

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

©NRJF, University of Sheffield, 2011/12 Semester 1 Medical Statistics - Clinical Trials 253

- Data of form $y_i = 0$ or 1 for Success/Failure
 - Observational Studies
 - Prospective – Relative Risks
 - Retrospective studies – Odds Ratios
 - Methods
 - ♦ McNemars's Test
 - Matched Pairs
 - ♦ Logistic Modelling
 - to incorporate covariates
- ©NRJF, University of Sheffield, 2011/12 Semester 1 Medical Statistics - Clinical Trials 254

- **Observational Studies**
 - ♦ Epidemiological studies where characteristic is observed and relationship with other factors is inferred as distinct from a controlled study where cases and controls are determined by experimenter (e.g. by randomization)
 - e.g. heart disease and smoking
 - ♦ Prospective and retrospective
- ©NRJF, University of Sheffield, 2011/12 Semester 1 Medical Statistics - Clinical Trials 255

- **Prospective Studies**
 - ♦ Subjects followed forward through time
 - ♦ e.g. known to have been exposed
 - e.g. smoker
 - ♦ outcome is observed
 - risk of outcome calculated for exposed group
 - compared with risk of outcome for control group known not to be exposed
- ©NRJF, University of Sheffield, 2011/12 Semester 1 Medical Statistics - Clinical Trials 256

	Outcome		Total	Risk
	Positive	Negative		
Exposed	a	b	a+b	a/(a+b)
Non-exposed	c	d	c+d	c/(c+d)

Relative Risk =RR= $[a/(a+b)]/[c/(c+d)]=a(c+d)/c(a+b)$

S.E. $\{\log_e(RR)\} = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$

©NRJF, University of Sheffield, 2011/12 Semester 1 Medical Statistics - Clinical Trials 257

	Apgar < 7		Total	Risk
	Yes	No		
Symmetric	2	14	16	12.5%
Asymmetric	33	58	91	36.2%

RR=0.345, $\log_e(RR) = -1.065 \pm 0.676$
so a 95%CI for the RR is (0.11, 1.05)

This includes 1.0, so evidence of effect of asymmetric growth pattern on Apgar score is not significant at 5% level

©NRJF, University of Sheffield, 2011/12 Semester 1 Medical Statistics - Clinical Trials 258



- Retrospective studies
 - ◆ Condition of interest
 - ◆ Cases identified & followed back through time to see if they were exposed to risk factor
 - Odds of being exposed calculated for cases
 - Controls not exhibiting condition of interest found
 - matched closely in other respects to cases
 - Compared with odds of exposure for controls
 - not sensible to calculate 'risk' of being a case for exposed group since can just get more or fewer controls

	Case	Control
Exposed	a	b
Non-exposed	c	d
odds	a/c	b/d

Odds ratio = $[a/c] / [b/d] = ad/bc$

S.E. $\{\log_e(OR)\} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

	Enamel Erosion		
swimming	Yes	No	Total
≥ 6 hours	32	118	150
< 6 hours	17	127	144
odds	1.88	0.93	

OR = 2.03, s.e. $\{\log_e(OR)\} = 0.323$ so 95% CI for the Odds Ratio is (1.07, 3.84) and so good evidence that the odds of enamel erosion are increased for those swimming more than six hours per week

- Matched pairs
 - χ^2 -test \leftrightarrow 2-sample t-test
 - McNemar's Test \leftrightarrow paired t-test
- Rheumatoid arthritis study, two treatments A & B.
- Response caused? 1=yes, 0=no

		response		
		yes	no	
treatment	A	11	37	48
	B	20	28	48

■ χ^2 -test?????

■ INVALID

- ◆ only 48 subjects in the table not 96
 - All subjects received both treatments



- Instead consider like/unlike responses

		B		
		yes	no	
A	yes	8	3	11
	no	12	25	37
		20	28	48

- Subjects who respond in a like way to the treatments give no information on **differences** between treatments.

