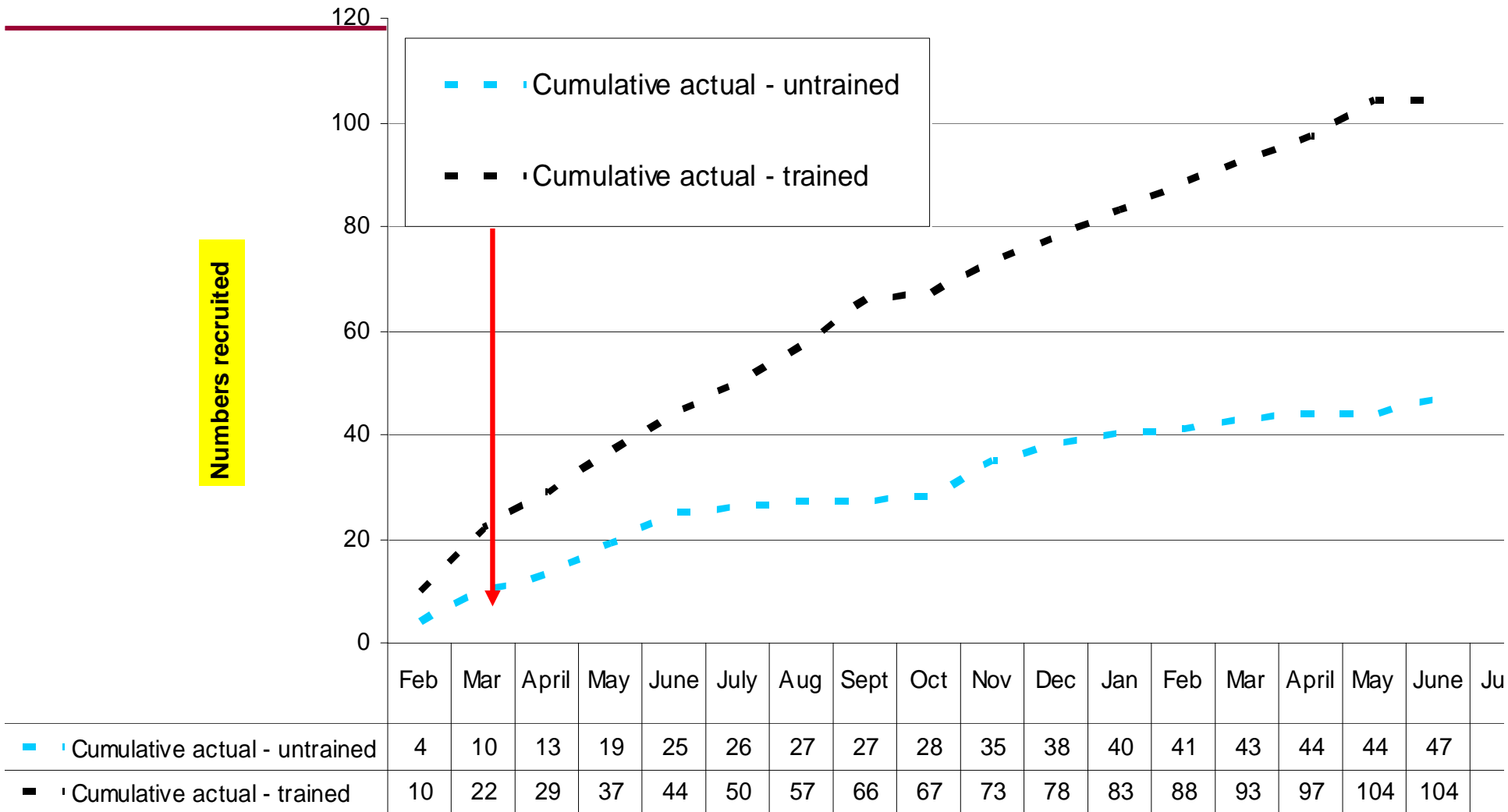
Numbers recruited



	Feb	Mar	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	Ju
Cumulative actual - untrained	4	10	13	19	25	26	27	27	28	35	38	40	41	43	44	44	47	
Cumulative actual - trained	10	22	29	37	44	50	57	66	67	73	78	83	88	93	97	104	104	

Month of recruitment





Month of recruitment

Why would you do that?

