Allocation concealment, prediction and selection bias

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Background

- Randomised controlled trials (RCTs) provide the strongest basis for causal inference by:
  - » Controlling for regression effects;
  - » Controlling for temporal effects;
  - » Providing a basis for statistical inference;
  - » Removing selection bias.

Selection Bias

- Selection bias can occur in non-randomised studies when group selection is related to a known or unknown prognostic variable.
- If the variable is either unknown or imperfectly measured then it is not possible to control for this confound and the observed effect may be biased.

Effects of selection bias

- Observational data on hormone replacement therapy consistently shows that this reduces cardiovascular disease, stroke, dementia.
- Trial evidence shows the opposite.
- BECAUSE women taking HRT tended to be different and at lower risk from these problems than women not taking HRT.

Randomisation

- Randomisation (or a similar technique, such as minimisation) removes selection bias across a ‘population’ of RCTs by ensuring all variables that may affect outcome are balanced across treatment groups at baseline.
- Other techniques may allow the introduction of selection bias.

Quasi-alternation

- One allocation method that can introduce selection bias is allocating participants by some defining characteristic, such as month of birth, first letter of surname etc.
- Such an approach can lead to selection bias if outcome is associated with method of allocation. For example, in England people born in August tend to fare badly educationally compared with those born in September.

Example: Quasi alternation

- *“Before mailing, recipients were randomized by rearranging them in alphabetical order according to the first name of each person. The first 250 received one scratch ticket for a lottery conducted by the Norwegian Society for the Blind, the second 250 received two such scratch tickets, and the third 250 were promised two scratch tickets if they replied within one week.”*(Finsen and Storeheier, Biomed Central 2006)

True Alternation

- This is where participants are alternated by attendance at a clinic or alternated within a list.
- True alternation can produce groups that are equivalent at baseline as effectively as random allocation.
- Alternation was originally favoured by Bradford Hill an early proponent of trials due to its ease of understanding.
- But interference with alternation can lead to selection bias.

Alternation and selection

- Alternation is always predictable. Once the first participant is assigned we will always know the allocation of the next participant will be the opposite of the previous one.
- This predictability allows conscious or unconscious manipulation of the allocation so that participants can be excluded or re-scheduled in order for them to receive their ‘desired’ treatment.
- This can lead to SELECTION bias.

Randomisation

- Randomisation offers the POSSIBILITY of preventing selection bias that occurs due to the predictability of alternation.

- Simple randomisation, when properly undertaken, cannot be predicted.

Subversion

- Subversion of the allocation mechanism introduces selection bias.
- This occurs when the next allocation can be predicted and participants are then selected to match a desired allocation rather than having the allocation assigned at random.

Foreknowledge of allocation

- The simplest approach of allowing subversion is to publicize the allocation sequence. People who recruit participants, if they have access to allocation schedule, will always be able to predict the next allocation just as effectively as if alternation had been used.
- This prediction allows the possibility of selection bias.

Subversion - evidence

- Schulz [1] has described, anecdotally, a number of incidents of researchers subverting allocation by looking at sealed envelopes through x-ray lights.
- Researchers have confessed to breaking open filing cabinets to obtain the randomisation code.
- In a survey [2] of 25 researchers 4 admitted to keeping ‘a log’ of previous allocations to try and predict future allocations.

Schulz JAMA 1995;274:1456.

Brown et al. Stats in Medicine, 2005,24:3715.

Quantitative Evidence

- Trials with adequately concealed allocation show different effect sizes, which would not happen if allocation wasn’t being subverted.
- Trials using simple randomisation are too equivalent for it to have occurred by chance.

Poor concealment

- Schulz et al. Examined 250 RCTs and classified them into having adequate concealment (where subversion was difficult), unclear, or inadequate where subversion was able to take place.
- They found that badly concealed allocation was associated with a 40% increased effect sizes.

Schulz et al. JAMA 1995;273:408.

Comparison of concealment

Allocation Concealment	Effect Size OR	
Adequate	1.0	
Unclear	0.67	P < 0.01
Inadequate	0.59	

Schulz et al. JAMA 1995;273:408.

Allocation concealment and sequence generation

- Kjaergard and colleagues found that inadequate sequence generation as well as poor allocation concealment were associated with increased effect sizes.
- Small trials tended to poor methodologically, which explained previous associations between trial size and effect sizes.

Kjaergard et al. Ann Intern Med 2001;135:982.