- ◆ 8 responded to both treatments
- ◆ 25 responded to neither treatment
- ◆ These give no evidence of differences

- ◆ 3 responded to A but not to B
- ◆ 12 responded to B but not to A

		B		
		yes	no	
A	yes	8	3	11
	no	12	25	37
		20	28	48

- Suggests more respond to B than to A
 - ◆ i.e. may be evidence of difference between the treatments

- McNemar's Test:

- ◆ If no difference then number responding to A but not B ~ Binomial(M,0.5) where M=number responding differently
 - Observed 3 out of 15

- McNemar's Test

- ◆ Can calculate (e.g. Neave 1.3)

$$P[3 \text{ or fewer} | B(15, 0.5)] = 0.035$$

- ◆ i.e. H_0 : no difference between treatments is rejected with $p < 0.05$ (actually $p = 0.035$)

- McNemar's Test

- ◆ For large samples then use

$$\frac{(n_{10} - n_{01})^2}{n_{10} + n_{01}} \sim \chi^2_1$$

- (Normal approx to binomial) $^2 \sim \chi^2_1$



- **Logistic Modelling**
 - ◆ Data are $y_i = 1$ or 0 (S or F)
 - ◆ Can't express y_i as a linear model
 - ◆ Idea is to model **probability of success** as a function of explanatory variables
 - ◆ However, must have probabilities in range 0 to 1

271

- Use a logistic function:
 - ◆ e.g. patients on treatment or placebo
 - Code as $x_i = 1$ or 0
 - ◆ Measure Success or Failure
 - Code as $y_i = 1$ or 0
 - ◆ Model:

$$P[Y_i = 1] = \frac{e^{\beta_0 + \beta_1 X_i}}{1 + e^{\beta_0 + \beta_1 X_i}} = 1 - P[Y_i = 0]$$

272

- Can estimate β_0 and β_1 from data:
 - **R**
 - function `glm()` with `family=binomial, weights=freqs`
 - followed by `anova()`
 - **SPSS:**
 - Analyze>Regression>Binary Logistic Regression
 - **Minitab:**
 - Stat>Regression>Binary Logistic Regression
 - **S-PLUS:**
 - Statistics>Regression>Logistic

273

- Interpretation
 - ◆ on placebo $P[Y_i = 1] = \frac{e^{\beta_0}}{1 + e^{\beta_0}}$
 - ◆ on treatment $P[Y_i = 1] = \frac{e^{\beta_0 + \beta_1}}{1 + e^{\beta_0 + \beta_1}}$
 - β_1 is 'effect' of treatment

274

- More specifically:

$$\ln \left\{ \frac{P[Y_i = 1]}{P[Y_i = 0]} \right\} = \beta_0 + \beta_1 x_i$$
 - ◆ $x_i = 0$ for placebo, 1 for treatment
 - ◆ i.e. **log-odds of success**
= **linear fⁿ. of covariate**

275

$$\ln \left\{ \frac{P[Y_i = 1]}{P[Y_i = 0]} \right\} = \beta_0 + \beta_1 x_i$$

- If $\beta_1 > 0$ then $P[Y_i=1|x_i=1] > P[Y_i=1|x_i=0]$
 - ◆ i.e. if $\beta_1 > 0$ then treatment improves chance of success
 - ◆ i.e. if $\beta_1 < 0$ then treatment lessens chance of success

276



- Can extend to include lots of covariates
 - $\beta_j > 0 \Rightarrow P(\text{success}) \nearrow$ as $x_j \nearrow$
& $P(\text{success}) \searrow$ as $x_j \searrow$
 - $\beta_j < 0 \Rightarrow P(\text{success}) \searrow$ as $x_j \nearrow$
& $P(\text{success}) \nearrow$ as $x_j \searrow$.

