Intervention Studies

Outline

- Introduction
  - Advantages and disadvantages
- Avoidance of bias
- Parallel group studies
- Cross-over studies

Introduction

- Intervention study, or clinical trial, is an experiment applied to
  - existing patients, in order to decide upon an appropriate therapy,
  - those presently free of symptoms, in order to decide upon an appropriate preventive strategy.
- Giving treatments to the subjects in the study.
  - Drugs
  - Hospital procedures
  - Field trials of vaccines
- Allocation of subjects to treatment is planned
  - Investigators decide who should receive which treatment.

An Example

- Vitamin and mineral supplementation to improve verbal and nonverbal reasoning of school children.
- Two groups of school children in Dundee
  - One received vitamin and mineral supplements.
  - The other received a placebo treatment.
  - IQ test performed at the beginning of the trial
- Tablets were taken for 7 months
  - IQ tests were repeated.

Initial and final values of IQ scores for 86 children.

Placebo group (n = 44)				Active group (n = 42)			
Nonverbal test		Verbal test		Nonverbal test		Verbal test	
Initial	Final	Initial	Final	Initial	Final	Initial	Final
89	83	87	84	70	87	57	63
82	97	73	87	91	91	68	75
107	107	59	72	106	104	78	89
95	101	105	108	92	87	86	84
110	100	97	105	103	114	81	93
106	97	75	84	105	115	85	89
114	112	113	118	106	106	85	86
97	96	86	89	82	78	80	82
103	103	95	97	101	98	86	84
109	122	101	94	86	106	76	86
97	80	84	89	101	102	99	97
93	103	93	93	97	97	100	93
107	110	96	94	84	85	76	85
84	102	73	86	90	100	87	97
69	79	70	80	88	90	77	85
109	100	97	95	121	106	95	92
98	101	77	76	101	110	82	89
72	78	86	87	100	97	91	89
70	78	82	87	116	126	108	110
99	122	79	79	108	121	98	111
105	118	96	104	127	125	94	98
133	133	130	126	95	100	88	88
87	93	84	82	90	91	83	92
104	120	101	89	112	117	101	93
118	112	98	95	115	119	98	109
113	121	105	118	112	111	80	87
89	99	90	92	104	108	99	107
101	97	76	79	107	98	88	88
95	95	82	83	137	131	109	109

Mean differences (with standard errors in parentheses) in IQ score deltas, together with tests of no difference between treatments.

IQ test	Placebo group	Active group	*t* test	
			Statistic	*p* value
Nonverbal	1.50 (1.49)	3.90 (1.24)	1.24	0.22
Verbal	2.64 (1.06)	3.14 (0.90)	0.36	0.72

Advantages

- We can ensure that the ‘cause’ precedes the ‘effect’.
- We can ensure that possible confounding factors do not confuse the results.
  - We can allocate subjects to treatment in any way we choose.
- We can ensure that treatments are compared efficiently.

Disadvantages

- Since intervention studies involve the prospective collection of data, they may share many of the disadvantages of cohort studies.
- Ethical problems are associated with giving experimental treatments.
- In many instances, intervention studies screen out 'problem' subjects, such as the very young, the elderly and pregnant women, who may have a special reaction to treatment.
  - This may restrict the generalizability of results.

Avoidance of Bias – Use of a Control Group

- Control group should be used in an intervention study.
  - may be treated with a placebo or another active treatment.
- If there had been no placebo group in the Dundee vitamin study
  - paired *t* test
    - *t* statistics are 3.16 and 3.50 with *p*-values being 0.003 and 0.001.
- Possible reason: increased experience of the children between testing dates.
- Without control, background causes cannot be ruled out.
  - psychological boost of the treatment.

Avoidance of Bias – Blindness

- Blindness: keeping someone unaware of which treatment has been given.
  - Single-blind
    - Subjects do not know which treatments they have received.
  - Double-blind
    - Both the Doctors and the subject are unaware of the treatment received.
    - Avoids observer bias.
  - Triple-blind
    - Doctor, subject, and the person interpreting the set of results are kept blind.
- Blindness may not be always possible.
  - Radiation treatment vs. surgical treatment.

