Contents

- **Parallel Group Designs**
  - Each patient receives 1 treatment
  - Comparisons are '**between**' patients
    - Average difference between groups needs to be much larger than between the patients

- 2 groups
  - t-test
  - Mann-Whitney
- >2 groups
  - 1-way ANOVA
  - Kruskal-Wallis

- **Aside on two-sample ttests:**
  - Two versions: pooled & separate variance
  - Separate: equal variances **not** assumed
    - Default in some packages (e.g. **R** & Minitab)
  - Pooled: equal variances assumed
    - Default in some packages (e.g. S-PLUS)
    - **SPSS** gives both
  - Always best to use separate variances
    - (equal variances **not** assumed)
  - If sample sizes equal then t-statistic same value
    - but p-value slightly different
    - unequal variance p-value bigger (i.e. less significant)

- Reason:–
  - model is $X \sim N(\mu_X,\sigma^2_X)$ & $Y \sim N(\mu_Y,\sigma^2_Y)$
    - estimate σ^2_X and σ^2_Y by s^2_X and s^2_Y
      - i.e. estimated variance separately
    - leads to a 'separate variance 2-sample t-test'
  - if we assumed σ^2_X and σ^2_Y were equal
    - would estimate variance differently & get a different t-test (on n_x+n_Y-2) d.f.
      - 'equal variance 2-sample t-test' (or 'pooled variance')

- **UNFORTUNATLEY**
  - 'equal variance' or pooled t-test is the default option in S-PLUS
    - even worse:–
      - S-plus calls it a 'Standard Two-Sample t-Test'
  - need to uncheck 'assume equal variance'
  - in many cases little numerical difference between two versions
    - if there is a big difference then the 'equal variance' value is **wrong**
    - so Good Statistical Practice (GSP) is **ALWAYS** to use separate variances

- **R** example:-

```
> hourssleep
PERIOD1 PERIOD2 GROUP  sum diff
      9       0     1  4.5    9
     11      14     2 12.5   -3
      7       3     2  5.0    4
     12       8     2 10.0    4
      8       8     1  8.0    0
     11       1     1  6.0   10
      4       4     1  4.0    0
      3       4     2  3.5   -1
     13       2     1  7.5   11
      7       3     2  5.0    4
      1       2     1  1.5   -1
     13       1     1  7.0   12
      6       3     1  4.5    3
      5       6     2  5.5   -1
      6       8     2  7.0   -2
      3       7     2  5.0   -4
> attach(hourssleep)
> t.test(PERIOD1,PERIOD2)
```

Two separate columns (unstacked)

- **R** example:-

```
> attach(hourssleep)
> t.test(PERIOD1,PERIOD2)
        Welch Two Sample t-test

data:  PERIOD1 and PERIOD2
t = 2.1422, df = 29.965, p-value = 0.04042
alternative hypothesis: true difference in
means is not equal to 0
95 percent confidence interval:
 0.1310748 5.4939252
sample estimates:
mean of x mean of y
   7.4375    4.6250
```


- **R** example:-

```
> hourssleep
PERIOD1 PERIOD2 GROUP  sum diff
      9       0     1  4.5    9
     11      14     2 12.5   -3
      7       3     2  5.0    4
     12       8     2 10.0    4
      8       8     1  8.0    0
     11       1     1  6.0   10
      4       4     1  4.0    0
      3       4     2  3.5   -1
     13       2     1  7.5   11
      7       3     2  5.0    4
      1       2     1  1.5   -1
     13       1     1  7.0   12
      6       3     1  4.5    3
      5       6     2  5.5   -1
      6       8     2  7.0   -2
      3       7     2  5.0   -4
> attach(hourssleep)
> t.test(PERIOD1~GROUP)
```

One column + group indicator (stacked)

- **R** example:-

```
> hourssleep
PERIOD1 PERIOD2 GROUP  sum diff
      9       0     1  4.5    9
     11      14     2 12.5   -3
      7       3     2  5.0    4
> attach(hourssleep)
> t.test(PERIOD1~GROUP)
 Welch Two Sample t-test

data:  PERIOD1 by GROUP
t = 0.7163, df = 13.183, p-value = 0.4863
alternative hypothesis: true difference in means is
not equal to 0
95 percent confidence interval:
 -2.766425  5.516425
sample estimates:
mean in group 1 mean in group 2
          8.125           6.750
```


SPSS Example:

Summary statistics for variable ‘diff’

Group Statistics

	group	N	Mean	Std. Deviation	Std. Error Mean
diff	1	8	5.50	5.529	1.955
	2	8	.13	3.357	1.187

Independent Samples Test

		t-test for Equality of Means						
		t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
diff	Equal variance assumed	2.350	14					
	Equal variance not assumed	2.350	11.543	.037	5.375	2.287	.370	10.380

Concentrate on this

ignore this bit

t-value and p-value

- Separate variance:

$$t_r = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

- Used as default in **R** & Minitab
  - Take [e.g.] r=min(n_1,n_2) (or use Welch formula)
  - **R** uses Welch formula

- Pooled variance

$$t_r = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{n_1+n_2-2}\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}}$$

- Default in S-Plus & available in **R,** Minitab:- $r=n_1+n_2-2$

- **In series designs**
  - Comparisons here are '**within**' patients
    - Differences between patients do not affect differences between treatment

- 2 groups
  - paired t-test (≡ t-test on differences)
  - Wilcoxon signed rank test
- >2 groups
  - 2-way ANOVA
  - Friedman's test

- Advantages
  - Patients can state preferences
  - Maybe apply treatments simultaneously
  - Comparisons **within** patients
    - reduces variability so more precise comparison