277

- Can test whether covariates affect probability of success:
- Package calculations provide standard errors of estimates

278

- Partial z-test:

$$H_0: \beta_j = 0$$
- test compares

$$\frac{\hat{\beta}_j}{\sqrt{\text{var}(\hat{\beta}_j)}}$$

with $N(0,1)$ points

279

- Example: $Y_i=1$ if heart disease:

factor	Numerical variable	logistic coef	z-value
	x_j	β_j	
1:treatment	0=placebo, 1=treatment	-0.32	-2.9
2:age	ln(age)	3.0	6.3
3:smoking	0=non-smok, 1=smoker	0.83	6.8
4:father's hist	0=alive, 1=dead	0.64	3.6
5:systolic BP	Systolic BP in mm Hg	0.011	3.7
6:cholesterol	Cholesterol in mg/dl	0.0095	5.6
constant term β_0		-19.60	

280

- $\Phi^{-1}(.005) = z_{.005} = -2.58$ $z_{.025} = -1.96$
 - (1% level)
 - (5% level)
- ◆ Treatment: significant, $p < 0.01$; $\beta_1 < 0$;
- Probability of IHD is lower on treatment than on placebo

281

- Prognostic factors:
 - ◆ all five significant ($p < 0.01$);
 - ◆ all have positive m.l.e.'s,
 - ◆ \therefore probability of IHD increases with
 - age
 - smoking
 - 'poorer heredity'
 - high blood pressure
 - high cholesterol.

282



■ **Relative Risks**

$$\frac{P[Y = 1 | x_1 = 1]}{P[Y = 0 | x_1 = 1]} \bigg/ \frac{P[Y = 1 | x_1 = 0]}{P[Y = 0 | x_1 = 0]}$$

is **relative risk of 'success' on treatment**

$= \exp\{\beta_1\}$

- strictly this is an **odds ratio** but conventionally is interpreted as an **approximate relative risk**

Medical Statistics: Clinical Trials 283

- ◆ estimated relative risk is $e^{-0.32} = 0.73 < 1$
- ◆ i.e. odds of getting IHD are 27% lower on treatment
 - (after allowing for the other prognostic factors)
- ◆ Can calculate approx confidence intervals for β_1 as estimate $\pm 2 \times \text{s.e.}$

Medical Statistics: Clinical Trials 284

- ◆ $-0.32 \pm 2 \times 0.11 = (-0.10, -0.54)$
- ◆ $\exp\{\beta_1\}$ has 95% C. I. $(e^{-0.54}, e^{-0.1}) = (0.58, 0.90)$
- 95% confidence limits for the reduction due to treatment in odds of getting IHD are 10% and 42%.

Medical Statistics: Clinical Trials 285

■ **Example**

	treatment	
	BP	CP
response	77	90
no response	61	45

- ◆ $Y_{11} = 77, E(Y_{11}) = 138 \times 167 / 273 = 84.42$
 $\text{var}(Y_{11}) = 138 \times 133 \times 167 \times 106 / (273^2 \times 272) = 16.268$
- So $T_{MH} = 3.38 < 3.84 = \chi^2_{1,0.95}$ and $p = 0.066$

Medical Statistics: Clinical Trials 286

Implementation in R

■ Same example:

- ◆ frequencies indicated by *Weights*

```

> bpcp
  frequency response treatment
1         77         1         1
2         61         0         1
3         90         1         0
4         45         0         0
    
```

```

> attach(bpcp)
> bpcp.glm<-glm(response~treatment,
  family=binomial, weights=frequency)
    
```

Medical Statistics: Clinical Trials 287

Implementation in R

```

> bpcp.glm<-glm(response~treatment,
  family=binomial, weights=frequency)
bpcp.glm

Call: glm(formula = response ~ treatment, family = binomial, weights = frequency)

Coefficients:
(Intercept)  treatment
 0.6931      -0.4602

Degrees of Freedom: 3 Total (i.e. Null); 2 Residual
Null Deviance:      364.7
Residual Deviance: 361.3      AIC: 365.3
    
```

Medical Statistics: Clinical Trials 288



Implementation in R

```

> bpcp.glm<-glm(response~treatment,
  family=binomial, weights=frequency)

> summary(bpcp.glm)
Coefficients:
      Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.994e-16  1.000e-01 -4.99e-15  1.00000
treatment    4.055e-01  1.429e-01  2.838  0.00454
***
---
    
```

289

Implementation in R

```

> anova(bpcp.glm)
Analysis of Deviance Table
Model: binomial, link: logit
Response: response

Terms added sequentially (first to last)

      Df Deviance Resid. Df Resid. Dev
NULL                                3    364.71
treatment  1      3.40             2    361.31
    
```