Avoidance of Bias – Randomization

- Subjects should be allocated to treatment group according to some chance mechanism.
  - Randomized controlled trial (RCT).
  - Necessary to avoid systematic bias.
- Controlled trial of free milk supplementation to improve growth among school children.
  - 10,000 children were allocated to the treated group and similar number to the control group
  - Well-intentioned teachers decided that the poorest children should be given priority for free milk, rather than using strictly randomized allocation.
  - Effect of milk supplementation is confounded with effects of poverty.
- Consent before randomization

Avoidance of Bias – Analysis by intention-to-treat

- Subjects may stop or modify their allocated treatment for some reasons.
- Treatment efficacy is normally analyzed according to treatment allocated rather than treatment actually received, ignoring any information on compliance
  - The principle of analysis by intention-to-treat
  - Protects against bias because someone who stops or even crosses to the other treatment may well have done so because of an adverse effect of the treatment.
  - It should reflect practice in the real world more accurately.
  - It will not measure actual comparative effectiveness.

Parallel Group Studies

- Subjects are allocated into two (or more) treatment groups and everyone within a group receives the same treatment, which is different from the treatment given to other groups.
- The number of subjects to be allocated to each group is fixed in advance.

Parallel Group Study Example

- Large-scale field trial of the Salk polio vaccine.
  - The vaccine of Jonas Salk for poliomyelitis.
- Ethical objections to the use of a placebo control group.
- Two different approaches to allocating children to treatment group were used.
  - National Foundation for Infantile Paralysis (NFIP)
    - Vaccinating all children in the second grade whose parents gave consent.
    - First and third grade children are controls without seeking parent consent.
  - Randomized controlled trial (RCT)
    - Include all children whose parents consented to their entering the trial.
    - These children were then randomly assigned to the vaccinated or control group.

Table 7.3. Polio incidence rates per 100 000 (with sample size, in thousands, in parentheses) in the two Salk vaccine trials.

Group	NFIP	RCT
Vaccinated	25 (225)	28 (200)
Control	54 (725)	71 (200)
Difference	–29	–43

- Both trials give significant results, but RCT is much more significant than NFIP.
  - The evidence of RCT played an important part in the subsequent decision to put the Salk vaccine into widespread use.

Parallel Group Studies – Number Needed to Treat

- Binary outcomes of controlled intervention studies are often quantified by stating the expected number needed to treat (NNT) with the intervention to avoid one bad outcome.
- Assume we have the risks of the outcomes, r_c in the control group and r_g in the intervention (treatment) group.
- When n people are exposed,
  - the expected number of events for control is $E_c = r_c n$.
  - the expected number of events for intervention is $E_c = r_g n$.
- If the intervention is to lead to one less outcome, $1 = r_c n - r_g n$.
- n will then be the NNT,
  - NNT = $1/(r_c - r_g)$.
  - If a drug has NNT of 5, it means you have to treat 5 people with the drug to prevent one bad outcome

Cross-over Studies

- One drawback of parallel group study is that any differences between the two treatment groups will affect the results.
- Cross-over study
  - Each treatment is given at different times, to each subject.
  - The simplest is two-period, two-treatment cross-over.
- Subjects are assigned to one of the two groups, A and B.
  - Subjects in group A receive treatment 1 for a period of time and then receive treatment 2.
  - Subjects in group B receive the treatments in the opposite order.
- Within-subject differences can be summarized to obtain an overall evaluation of efficacy.
  - Within-subject variation < between-subject variation.
- Saving of resources.

