

## Contents

### Preliminaries

#### 0: Introduction

#### 1: Background & Basic Concepts

#### 2: Basic Trial analysis

### 3: Randomization

#### 4: Protocol Deviations

#### 5: Size of the Trial

#### 6: Multiplicity & Interim Analysis

#### 7: Crossover Trials

#### 8: Combining Trials

#### 9: Binary Response Data

#### 10: Comparing Methods of Measurement



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85

### 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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86

### 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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87

### 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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88

#### 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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89

- ◆ 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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103

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



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104

- **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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106

- 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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107

- 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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108



- **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
<b>withdrawn</b>	<b>6</b>	<b>8</b>	<b>1</b>	<b>15</b>
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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