290

Example of combining trials in R

- Data from § 8.2 on Simpson's Paradox

centre 1			centre 2		
trt	S	F	trt	S	F
	30	70		210	90
plac	120	180	plac	80	20
	150	250		290	110

```

> frequency<-c(30,120,70,180,210,80,90,20)
> response<-c(rep(c(1,1,0,0),2))
> treatment<-c(rep(c(1,0),4))
> centre<-c(rep(0,4),rep(1,4))
> simpson<-cbind(frequency,response,treatment,centre)
> simpson
    
```

291

Example of combining trials in R

- Data from § 8.2 on Simpson's Paradox

centre 1			centre 2		
trt	S	F	trt	S	F
	30	70		210	90
plac	120	180	plac	80	20
	150	250		290	110

```

> simpson
  frequency response treatment centre
[1,]      30         1         1     0
[2,]     120         1         0     0
[3,]      70         0         1     0
[4,]     180         0         0     0
[5,]     210         1         1     1
[6,]      80         1         0     1
[7,]      90         0         1     1
[8,]      20         0         0     1
    
```

292

Example of combining trials in R

```

> simpson.glm<-glm(response~treatment+centre,
+ family=binomial, weights=frequency)
> summary(simpson.glm)

Coefficients:
      Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.3958      0.1117  -3.543  0.000396 ***
treatment    -0.4849      0.1853  -2.616  0.008891 **
centre        1.7391      0.1859   9.357  < 2e-16 ***
    
```

coefficient < 0 so treatment reduces chance of success

p-value small so significant evidence of effect

293

S-Plus calculation

- Same example:
 - Frequencies indicated by Weights

	1	2	3	4	5	6
frequency	77.00	61.00	90.00	45.00		
resp	1.00	0.00	1.00	0.00		
treat	1.00	1.00	0.00	0.00		

294



S-Plus calculation

295

S-Plus calculation

296

S-Plus calculation

297

S-Plus calculation

298

S-Plus calculation

Coefficients:

	Value	Std. Error	t value
(Intercept)	0.693033	0.181784	3.81239
treat	-0.460102	0.249845	-1.84155

(Dispersion Parameter for Binomial family taken to be 1)

Null Deviance: 364.713 on 3 degrees of freedom

Residual Deviance: 361.308 on 2 degrees of freedom

Number of Fisher Scoring Iterations: 2

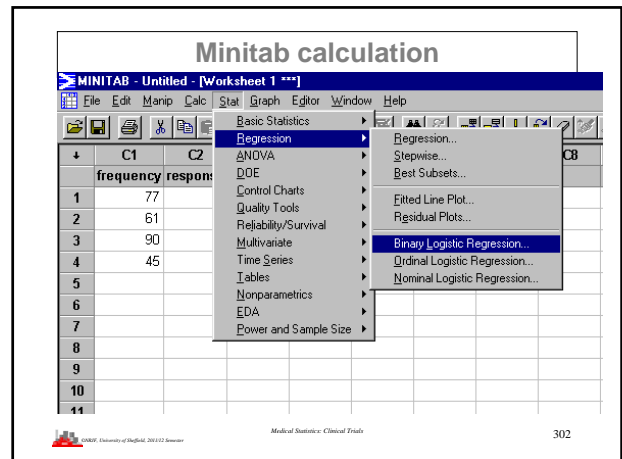
299

Minitab calculation

300



	treatment	
	BP	CP
response	77	90
no response	61	45



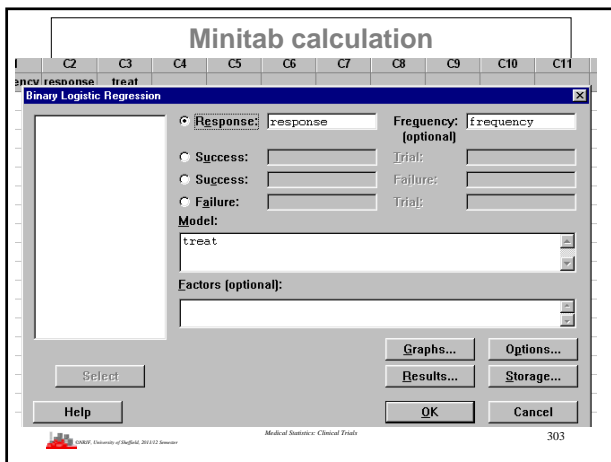
Minitab calculation

MINITAB - Untitled - [Worksheet 1 ***]

