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Why Randomize?

- ◆ To safeguard against selection bias
- ◆ To try to avoid accidental bias
- ◆ To provide a basis for statistical tests
 - t-tests etc can be justified on basis of the randomization — don't need to appeal to theory of Normal distributions: the t-distribution is a good approximation to the randomization distribution — shown by Student [W.S. Gossett]



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Simple randomization

- ◆ randomization list
 - List assigning next subject to treatment constructed using random numbers
 - Made **before** trial starts
 - Easy to produce using computer package



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Restricted Randomization

Blocking

- ensures equal treatment numbers at certain equally spaced points in the sequence of patient assignments.
- next random digit assigns a block of treatments
- easy to guess next treatment in small blocks
- large block size vs potential imbalance



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Unequal Collection

- may want a treatment used more frequently than others — use blocks of treatments repeated in desired ratios

e.g. AAABB (permuted), $5!/3!2!=10$ possibilities, AAABB, AABAB,
choose sequence of blocks randomly from list of permutations



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- ◆ NB may have large number of different permutations — no need to use them all; a subset is adequate

- 5 treatments equally replicated
- need list for 200 subjects
- 120 different blocks of size 5, but only need 40
- use (say) 10 or 15 of these to construct list — avoids enumerating all 120



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◆ Stratified Randomization

- Strata defined by combinations of relevant patient factors
- Prepare separate randomization lists for each strata
- Alternative is to include strata indicators in analysis (e.g. by regression)

◆ Implementation in R

- key command is `sample(.)`

```
> x<- c(0:9)
> x
[1] 0 1 2 3 4 5 6 7 8 9
> sample(x)
[1] 6 3 1 7 5 4 9 8 0 2      permutation
> sample(x,4)
[1] 3 1 6 7      subsample without replacement
> sample(x,4,replace=TRUE)
[1] 0 9 0 7      subsample with replacement
> sample(x,20,replace=T)
[1] 3 8 1 4 0 9 4 7 5 1 6 4 2 3 1 8 3 3 7 0
```

```
> z<-c(rep("A",5),rep("B",5),rep("C",5))
> z
[1] "A" "A" "A" "A" "A" "B" "B" "B" "B" "B"
   "B" "C" "C" "C" "C" "C"
> sample(z)
[1] "B" "A" "A" "A" "C" "C" "B" "B" "C"
   "A" "B" "C" "B" "A" "C"
> sample(c(rep("A",4),rep("P",2)))
[1] "A" "A" "P" "A" "P" "A"
```

How can you produce a randomization list of length 25 with blocks of this form??

■ Minimization

- ◆ large number of relevant factors
 - very large number of strata
 - some combinations of factors very rare
- ◆ separate randomization lists unrealistic
 - Determine new subjects factor status
 - Count numbers of subjects with those factors on each treatment — allocate to balance up scores (see course notes)

■ Randomization Software

- ◆ A directory of randomisation software is maintained by Martin Bland at:

<http://www-users.york.ac.uk/~mb55/guide/randsery.htm>

- ◆ Downloadable programmes for simple and blocked randomization [some free]
- ◆ Easy to programme in R
- ◆ some commercial software including add-ons for standard packages such as STATA
- ◆ links to various commercial *randomization services* used to provide full blinding of trials
- ◆ notes on randomization with references etc.



▪ **Summary and Conclusions**

- ◆ Protects against accidental & selection bias
- ◆ provides a basis for statistical tests (e.g. use of normal and t-distributions)

- ◆ simple
 - but may be unbalanced over treatments
- ◆ blocked
 - but small blocks may be decoded
- ◆ stratified
 - but may require small blocks
- ◆ minimization
 - but lessens randomness



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- **Protocol**
 - ◆ written document
 - all details of trial conduct
- **Purpose**
 - ◆ motivation
 - ◆ aims

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- **Design & conduct**
 - ◆ number of patients
 - and why
 - ◆ trial design & randomization
 - ◆ evaluation of response
 - baseline measure
 - principal response
 - subsidiary criteria

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- techniques for analysis
 - ◆ Parametric or non-parametric
 - ◆ Adjustment for baseline imbalance
- **'informed consent' form**

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- These details should be registered in registry of clinical trials
<http://clinicaltrials.gov/>
 - ◆ In 2005, the International Committee of Medical Journal Editors announced they would only publish trials that had been registered
 - ◆ **BUT**
 - Mathieu, S. et al., 2009. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. *JAMA*, 302(9), 977-984.

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- Mathieu, S. et al., 2009. Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials. *JAMA*, 302(9), 977-984.
- 323 trials in 10 leading journals
- Less than half were registered with primary outcome stated
 - » (89 not registered at all)
- A third of properly registered trials switched primary outcome in publication
- In most of these registered outcome showed no positive result but published primary did
- ◆ See Ben Goldacre, *Guardian*, 03/10/09
 - Links on course web page (and to registry of clinical trials)

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- **Protocol deviations**
 - ◆ aim is to minimize bias in the treatment comparison of interest

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- **intention to treat analysis**
 - ◆ include all **eligible** patients as originally randomized and assigned to treatments
 - only exclusions are inclusion criteria violations
- **per protocol analysis**
 - ◆ where patients who deviate from the protocol are excluded from the analysis

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- **Example**

	surgery	radiotherapy	
		Perhaps includes some inoperables	?
	in fact inoperable		

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- ◆ **Intention to treat**
 - initial randomization OK,
 - but deviates may give very odd responses
- ◆ **Per protocol**
 - randomization is compromised
 - is withdrawal of patient related to treatment?
 - If so then bias if not allowed for
 - if the numbers of patients are reduced there is a loss of power .

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clinical assessment	low dose	high dose	control	
very effective	2	8	6	
effective	4	2	8	
ineffective	3	2	0	
total assessed	9	12	14	35
withdrawn	6	8	1	15
total randomized	15	20	15	50


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- **per protocol**
 - ◆ 67% of those on high dose reported 'very effective'
 - much higher than on low dose or control
- **intention to treat**
 - ◆ 40% on high dose reported 'very effective'
 - same as on control

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- **Summary and Conclusions**
 - ◆ Protocols specify trial conduct
 - Medical aspects
 - Statistical aspects
 - ◆ Protocol deviations
 - **intention to treat analysis**
 - treatment groups not homogenous
 - comparison loose power
 - **per protocol analysis**
 - randomization compromised so bias
 - may also loose power by reducing numbers of subjects

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