- “You learn nothing by being kicked by the same mule twice”.

Original design

- When trial design was originally sent to MRC it was as follows:
 - » Cluster level randomisation for GPs to be trained or not trained;
 - » Patient level randomisation where patients were recruited and randomised to either see their GP or be referred to be seen by a rheumatologist.
 - » This design would have been able to compare patient level outcomes between different GPs and the rheumatologists.
 - » MRC didn't like this design!

Cluster Trials: Rule 1

- All eligible participants or a random sample ideally **MUST** be identified **BEFORE** clusters are randomised.
- Alternatively systems must be put into place to **PREVENT** selective recruitment.

Consent Bias

- This occurs when consent to take part in the trial occurs **AFTER** randomisation.
- Another danger in Cluster trials.
- For example, Graham et al, randomised schools to a teaching package for emergency contraception. More children took part in the intervention than the control.

Graham et al. BMJ 2002;324:1179.

Consent bias?

	Intervention N= 1768	Control N = 2026
% recruited	88%	83%
Knowledge	17%	21%

Knowledge of emergency contraception at baseline

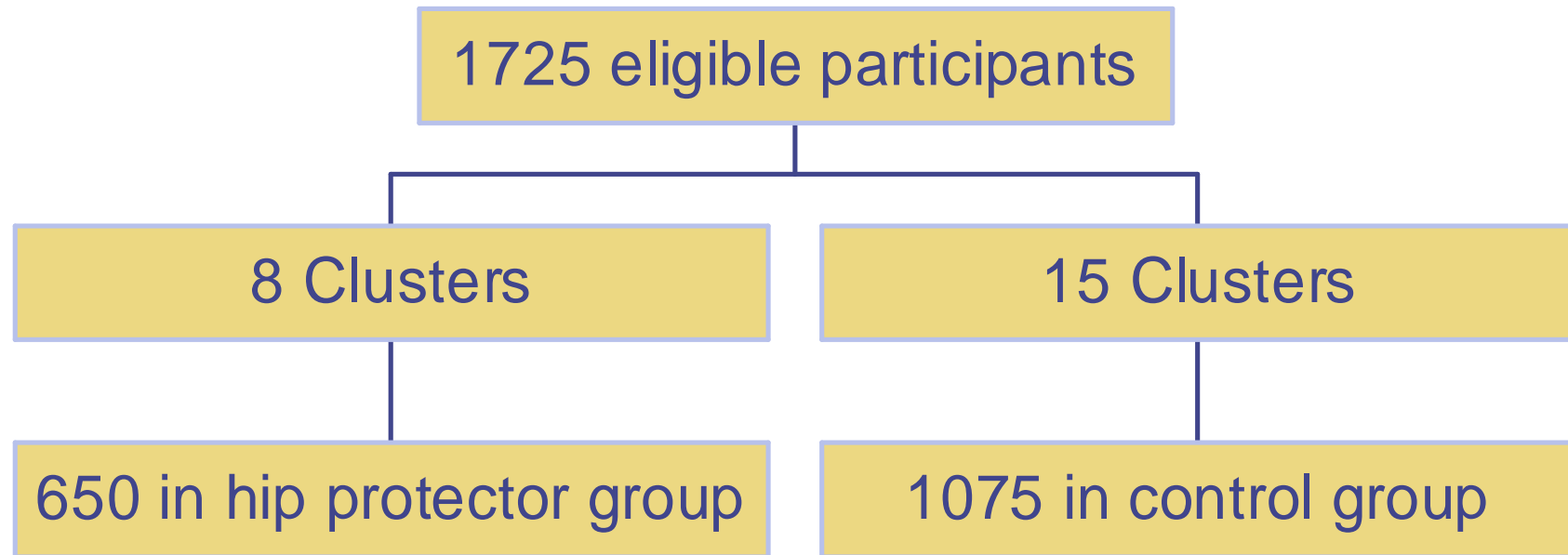
Consent Bias?

- Because more children consented in the intervention group we would expect their knowledge to be less (as we include children less likely to know).
- Conversely we get a volunteer or consent effect with the intervention group only those most knowledgeable agreeing to take part.

Trial Consent Problems

- Even when it is possible to identify all eligible members of a cluster some may not consent to take part in the trial. If there is differential consent, in particular, this can lead to selection bias again.
- To prevent this we must use the same approach as we do for individually randomised trials: recruit participants on the basis that they can get either intervention and then randomise.