- Disadvantages
  - Trend in results
  - Treatments may persist
  - Not suitable if treatment **cures** subject! i.e. only suitable for chronic conditions
  - Withdrawals complicate analysis

- **Crossover Designs**
  - Similar to *in series design* but different groups have treatments in different orders
    - (see later)
  - Similar advantages and disadvantages

Factorial Designs

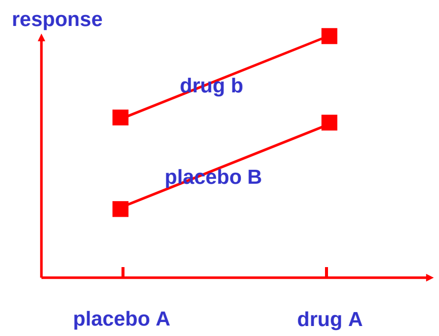
- Patients receive combinations of treatments

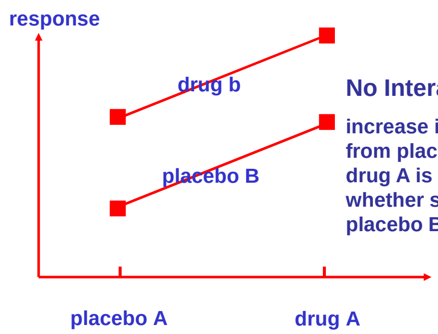
Placebo (10)	A (10)	**Not B (20)**
B (10)	A+B (10)	**B (20)**
Not A (20)	**A (20)**	**40**

Interaction

- No interaction
  - Drug A increases response by same amount irrespective of whether patient is also taking B or not

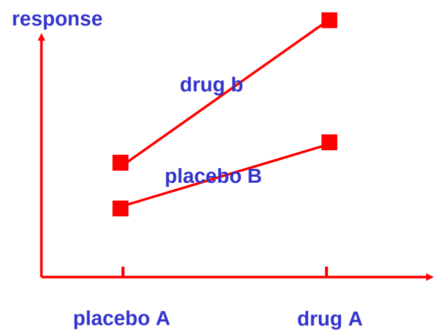
- Quantitative
  - effect of A more marked when patient is also taking B
- Qualitative
  - A increases response when alone, but decreases response when with B

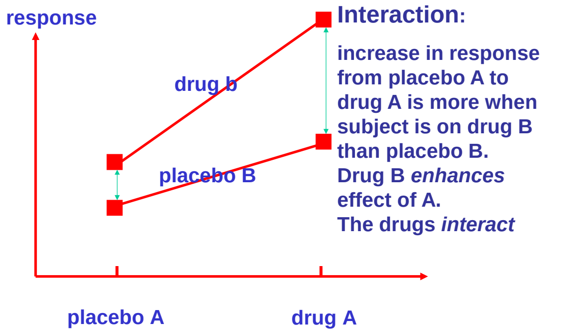




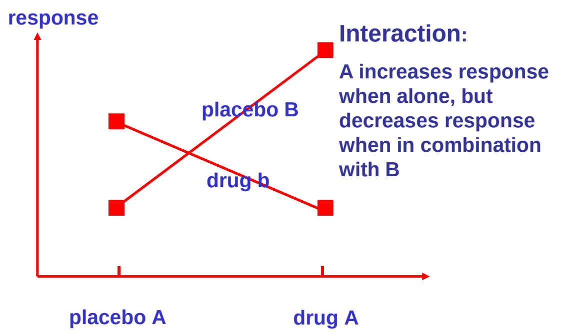
No Interaction:

increase in response from placebo A to drug A is same whether subject is on placebo B or drug B

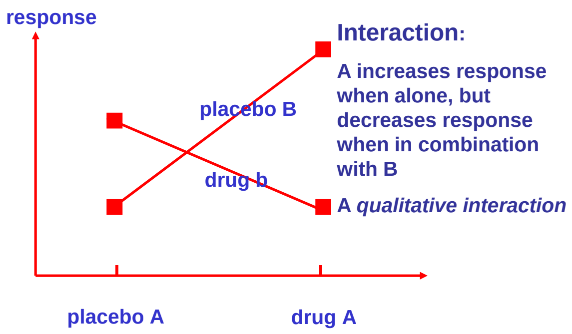




Quantitative interaction



Qualitative interaction



- **Sequential Designs**
  - Assess results after each few subjects and decide either
    - One treatment superior so stop trial

      or
    - Test more subjects

- **Advantages**
  - Detect large differences quickly
  - Avoids ethical problem of fixed size designs
    - no patient should receive treatment known to be inferior

- **Disadvantages**
  - complicated statistical design and analysis
  - Responses needed quickly (before next group of patients arrive)
  - Dropouts cause difficulties
  - Constant surveillance necessary
  - Requires grouping of patients

- **Summary & Conclusions**
  - Parallel group designs
    - different groups receive different treatments
    - comparisons ***between*** patients
  - In series designs
    - patients receive all treatments in sequence
    - comparisons ***within*** patients
  - Crossover designs
    - patients receive all treatments in different orders
    - comparisons ***within*** patients

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- Factorial designs
  - some patients receive combinations of treatments simultaneously
  - difficulties if ***interactions***
    - quantitative or qualitative
  - comparisons are *between* patients but more available than in series designs

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- Sequential designs
  - suitable for rapidly evaluated outcomes
  - minimizes numbers of subjects when clear differences between treatments

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- **Efficient design of clinical trials is a crucial ethical element contributed by statistical theory and practice**

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