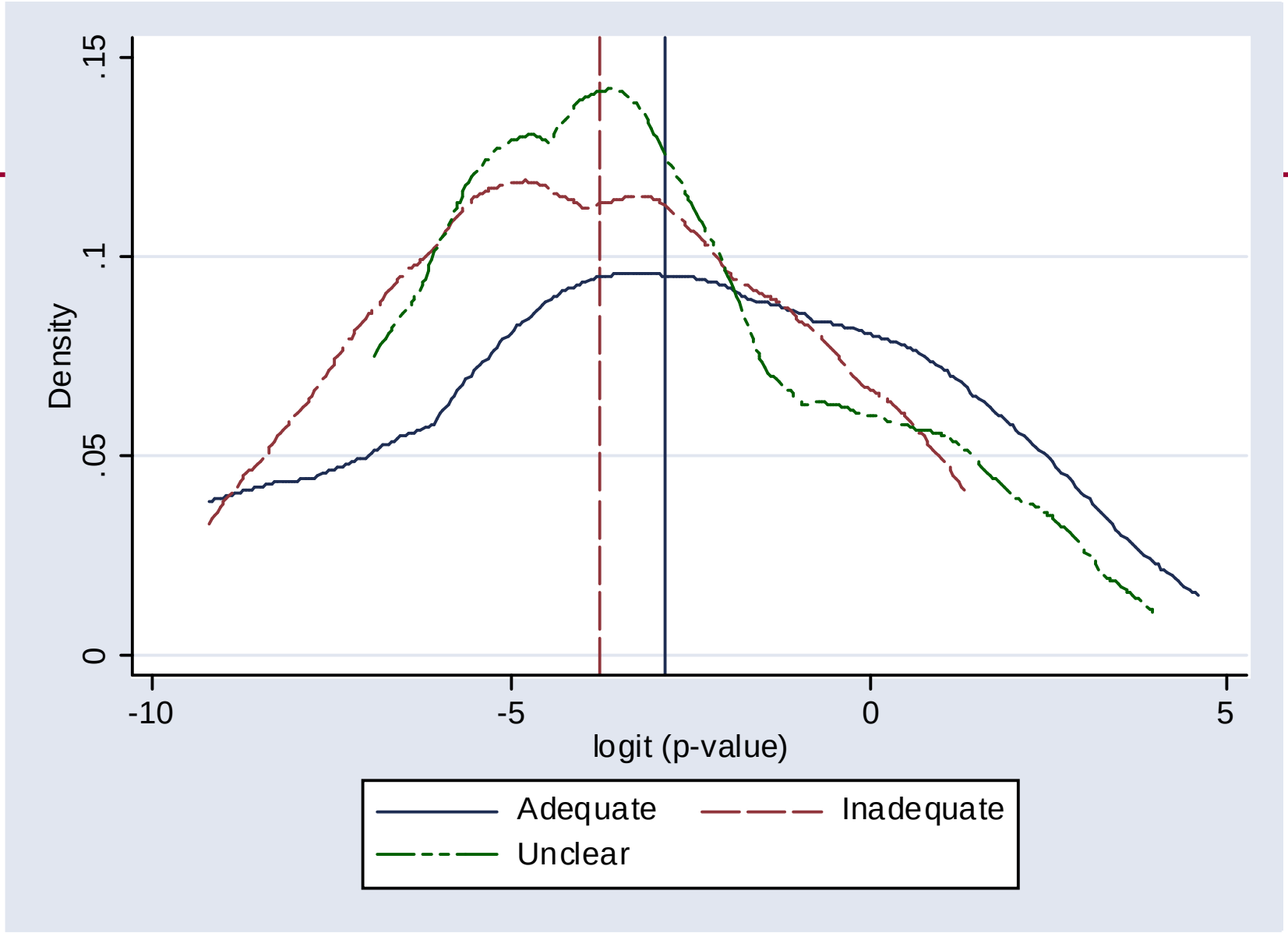
Concealment

- Both the Schulz and Kjaergard considered sealed opaque envelopes to be ‘adequate’ measures of conealment.
- Envelopes can be subverted by being opened in advance.

More Evidence

- Hewitt and colleagues examined the association between p values and adequate concealment in 4 major medical journals.
- Inadequate concealment largely used opaque envelopes.
- The average p value for inadequately concealed trials was 0.022 compared with 0.052 for adequate trials (test for difference p = 0.045).

Hewitt et al. BMJ;2005: March 10th.