Hip Protector Trial



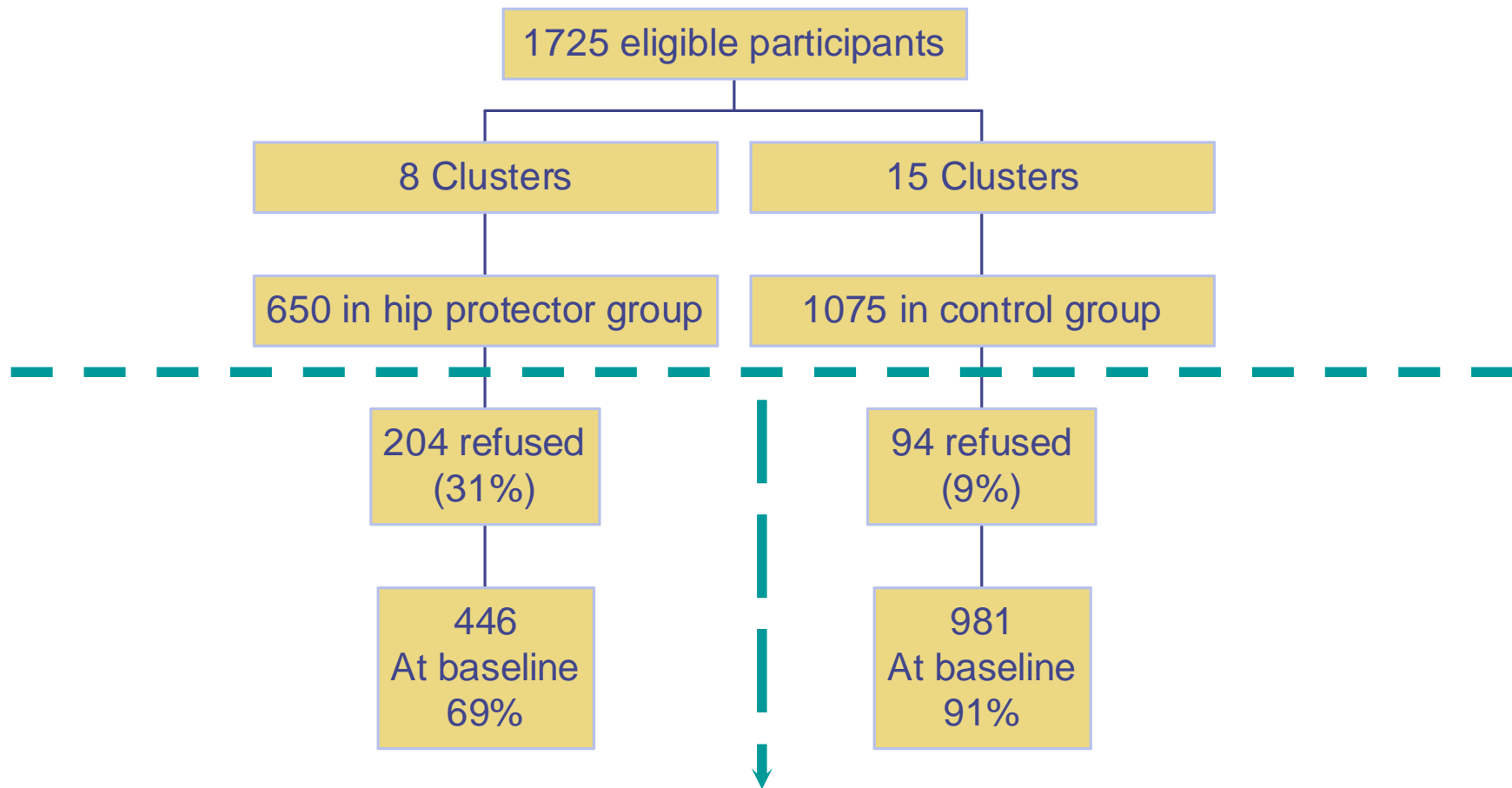
At this point trial is balanced for all co-variates

Kannus. N Eng J Med 2000;343:1506.

First Rule

- Kannus trial DID identify all eligible patients at baseline, thus, fulfilling first rule of cluster randomisation.