Cross-over Studies – Disadvantages

- Justification
  - The advantage of more precision, or fewer subjects, is valid only when within-subject variation is less than between-subject variation.
- Suitability
  - Only good for long-term conditions for which treatment provides only short-term relief.
    - Bronchitis, angina, migraine, jet lag…
- Duration
  - Each subject must spend a long time in the trial, possibly twice as long as in the comparable parallel group study.
- Carry-over effects
  - It is possible that, when given first, one treatment has a residual effect in the second period, called a carry-over effect.
    - Treatment 1 is active and treatment 2 is placebo.
  - Treatment by period interaction
    - A differential effect of treatment in different periods.
- Complexity
  - More complex to analyze than parallel group studies.

Cross-over Studies – Graphical Analysis

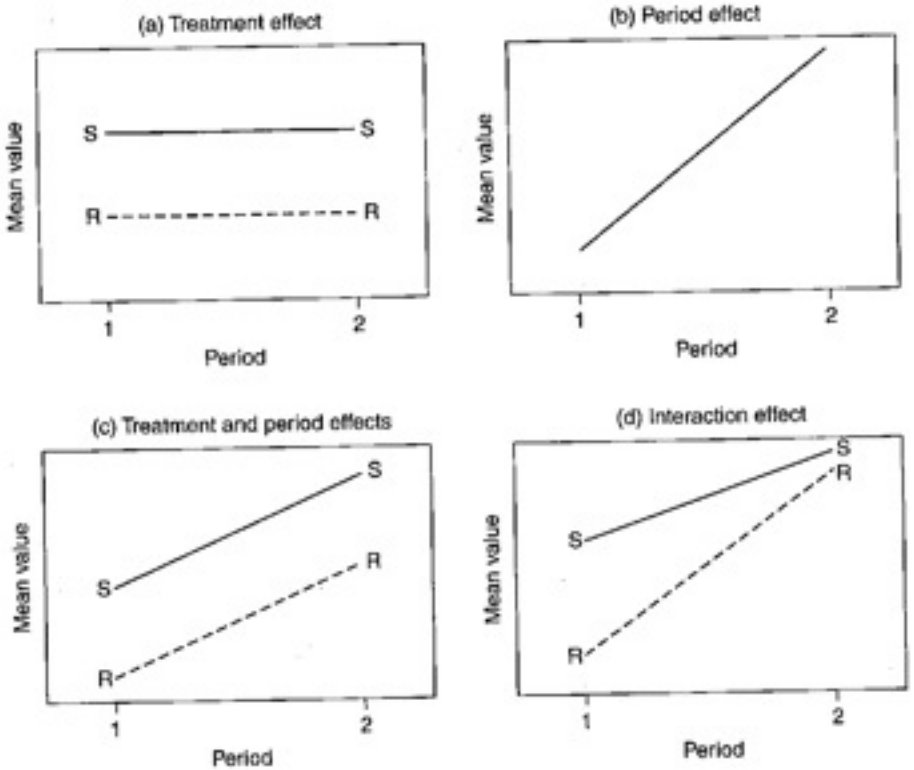

Figure 7.1. Plots of mean response against treatment period with interpretation of result: 'R' denotes that treatment R was used, 'S' denotes that treatment S was used (points are coincident in (b)).

Cross-over Studies – Comparing Means

- Assessing statistical significance of the various possible effects.
- x_{A1}: an observation from group A in period 1.
- x_{A2}: an observation from group A in period 2.
- t_A: the total of the two observations for a subject in group A.
- d_A: the difference between first- and second-period observations for subjects in group A.

$$t_A = x_{A1} + x_{A2}, \quad d_A = x_{A1} - x_{A2},$$

$$t_B = x_{B1} + x_{B2}, \quad d_B = x_{B1} - x_{B2}.$$

Cross-over Studies – Comparing Means

n_A : the number of subjects in group A;

$\overline{t}_A$ and $s(t)_A$: the mean and standard deviation fo the t_A;

$\overline{d}_A$ and $s(d)_A$: the mean and standard deviation of the d_A.

Similar for group B.