Density
0
.05
.1
.15
-10
-5
0
5
logit (p-value)
Adequate
Inadequate
Unclear

Case Study

- Subversion is rarely reported for individual studies.
- One study where it has been reported was for a large, multicentred surgical trial.
- Participants were being randomised to 5+ centres using opaque, sequentially numbered, sealed envelopes.

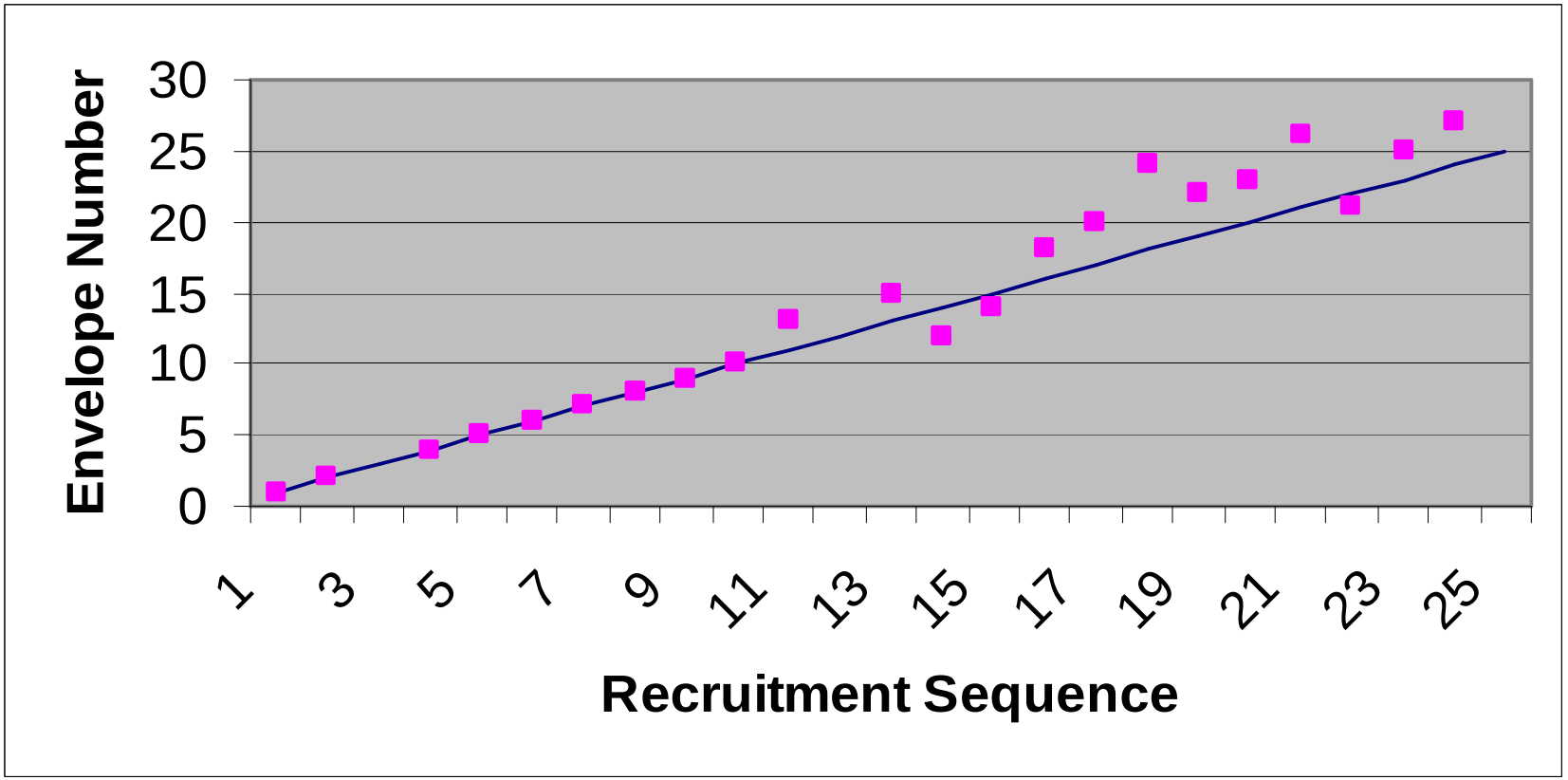
Case-study (cont)

- After several hundred participants had been allocated the study statistician noticed that there was an imbalance in age.
- This age imbalance was occurring in 3 out of the 5 centres.
- Independently 3 clinical researchers were subverting the allocation.