Hip Protector Trial



Selection Bias

Cluster Trials: Rule 2

- As in individually randomised trials imperative to use intention to treat analysis.

Inadequate uptake of intervention

- Because a robust cluster trial consent to randomisation is not given only consent to treatment this results in a proportion of eligible participants declining the intervention BUT have to stay in the trial for intention to treat analysis and this reduces study power.
- This also leads to DILUTION BIAS.

Accident prevention

- In a cluster trial of accident prevention among young children 25% of parents in the experimental arm did not receive the intervention. Clearly this will reduce the power of that trial AND dilute any likely 'treatment' effect.

Kendrick et al. BMJ 1999;318:980.

Cluster Trials: Rule 3

- Increase sample size to compensate for less than 100% uptake of intervention.
- Or alternatively and in conjunction identify and consent before randomisation and then only use those participants who have expressed a willingness to take part in the trial.

Review of Cluster Trials

- Because of the 'BEAM' problem we decided to undertake a methodological review of cluster trials.
- We identified all cluster trials published in the BMJ, Lancet, NEJM since 1997.

Puffer et al. BMJ 2003;327:785.

Results

- We identified 36 relevant trials. ONLY 13 had identified participants prior to randomisation.
- Of the 23 not identifying participants a priori 7 showed evidence of differential recruitment or consent.
- Other biases included differential of inclusion criteria or attrition.
- In total 14 (39%) showed evidence of bias.

Underestimate of problem

- Only in 5 papers did authors alert reader to possible problem.
- Subsequently one of the trials that 'looked' OK was published elsewhere where recruitment bias was admitted to have occurred.

Misleading trial

- One trial (Jorhdoy, Lancet 2000) where there was no evidence of biased recruitment was later found to have suffered recruitment bias in another publication.
- This was an RCT for home care for terminally ill patients.
- We found, no evidence, in the Lancet paper of a problem. BUT...

Baseline Characteristics

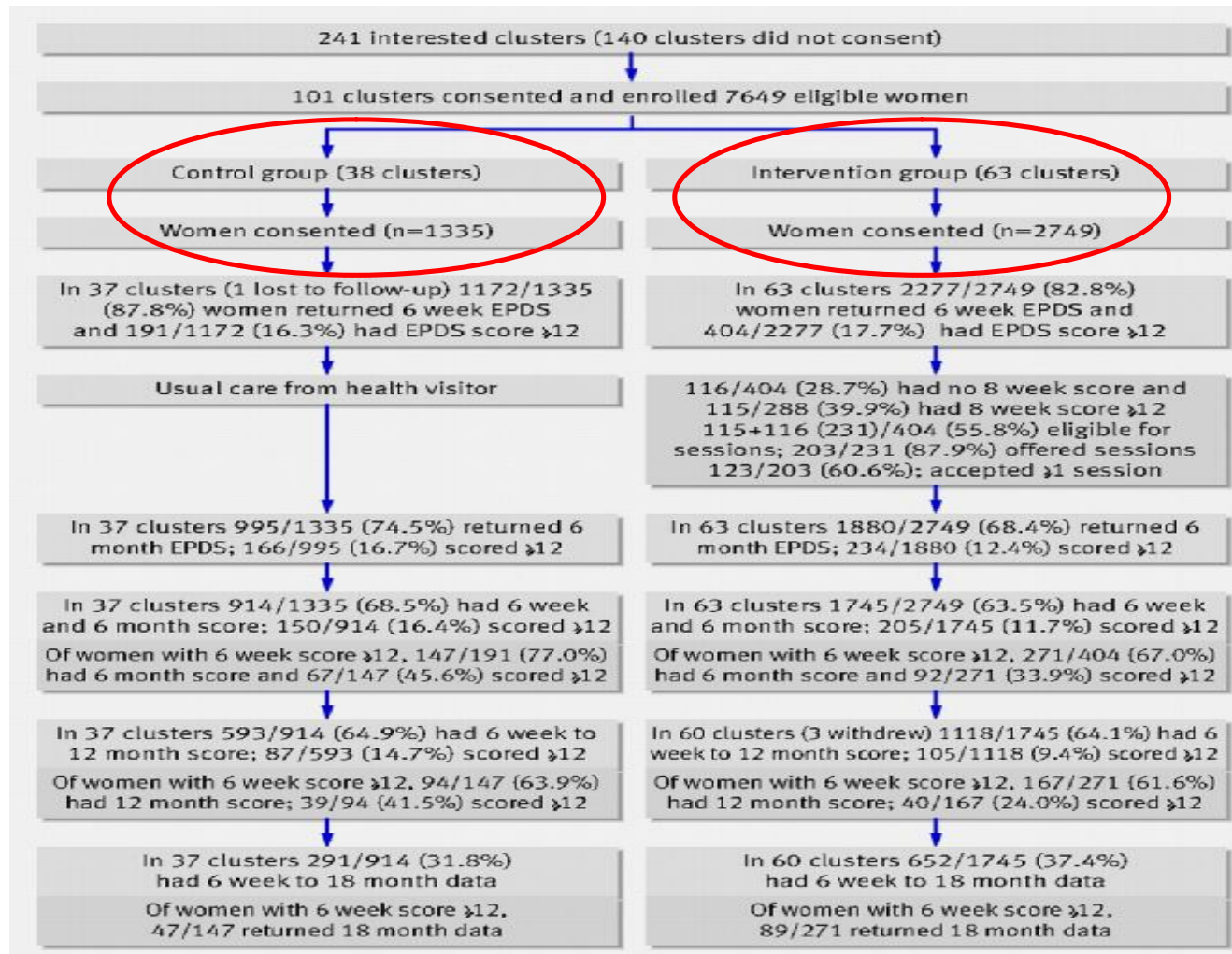
	Intervention	Control	
Live in Flat	40%	23%	P < 0.001
Married	67%	59%	P = 0.07
Access to help	80%	70%	P = 0.04
P values adjusted for clustering.			