File Edit Manip Calc Stat Graph Editor Window Help

Basic Statistics
 Regression
 ANOVA
 DOE
 Control Charts
 Quality Tools
 Reliability/Survival
 Multivariate
 Time Series
 Tables
 Nonparametrics
 EDA
 Power and Sample Size

Regression...
 Stepwise...
 Best Subsets...
 Fitted Line Plot...
 Residual Plots...
Binary Logistic Regression...
 Ordinal Logistic Regression...
 Nominal Logistic Regression...



Minitab calculation

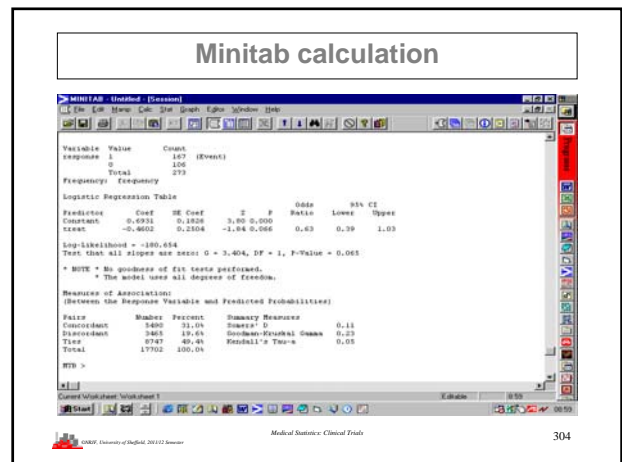
Binary Logistic Regression

Response: response
 Frequency (optional): frequency

Model: treat

Factors (optional):

Graphs... Options...
 Results... Storage...
 Select OK Cancel



Minitab calculation

MINITAB - Untitled - [Session]

Variable Value Count
 response 1 167 (Event)
 0 106
 Total 273

Frequency: frequency

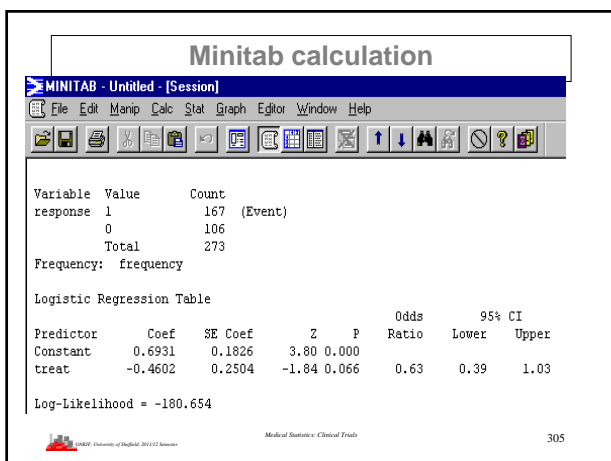
Logistic Regression Table

Predictor	Coef	SE Coef	Z	P	Odds Ratio	Lower	Upper
Constant	0.6931	0.1826	3.80	0.000			
treat	-0.4602	0.2504	-1.84	0.066	0.63	0.39	1.03

Log-likelihood = -180.654
 Test that all slopes are zero: G = 3.404, DF = 1, P-Value = 0.066

MEASURE OF ASSOCIATION:
 (Between the Response Variable and Predicted Probabilities)

Field	Measure	Percent	Summary Measure
Contingency	0.480	31.0%	Somers' D
Dispersion	0.465	29.6%	Goodman-Kruskal Gamma
Tier	0.747	49.4%	Kendall's Tau-B
Total	1.702	100.0%	



Minitab calculation

MINITAB - Untitled - [Session]