Mean ages of groups

Clinician	Experimental	Control
All $p < 0.01$	59	63
1 $p = .84$	62	61
2 $p = 0.60$	43	52
3 $p < 0.01$	57	72
4 $p < 0.001$	33	69
5 $p = 0.03$	47	72
Others $p = 0.99$	64	59

Example of Subversion



Using Telephone Allocation

Clinician	Experimental	Control
All p = 0.37	59	57
1 p =.62	57	57
2 p = 0.24	60	51
3 NA	61	70
4 p =0.99	63	65
5 p = 0.91	57	62
Others p = 0.99	59	56

More Examples

- Berger has collected 30 case examples of potential subversion of the allocation process in clinical trials.
- Because allocation subversion is scientific misconduct it is likely that there are many other, undetected, cases.

Berger. *Selection Bias and Covariate Imbalances in Randomized Clinical Trials* 2005: Wiley, Chicester.

Recent Blocked Trial

"This was a block randomised study (four patients to each block) with separate randomisation at each of the three centres. Blocks of four cards were produced, each containing two cards marked with "nurse" and two marked with "house officer." Each card was placed into an opaque envelope and the envelope sealed. The block was shuffled and, after shuffling, was placed in a box."

Kinley et al., BMJ 325:1323.

What is wrong here?

Southampton		Sheffield		Doncaster	
Doctor	Nurse	Doctor	Nurse	Doctor	Nurse
500	511	308	319	118	118

Kinley et al., BMJ 325:1323.

Problem?

- If block randomisation of 4 were used then each centre should not be different by more than 2 patients in terms of group sizes.
- Two centres had a numerical disparity of 11. Either blocks of 4 were not used or the sequence was not followed.

Why manipulation?

- “To provide best patient care…”
- “He fancied her! She was pretty!”
- “Individual was putting younger fitter individuals into the intervention..they were trying to improve the results”
- “Prefer to do certain procedures”
- “Researcher overode the random allocation, thought there should be same numbers in each group”

Hewitt et al. *J Clin Epidemiol* 2009;62:261-69

Concealment: Recommendations

- Allocation sequence must be independently generated and kept secret from the people who are enrolling participants.
- A secure method of giving allocation to the recruiters must be developed, opaque envelopes are inadequate.

Simple or Restricted Randomisation?

Restricted Allocation

- Many RCTs use some form of restricted allocation.
- Restricted allocation is used to reduce the possibility of chance imbalances by keeping the proportion of people with pre-specified characteristics the same throughout the trial.
- Usually restricted randomisation uses some form of ‘blocked allocation’.

Blocking

- Blocked randomisation takes a recurring sequence of allocations. For instance a block of 4 would be: AABB; ABAB; BBAA; BABA; BAAB; ABBA.
- These are put in a random order, this ensures that if the allocation were stratified by Centre no centre will be numerically imbalanced by more that 2 participants.

What is current practice?

- In a review of 232 RCTs published in 2002 in the BMJ, JAMA , Lancet, New Engl J Med only 9% (21) used simple randomisation.
- All the other studies used some form of restricted allocation.

Hewitt & Torgerson BMJ 2006.

Restricted allocation and subversion

- The drawback with any form of allocation restriction is that it allows some prediction.
- Simple randomisation has no ‘memory’ of the previous allocation. In contrast, blocked allocation allows the probability of an allocation to be linked to the previous allocation.
- Merely guessing that the next allocation will be the opposite of the previous one will result in a prediction more accurate than by chance.
- This can, in theory, allow subversion.

Possible subversion

- In a RCT of rehabilitation for the treatment of hip fracture gross baseline imbalances were detected favouring the control group.
- Secure telephone allocation had been used. But blocked allocation, size 6, had been used.
- Exploratory analysis of imbalances suggested partially successful prediction of block allocation.

Turner J. 2002, Unpublished PhD Thesis, University of York.

Technical problems

- This occurs when the allocation system breaks down often due a computer fault.
- A great example is the COMET I trial (COMET II was done because COMET 1 suffered bias).

COMET 1

- A trial of two types of epidural anaesthetics for women in labour.
- The trial was using MIMINISATION via a computer programme.
- The groups were minimised on age of mother and her ethnicity.
- Programme had a fault.

COMET Lancet 2001;358:19.