Jordhoy Palliative Medicine 2002 16:43-49.

Recently Published Cluster Trials

- A non-random selection of recent papers published in the BMJ shows that the problem is still prevalent – with some authors being aware of the issue and others not.

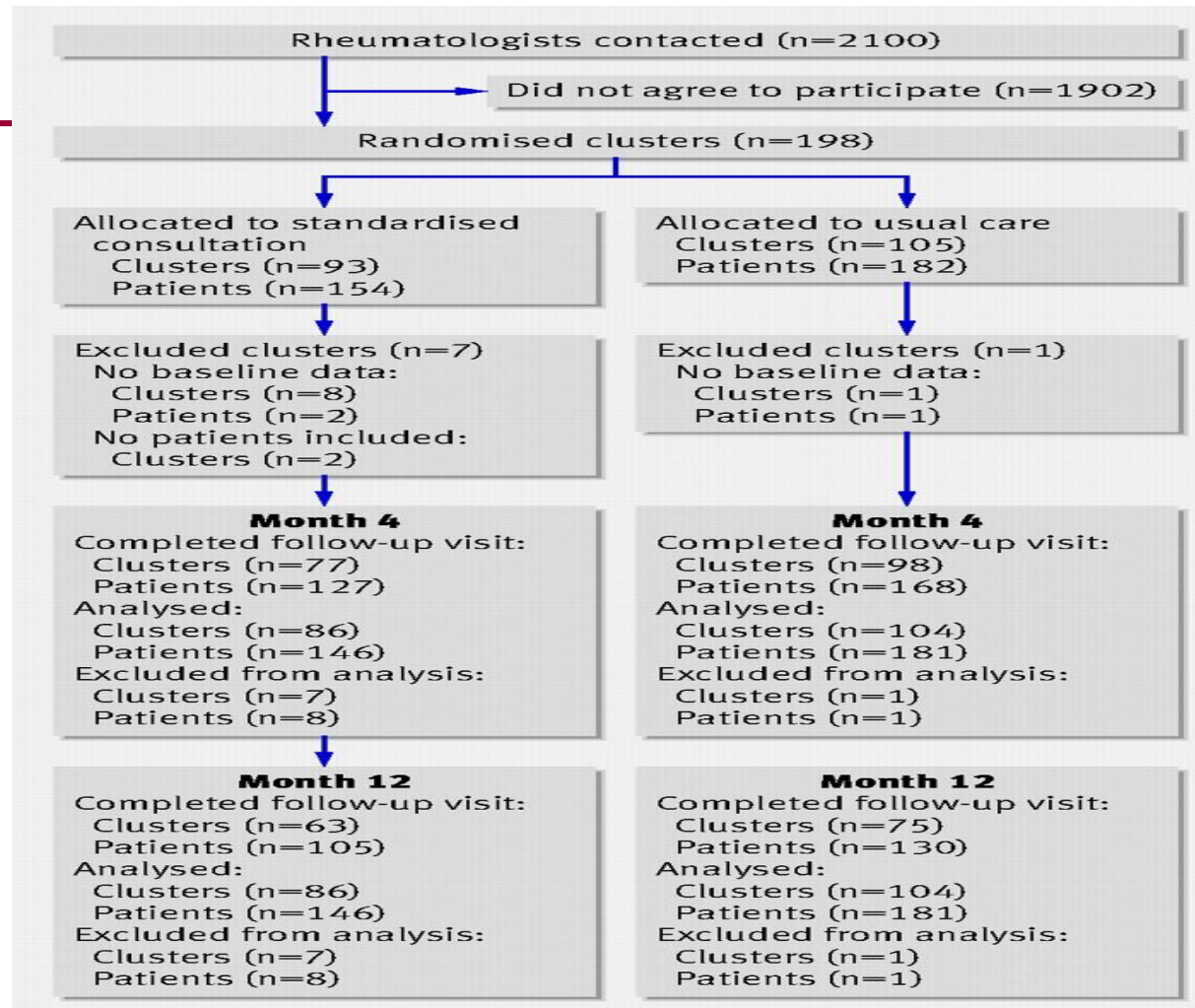
Fig 1 Trial profile of clusters, all women and women with six week EPDS score ≥ 12 in control and intervention groups. Note: 597 women were not sent 12 month questionnaire as their baby was < 12 months, and 1879 women were not sent 18 month questionnaire as their baby was not 18 months when follow-up interval ended