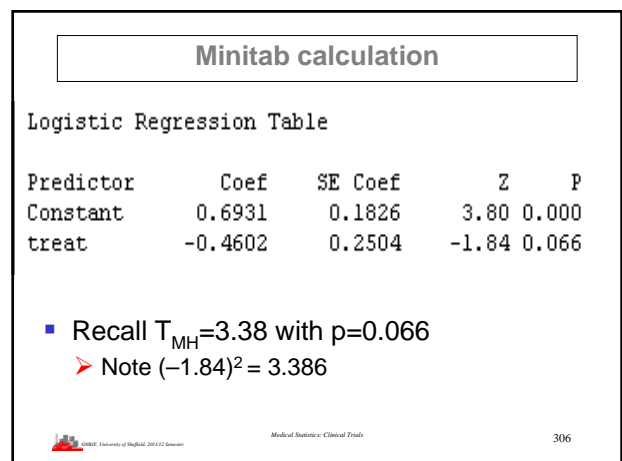
Variable Value Count
 response 1 167 (Event)
 0 106
 Total 273

Frequency: frequency

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P	Odds Ratio	Lower	Upper
Constant	0.6931	0.1826	3.80	0.000			
treat	-0.4602	0.2504	-1.84	0.066	0.63	0.39	1.03

Log-likelihood = -180.654



Minitab calculation

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	0.6931	0.1826	3.80	0.000
treat	-0.4602	0.2504	-1.84	0.066

- Recall $T_{MH}=3.38$ with $p=0.066$
- Note $(-1.84)^2 = 3.386$



Minitab calculation

Variable Value Count
 response 1 187 (Event)
 response 0 106
 Total 293

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P	Odds Ratio	Lower	Upper
Constant	-0.4931	0.1808	-3.80	0.000			
treatm	-0.4602	0.2304	-1.94	0.056	0.63	0.39	1.03

Log-likelihood = -180.654
 Test that all slopes are zero: G = 3.404, DF = 1, P-Value = 0.063

MEASURE OF ASSOCIATION (Between the Response Variable and Predicted Probabilities)

Value	Measure	Percent	Success Measure
Chi-Square	3.40	31.0%	0.11
F	3.40	31.0%	0.23
T	0.747	49.4%	0.05
Total	17.02	100.0%	

307

Minitab calculation

(S-plus left as exercise)

- Example of combining trials
 - Data from § 8.2 on Simpson's Paradox

	C1	C2	C3	C4	C5
	frequency	response	treatment	centre	
1	30	1	1	0	
2	120	1	0	0	
3	70	0	1	0	
4	180	0	0	0	
5	210	1	1	1	
6	80	1	0	1	
7	90	0	1	1	
8	20	0	0	1	
9					

308

Minitab calculation

(S-plus left as exercise)

Binary Logistic Regression

Response: response Frequency: frequency

Model: treatment centre

309

Minitab calculation

(S-plus left as exercise)

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P	Odds Ratio	Lower	Upper
Constant	-0.3958	0.1117	-3.54	0.000			
treatmen	-0.4649	0.1854	-2.62	0.009	0.62	0.43	0.89
centre	1.7391	0.1859	9.36	0.000	5.69	3.95	8.19

Log-Likelihood = -496.323

- This shows that there is strong evidence that the odds of success on treatment are markedly lower than on placebo, even allowing for the difference in success rates between the centres.
 - Note also strong evidence of a higher success rate in centre 2

310

Summary and Conclusions

- Observational Studies
 - Prospective and retrospective studies
- Prospective:–
 - Calculate risk of outcome
 - Look at **relative risks**
- Retrospective:–
 - Calculate odds of exposure
 - Look at **odds ratios**

311

Summary and Conclusions

- McNemar's test
 - Matched pairs binary responses: uses only **unlike pairs**
- Logistic Regression
 - models log-odds as a linear in the covariates
 - positive coefficients indicate factor increases the risk of 'success'

312



- Logistic models allow estimation of **relative risks** (including C.I.s)

- Logistic models can be implemented in most standard statistical packages
 - SPSS
 - S-PLUS / R
 - Minitab