- Assuming the data obtained approximate to a normal distribution.
- The pooled variance for the totals

$$s(t)_p^2 = \frac{(n_A - 1)s(t)_A^2 + (n_B - 1)s(t)_B^2}{n_A + n_B - 2}$$

- The pooled variance for the differences

$$s(d)_p^2 = \frac{(n_A - 1)s(d)_A^2 + (n_B - 1)s(d)_B^2}{n_A + n_B - 2}$$

Cross-over Studies – Comparing Means

- Three tests are possible:
- Treatment by period interaction
  - Compare $\dfrac{\bar{t}_A - \bar{t}_B}{\sqrt{s(t)_p^2\left[\dfrac{1}{n_A} + \dfrac{1}{n_B}\right]}}$ with $t_{\text{nA+nB-2}}$.

- Treatment difference
  - Compare $\dfrac{\bar{d}_A - \bar{d}_B}{\sqrt{s(d)_p^2\left[\dfrac{1}{n_A} + \dfrac{1}{n_B}\right]}}$ with $t_{\text{nA+nB-2}}$.

- Period Difference.
  - compare the average of the d_A against the average of the negative values of d_B.

- 2×2 cross-over trial to compare lysine acetyl salicylate (Aspergesic) with ibuprofen in the treatment of rheumatoid arthritis.
- Thirty-six patients were randomly assigned to the two treatment order groups at entry (half to each). After two weeks on their first treatment, patients crossed over to the opposite treatment. A further 2 weeks later, the trial ended.
- At baseline, a general medical examination found the two treatment groups to be similar.
- At the two subsequent clinic visits (at the half-way point and the end), patient and investigator assessments of progress were recorded and several measurements (grip strength, blood pressure, haematology, etc.) were taken.
- Between the clinic visits, diary cards were completed each day by the patients. The data recorded included a pain assessment score on 1 to 5 scale (1 = no pain, 5 = unbearable pain). Data is shown in the following table.

Table 7.5. Average pain scores from the rheumatoid arthritis study, showing sums and differences across treatment periods.

Ibuprofen–Aspergesic group (n = 15)				Aspergesic–ibuprofen group (n = 14)			
Period 1	Period 2	Sum	Diff.	Period 1	Period 2	Sum	Diff.
3.143	3.286	6.429	–0.143	1.286	2.214	3.500	–0.928
3.000	2.429	5.429	0.571	4.100	4.444	8.544	–0.344
3.071	2.357	5.428	0.714	3.357	3.267	6.624	0.090
3.286	2.929	6.215	0.357	3.214	2.929	6.143	0.285
2.846	2.200	5.046	0.646	3.286	3.714	7.000	–0.428
2.571	2.071	4.642	0.500	3.800	3.231	7.031	0.569
3.214	3.143	6.357	0.071	3.143	2.214	5.357	0.929
3.929	3.571	7.500	0.358	3.467	3.615	7.082	–0.148
3.909	3.000	6.909	0.909	2.714	2.154	4.868	0.560
2.615	2.692	5.307	–0.077	1.786	1.929	3.715	–0.143
1.786	2.214	4.000	–0.428	2.714	2.857	5.571	–0.143
1.429	1.286	2.715	0.143	2.930	3.710	6.640	–0.780
3.000	2.929	5.929	0.071	2.143	2.071	4.214	0.072
3.250	4.000	7.250	–0.750	2.860	2.430	5.290	0.430
2.500	1.214	3.714	1.286				
	Total	82.87	4.228		Total	81.58	0.021
	Mean	5.52	0.282		Mean	5.83	0.0015
	Std.dev.	1.35	0.524		Std.dev.	1.45	0.527