Note: 35 per cluster for control group and 44 per cluster for intervention – 26% difference



Flow diagram of participants in the trial



Ravaud, P et al. BMJ 2009;338:b421

BMJ

ARTIST trial

- Had similar numbers recruited; however, there was a suggestion that in at least two observable covariates (i.e., BMI, time since onset of pain) the groups were imbalanced.
- Authors tried to correct for these in the analysis; however, this will not correct for unobserved covariates.

Cluster Trials: Should I do one?

- Yes, BUT do them properly.
- Is it possible to avoid doing them and do an individually randomised trial?

Contamination

- An important justification for their use is **SUPPOSED** 'contamination' between participants allocated to the intervention with people allocated to the control.

Spurious Contamination?

- Trial proposal to cluster randomise practices for a breast feeding study – new mothers might talk to each other!
- Trial for reducing cardiac risk factors patients again might talk to each other.
- Trial for removing allergens from homes of asthmatic children.

Patient level contamination

- In a trial of counselling adults to reduce their risk of cardiovascular disease general practices were randomised to avoid contamination of control participants by intervention patients.

Steptoe. BMJ 1999;319:943.

Counselling Trial

- Steptoe et al, wanted to detect a 9% reduction in smoking prevalence with a health promotion intervention. They needed 2000 participants (rather than 1282) because of clustering.
- If they had randomised 2000 individuals this would have been able to detect a 7% reduction allowing for a 20% CONTAMINATION.

Accepting Contamination

- We should accept some contamination and deal with it through individual randomisation and by boosting the sample size rather than going for cluster randomisation

Torgerson BMJ 2001;322:355.

Comparison of Sample Sizes

Contamination and Sample Size

0	10%	20%	30%
116	144	182	236

Cluster and Sample Size

1	20	50	100
116	160	230	346

NB: Assuming an ICC of 0.02.

What about dilution bias?

- If, in the presence of contamination, we use individual allocation we might observe a difference that is statistically significant but is not clinically or economically significant.
- Dilution has biased the estimate towards the mean.
- If we can measure contamination we can deal with this using 'instrumental' or CACE analysis
- Generally if contamination is 30% or less it is more efficient to use individual allocation.