COMET 1 – Technical Bias

AGE	Traditional	Combined	Low dose
Total	388	335	331
<25 years	13 (3%)	179 (53%)	173 (52%)

COMET II

- This new study had to be undertaken and another 1000 women recruited and randomised.
- LESSON – Always check the balance of your groups as you go along if computer allocation is being used.

Wither restricted allocation?

- Simple randomisation followed by regression analysis is as efficient as restricted randomisation and regression analysis for sample sizes > 50.
- Restricted allocation increases risk of prediction and predictability.
- For large trials simple allocation followed by regression reduces risk of prediction.

Rosenberger WF, Lachin JM. *Randomisation in clinical trials: Theory and practice*. Wiley Interscience, 2002, John Wiley and Sons, New York.

But some like to block

The applicants do not intend to stratify the randomisation because they consider they have a large sample size. I would disagree with this and ask them to reconsider. A trial with imbalance between arms in important factors will not be convincing regardless of adjustments made in analysis.

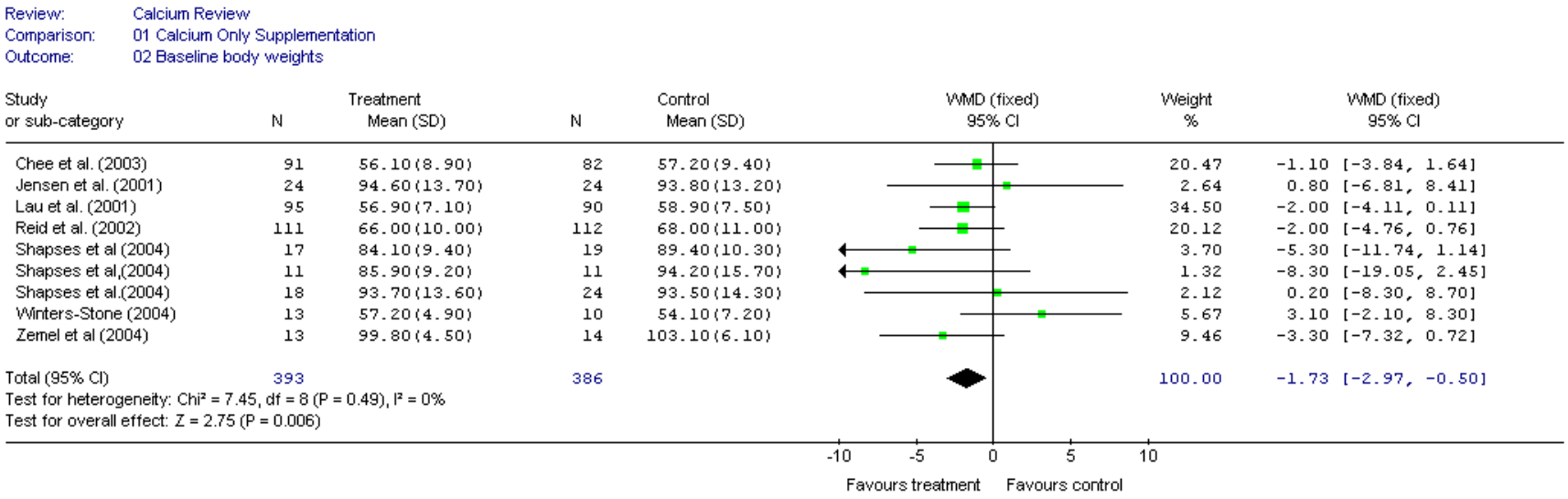
Testing for subversion

- Comparison of baseline characteristics may help if subversion is suspected. Although this will only identify gross subversion.
- If blocked allocation is used a statistical test – Bergner-Exner test, may help identify subversion.

Evidence from a systematic review.

- In a systematic review of the use of calcium supplements to enhance weight loss Trowman et al found a significant relationship between calcium use and reductions in body weight.
- HOWEVER, examination of baseline characteristics found that people with lower body weights tended to be allocated to the calcium group. In no single trial was this difference significant but in a meta-analysis of baseline weights the difference was highly significant ($p = 0.006$).

Meta-analysis of baseline body weight.



Trowman et al. The impact of baseline imbalances should be considered in systematic reviews: a methodological case study. *Journal of Clinical Epidemiology* 2007;60:1229-1233

Selection bias in Trials: Summary

- Selection bias can occur in RCTs.
- To reduce the risk of selection bias we should do the following:
  - » Adopt secure randomisation from a third party;
  - » Keep allocation a secret until after participant is recruited;
  - » Avoid restricted forms of allocation if possible;
  - » Trust no-one.