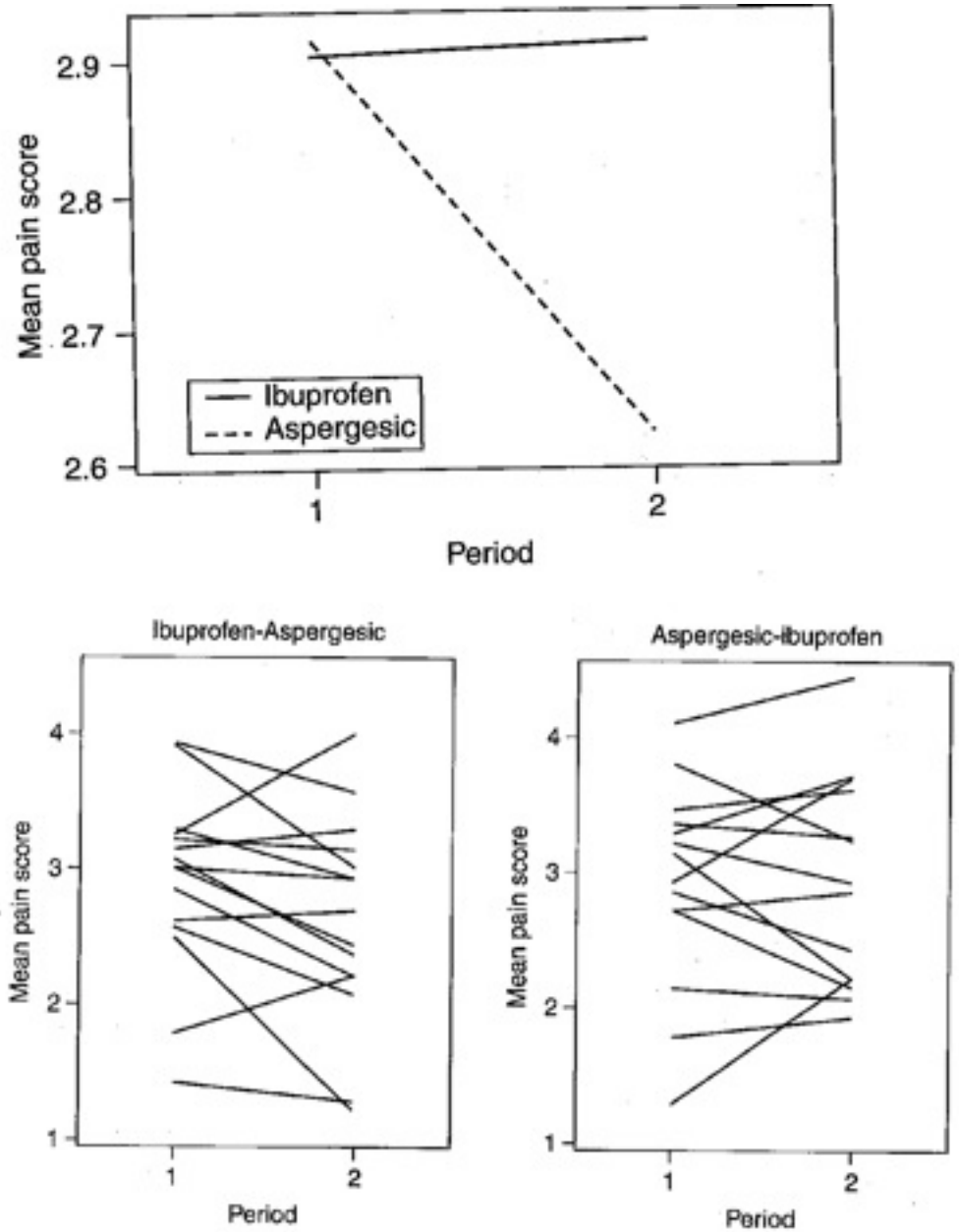

Figure 7.3. Mean pain score (over a 2-week period) against treatment period classified by treatment group; arthritis study.