Hewitt et al. Taking account of non-compliance in randomised trials.
Canadian Medical Association Journal 2006;175:347-48

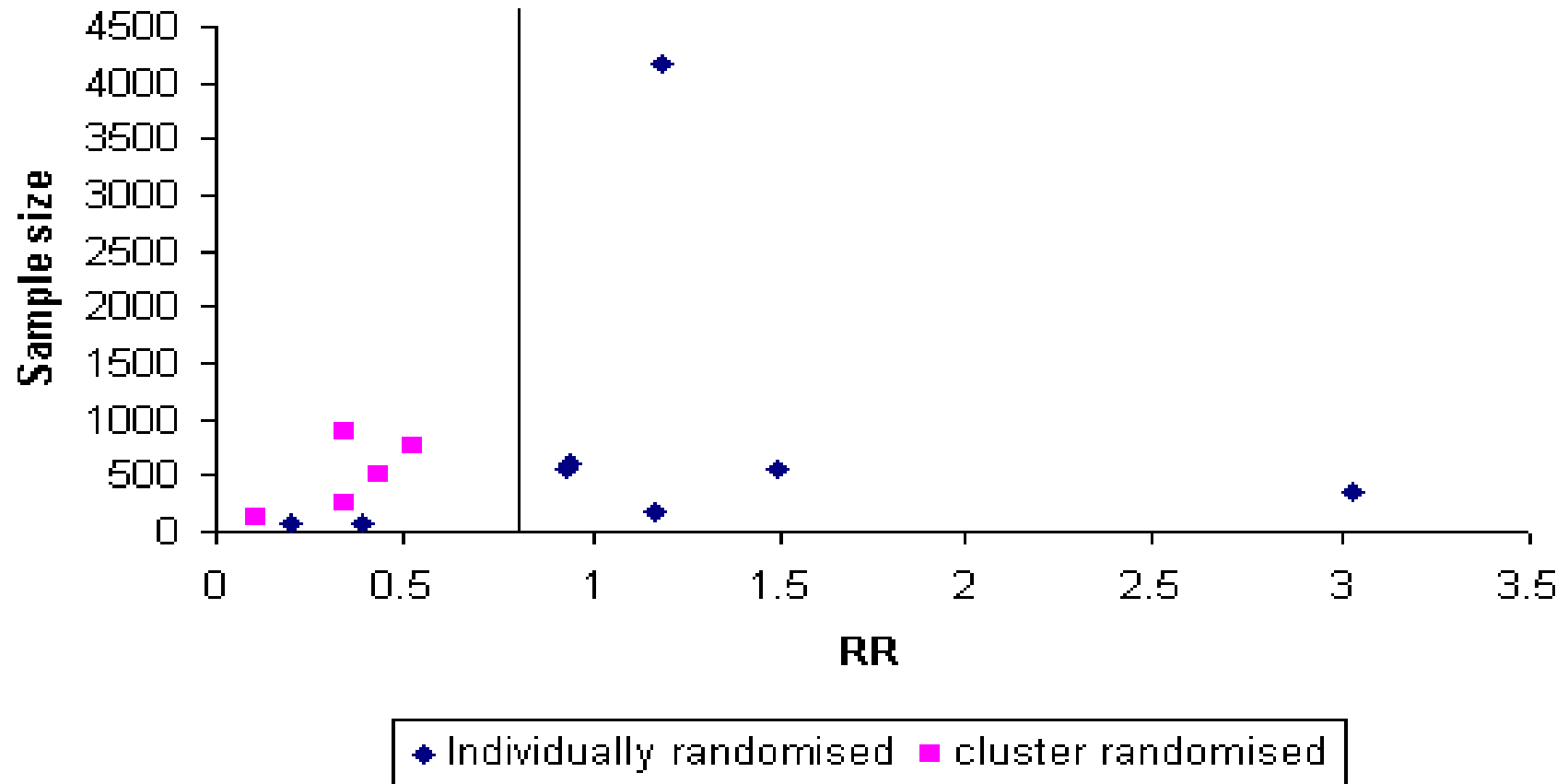
Cluster Trials

- Can cluster trials give different results?
- All things being equal this shouldn't happen (except for a more imprecise estimate). BUT because of the greater potential for selection bias cluster trials MAY give the 'wrong' answer.

An example.

- There are 14 RCTs of hip protectors for the prevention of hip fracture.
- Nine RCTs are individually randomised trials, whilst 5 are cluster trials (e.g., hospital ward, nursing home).
- Cluster trials, without exception show a benefit of hip protectors.

Hip Protector Trials: Cluster vs Individually Randomised.



