UNIVERSITY OF LIVERPOOL

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

NHS

Study Design

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Types of Studies

- Observational
  - Data are collected on one or more groups of subjects purely from an observer's point of view. The observer does not interfere with the clinical management of these subjects.
- Experimental
  - The researcher deliberately influences the clinical management of the subjects in order to investigate the outcome

Observational Studies

- Case-control studies
  - subjects with the disease in question (cases) are identified and compared with those without the disease but who are otherwise comparable (controls). The past history of these groups is examined to determine their exposure to a particular risk.
- Cohort (longitudinal) studies
  - two groups are identified, one exposed and one not exposed to a particular risk. The groups are followed up over time and the occurrence of the disease in question in each group is identified.

Cohort Studies
Pros and Cons

Advantages	Disadvantages
They do not rely on the accuracy of medical records which can sometimes contain errors or be incomplete	If the disease in question is rare, it will need a large number of subjects to be recruited and may take years
	Subjects might drop out of the study for a variety of reasons
	Might not always be feasible or ethical

Other types of Clinical Studies

- Cross-sectional: surveys where subjects are contacted once
- Within subjects trial: subjects are assessed before and after an intervention
- Cross-over trial: subjects receive both intervention and control treatments in a randomised manner with a washout period in between
- Multi-factorial designs: Studies that investigate the effects of more than one variable on the outcome

Type of trial	Outcome	Typical design
Preclinical: Theory	Rationale for decision support	Identify best practice for each component of the intervention
⇩		
Phase I: Modelling	Mechanism by which the system components influence healthcare outcomes and how they interact	Analysis of case studies
⇩		
Phase II: Exploratory trial	Specification for a replicable intervention and assessment of its effectiveness	Clinical trial typically comprising a multi-centre study
⇩		
Phase III: Definitive trial	Comparison of outcomes between the trial intervention and a standard intervention	Randomised controlled trial rigorously designed to avoid implementation bias
⇩		
Phase IV: Long term follow-up	Post-market surveillance	Systematic reporting of healthcare outcomes including adverse effects

Randomization

- One of the main problems in clinical trials is selection bias. Randomization is a process designed to reduce the effect of bias

Randomization

- Simple randomization
  - Each patient has an equal chance of being allocated to treatment given
- Block randomization
  - Subjects are randomly allocated to blocks which determine the order in which they receive the treatment
- Stratified randomization
  - Subjects are first divided into subgroups according to a particular characteristic and randomization is balanced within the subgroups

Simple Randomization

- Subjects allocated into 2 groups, those receiving new treatment (T) and those receiving placebo (P)

- Random sequence:
  - 00 – 49 = T 50 – 99 = P

91	47	03	87	54	01	15	33	12	76
P	T	T	P	P	T	T	T	T	P

Block Randomization

- In pure tone audiogram, subjects are tested using 3 frequency tones: 1, 3 and 8 kHz
- Possible combinations:
  - A: 138 B: 183 C: 318 D: 381 E: 813 F: 831
- Possible randomization strategy:
  - 00 – 15: A
  - 16 – 31: B
  - 32 – 47: C
  - 48 – 63: D
  - 64 – 79: E
  - 80 – 95: F
  - 96 – 100: ignore

91	47	03	87	54	01	15	33	12	76
F	C	A	F	D	A	A	C	A	E

Balanced Block (Latin Squares)

– 4 subjects are tested under all 4 conditions

Subject	Order			
	4	**3**	**1**	**2**
2	A	B	D	C
3	D	C	A	B
1	C	D	B	A
4	B	A	C	D

Incomplete Block

	Wheelchair					
Subject	**3**	**6**	**1**	**4**	**2**	**5**
3	√	√				
6			√	√		
8					√	√
1	√		√			
11		√		√		
2			√		√	
10				√		√
12	√			√		
5		√			√	
7			√			√
4	√				√	
9		√				√

