



Randomization

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OUTLINE

Randomization

- **Key methodologic design feature**
- **Intention to treat principle**
- **How to do the scheme**
- **How to administer**

Why Randomize?

- **Best way to assure compatibility**
- **In the long run balance of factors**
 - Known**
 - Unknown**
- **Statistical hypothesis test based on random assignment**
- **Selection is impartial: “dice not trying to prove a point”**
- **Must convince others of validity of comparison**

Randomization

FIXED ALLOCATION: Assigns with pre-specified probability (not necessarily, though usually, equal)

ADAPTIVE: Changes probabilities during study

Baseline adaptive: - on basis of number per group
- on basis of variables

Responsive adaptive: - depends on prior outcome

Assumes - rapid response

- stable population source

Internal Validity

compare treatments

External Validity/ Generalizability

extrapolate to other patients, people

Not realistic to find a random sample of patients for recruitment (at the very least they have to consent)

More important to establish efficacy of treatment before deciding if it can be broadly applied

A Classification of Trials

Explanatory (efficacy) - acquire information on the true treatment effects

Pragmatic (management, effectiveness) - make a decision about therapeutic strategy after taking into account “cost” (withdrawals, side effects) of administering treatment

- most closely resembles clinical scenario

- treatment policy

- treatment intention

Intention to Treat Principle

Intention to treat analysis based on random assignment

“Once randomized - always analyzed”

entrance criteria

treatment actually received

“Crossovers”

withdrawal from treatment

deviation from protocol (adherence to protocol)

Adherence to Intervention

Should We Only Do One Analysis?

Intention-to-treat primary espoused by FDA and NIH

Secondary analysis

Efficacy subset analysis

Are the results similar? Try to reconcile

Compare baseline characteristics of adherers versus non-adherers

Can show not comparable but can't prove they are comparable

Make various assumptions for missing outcome data

Last observation carried forward

Worst case scenario

Practical Issues

Minimize lost to follow-up

Even if poor or no adherence, follow patients

“Fire the statistician if doing so frees enough resources to allow completed data to be obtained. Complete data worth innumerable statistical models to adjust for ignorance”

- Patrick Shrout

How To Do The Scheme

Simple randomization

Biased coin, urn models

Example:

Start with 2 balls, one black and one white

Draw-replace and add one of opposite color

Prevents imbalance with high probability early on

Random permuted block

Balance at the end of block

Could predict with unmasked trial

Blocks Of Size 4

$$\binom{4}{2} = \frac{4!}{2!2!} = \frac{4*3*2*1}{2*1*2*1} = 6$$

1) 1100

2) 1010

3) 1001

4) 0110

5) 0101

6) 0011

How To Use Blocks When Treatment Is Not Masked

Choose the block sizes at random, too

Example: 2 treatments, equal allocation

Block sizes 4, 6, and 8 – random order

Balance in each block

Should You Stratify?

Factors:

Clinical sites – generally yes

Prognostic variables – generally not necessary

Issues:

Size

Practical considerations

Often governed by custom rather than statistical justification

Stratified ANALYSIS is usually preferred

Minimization

Advantages:

- Balance several prognostic factors
- Balance marginal treatment totals
- Good for small trials (<100 patients)
- Computer makes this fairly easily

Disadvantages:

- Can't prepare treatment assignment scheme in advance
- Need up-to-date record
- Not really random - could predict but can introduce random element by using say 3/4, 1/4

Table 5.7. - Treatment Assignments by the Four patient Factors for 80 Patients in an advanced Breast Cancer Trial

Factor	Level	No. on each treatment		Next patient
		A	B	
Performance status	Ambulatory	30	31	←
	Non-ambulatory	10	9	
Age	<50	18	17	←
	≥50	22	23	
Disease-free interval	<2 years	31	32	←
	≥2 years	9	8	
Dominant metastatic lesion	Visceral	19	21	←
	Osseous	8	7	
	Soft tissue	13	12	

Thus, for A this sum = $30 + 18 + 9 + 19 = 76$
 while for B this sum = $31 + 17 + 8 + 21 = 77$

Pocock S. *Clinical Trials: A Practical Approach*. John Wiley & Sons, Chichester, England, 1991, p. 85.

Practical Steps in the Randomization of a Patient

Check eligibility

Check Informed consent

Formal identification (Trial ID)

RANDOMIZE

Confirmation of patient entry

How Random Treatment Assignments Are Made

Model: Slips in a hat or flipping a coin

Masked drugs numbered and given in order:
pharmacy, drug manufacturer

Envelopes

Telephone to central unit

Real person

trained

untrained

Computer

Automated answering machine

Microcomputer at the site

local

central computer

Masked Evaluation of Endpoint

- Most behavioral interventions can't be masked: patients or those delivering intervention.
- Can evaluator be masked? Strong design feature.

Examples: Measure of blood pressure,
pain scale.

Coronary Drug Project

Lipid lowering drugs after myocardial infarction

Mortality

clofibrate	18.2%
placebo	19.4%

Overall

Clofibrate Adherence

≥ 80

< 80%

Clofibrate

18.2%

15.0%

24.6%

Percent Mortality in the Coronary Drug Project

		Drug Adherence	
	Overall	$\geq 80\%$	$< 80\%$
Clofibrate	18.2%	15.0%	24.6%
Placebo	19.4%	15.1%	28.2%