## 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



- **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 — shewn by Student [W.S. Gossett]



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



- **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



- **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



- 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





- **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" "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



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



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



- 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.



- 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)





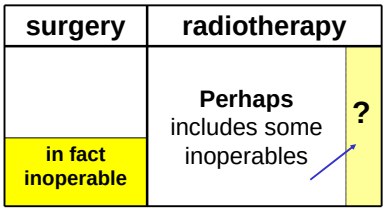
- **Protocol deviations**
  - aim is to minimize bias in the treatment comparison of interest



- **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



- Example






- **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 .



| 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 |



- **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





- **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