Stratified Randomization

- Example: subjects are divided into 2 age groups

Age Group 1

Treatment	3	5	6	8	11	13	14	15
Placebo	1	2	4	7	9	10	12	16

Age Group 2

Treatment	2	4	6	7
Placebo	1	3	5	8

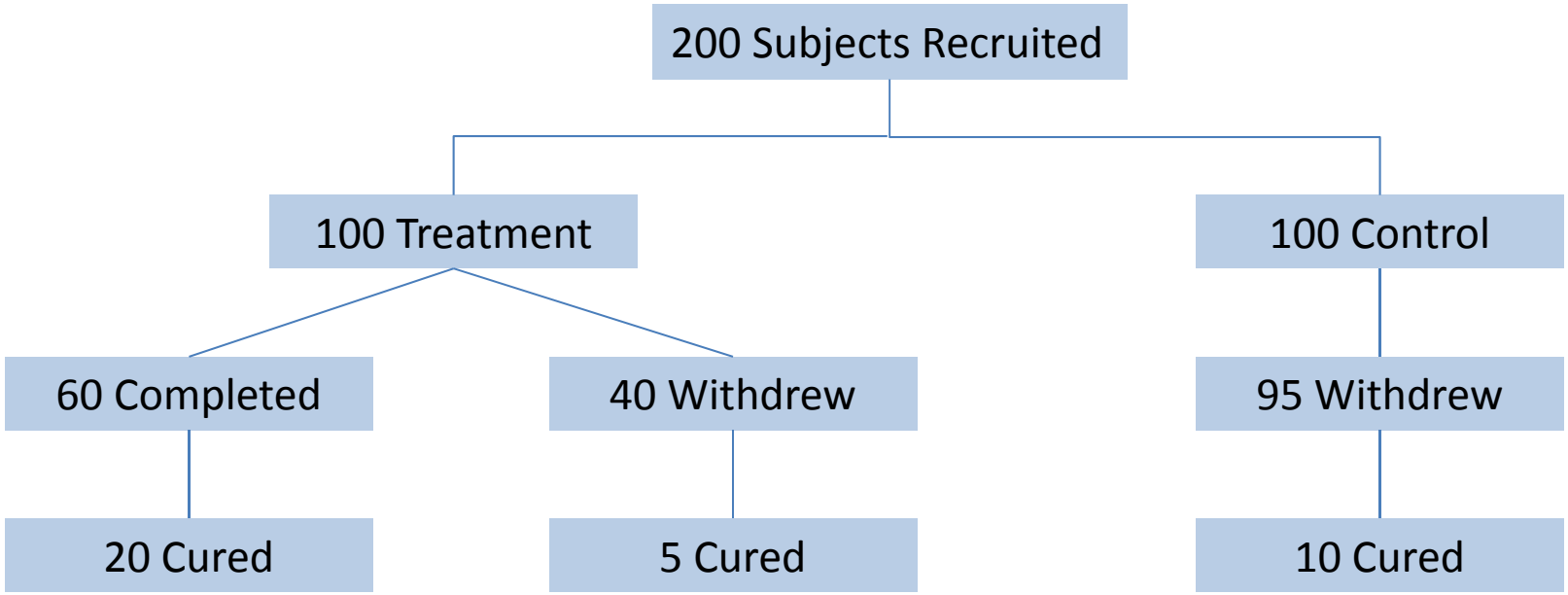
Blinding

- Blinding is done to reduce bias due to observer's or subject's judgment.
- A single blind study is where the subject does not know what treatment he or she is receiving
- A double blind study is where both subject and observer do not know which treatment is given

Selection Bias After Randomization

- Subjects in the treatment arm might drop out of the study if they experience problems. This can cause selection bias

Selection Bias After Randomization Example



RR (intention-to-treat) = 2.5

RR (per protocol) = 3

Selection Bias After Randomization

- Per protocol analysis can make the treatment look better than it is if the number of dropouts is large
- Intention-to-treat analysis uses denominators that are created purely by random
- A large number of dropouts in the treatment group however can be indicative of problems with the treatment
- Clinical trials should aim to reduce the number of dropouts as much as possible
- It is good practice when writing up the findings of a clinical trial to draw up a flow chart showing the numbers at each stage