Cluster Trials- What Should We Do?

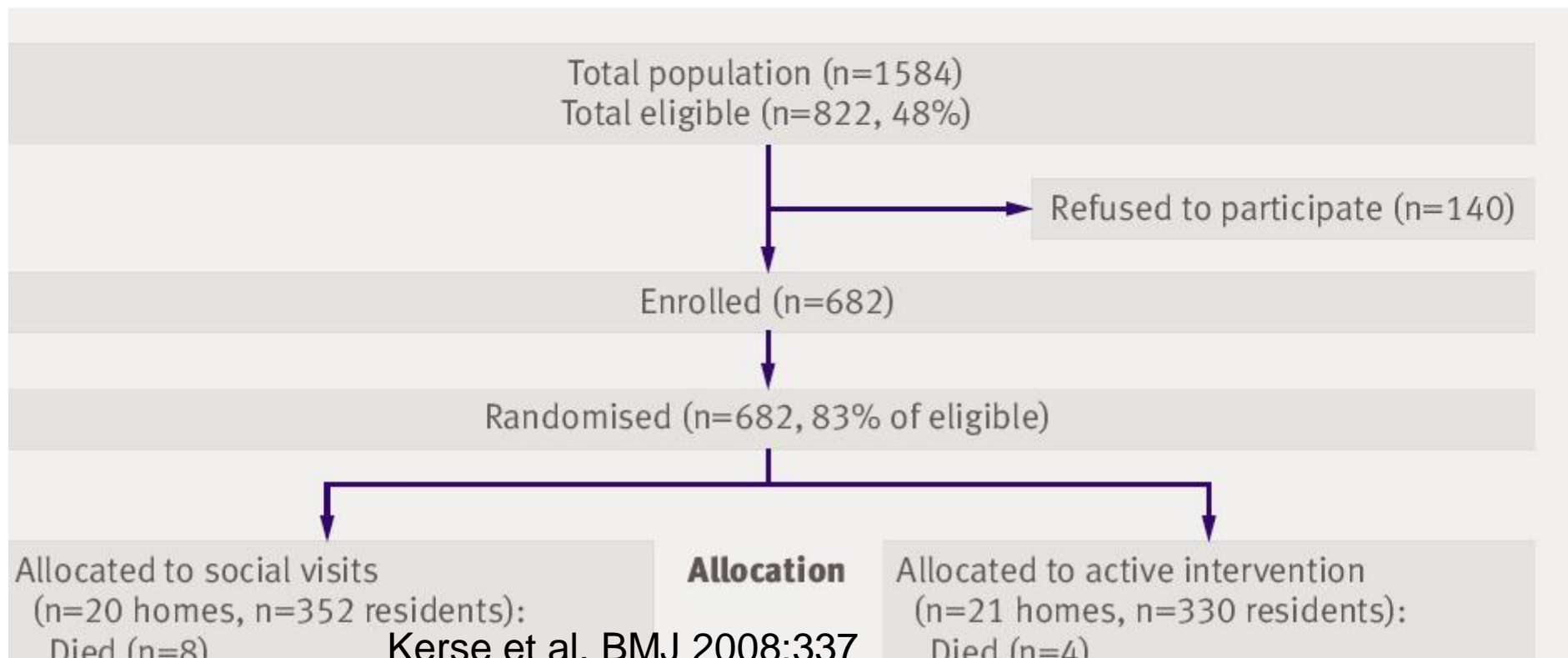
- Identify ALL eligible people if possible BEFORE randomisation
- ALWAYS use Intention To Treat analysis
- Blind the person applying inclusion/exclusion criteria.
- Blind follow-up/data collection.
- INCREASE sample size not only for cluster effects but also because of treatment refusal

Fall prevention trial

- In this study the authors identified and recruited residents in nursing homes **BEFORE** randomisation of the clusters. Thus avoiding selection bias.

Randomisation and blinding

After recruitment of all homes and residents and collection of baseline data, a biostatistician not involved in recruitment randomised homes to the intervention or control group by using computer generated random numbers. We used randomisation by home (cluster) to avoid contamination between



Summary

- Cluster Trials are currently very trendy
- Whilst in principle they are a robust design in practice fraught with difficulty.
- If possible avoid and opt for individual randomisation
- If cluster trial is necessary follow rules to avoid bias.