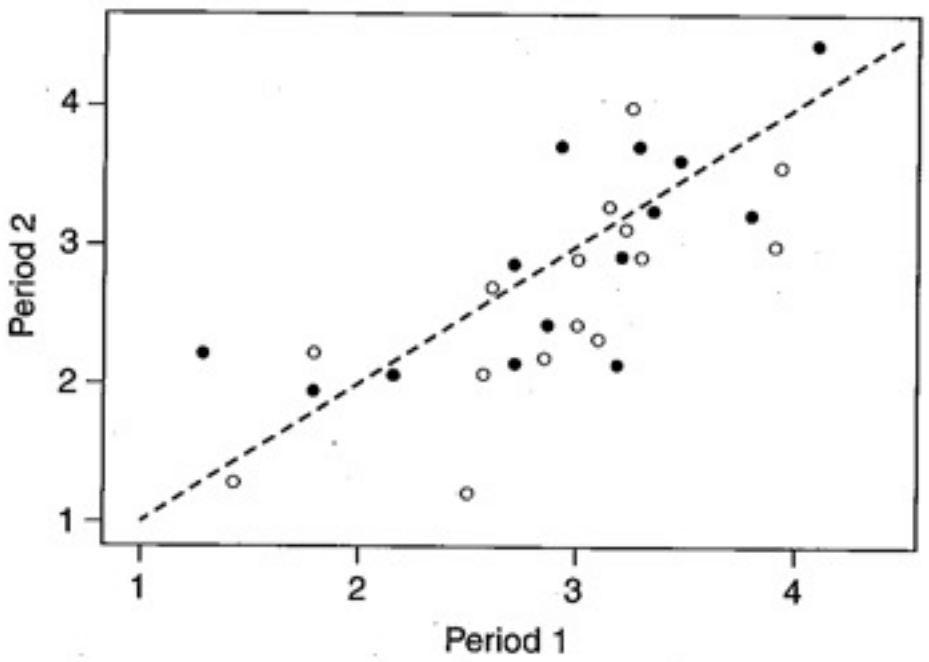

Figure 7.4. Mean pain score (over a 2-week period) in the second period against the same quantity (for the same subject) in the first period of treatment; arthritis study. Open circles represent the ibuprofen–Aspergesic group; closed circles represent the Aspergesic–ibuprofen group.

- There could be a treatment by period interaction. A test of it involves computing

$$s(t)_p^2 = \frac{14 \times 1.35^2 + 13 \times 1.45^2}{15 + 14 - 2} = 1.96$$

Substituting it into $\dfrac{\bar{d}_A - \bar{d}_B}{\sqrt{s(d)_p^2\left[\dfrac{1}{n_A} + \dfrac{1}{n_B}\right]}}$

gives $\dfrac{5.52 - 5.83}{\sqrt{1.96\left(\dfrac{1}{15} + \dfrac{1}{14}\right)}} = -0.60$

which is not significant.

- Test for treatment effect

$$s(d)_p^2 = \frac{14 \times 0.524^2 + 13 \times 0.527^2}{15 + 14 - 2} = 0.276$$

substituting it into the formula

gives $$\frac{0.282 - 0.0015}{\sqrt{0.276\left(\frac{1}{15} + \frac{1}{14}\right)}} = 1.44$$

which is not significant.

Cross-over Studies – Analyzing Preferences

- At the end of a cross-over trial, subjects are sometimes asked to state which treatment period they preferred.
  - We wish to analyze such data to discover which treatment is preferred.
- Prescott's test
  - Test for linear trend in a contingency table of treatment group against preference stated.

Table 7.6. Display of preference data.

Treatment group	Prefer 1st period treatment	No preference	Prefer 2nd period treatment	Total
A	n_{A1}	n_{A2}	n_{A3}	n_A
B	n_{B1}	n_{B2}	n_{B3}	n_B
Total	n_1	n_2	n_3	n

$$\frac{n\left(n\left(n_{A3}-n_{A1}\right)-n_A\left(n_3-n_1\right)-\frac{1}{2}n\right)^2}{n_A n_B\left(n\left(n_3+n_1\right)-\left(n_3-n_1\right)^2\right)}$$

Compare with chi-square with 1 d.f.