SESSION 5

PROPORTIONAL ODDS MODELLING PRACTICAL

THE POST-OPERATIVE PAIN STUDY (POPS)

A Simulated Clinical Trial

1. Post-Operative Pain

Patients undergoing major surgery often experience pain for up to a week afterwards, and occasionally for longer. Some patients report only slight pain, but others refer to it as severe. The incidence and intensity of pain is related to the type of surgery and to the age and sex of the patient. It is standard practice to prescribe pain-killing drugs to control this post-operative pain.

2. Painendil

The successful new company Edinburgh Pharmaceutical have developed a new pain-killing drug named "Painendil". Its makers believe that it will be more effective than its competitors in the control of post-operative pain. It is administered intra-venously at 8-hour intervals.

3. The Clinical Trial

Edinburgh Pharmaceuticals have conducted a two-centre clinical trial of Painendil. Patients presenting for abdominal, cardiovascular or brain surgery were allocated to Painendil or to a control group. The centres were London and Aberdeen.

The principal endpoint of interest was the patient's assessment of pain 24 hours after regaining consciousness after the operation. The patient was asked to rate the pain as NONE, SLIGHT, MODERATE or SEVERE. The question was asked by a nurse with no knowledge of the identity of the pain-killing treatment.

About 25 eligible patients were recruited each month in London and 5 in Aberdeen. Patients were recruited for 8 months.

The data are recorded in the file POPAIN.

Description of POPAIN

PATNO	=	Patient Identification Number
AGE	=	Age of Patient
AGEG	=	Age of Patient (Grouped) 1: (20-29) 2: (30-39) 3: (40-49) 4: (50-59)
SEX	=	Sex of Patient 1: Male 2: Female
CEN	=	Centre of Study 1: London 2: Aberdeen
SURG	=	Type of Surgery 1: Abdominal 2: Cardiovascular 3: Brain
DRUG	=	Drug 1: Control 2: Painendil
PAIN	=	Pain Score at 24 hours 1: None 2: Slight 3: Moderate 4: Severe

Using either the SAS or R output appended answer the following questions

1) **Testing for Treatment effect**

Model 1 fits a proportional odds model involving only the factor DRUG.

(a) Looking at the likelihood ratio test, is the drug effect statistically significant?

(b) Using the parameter estimate calculate the odds ratio (Painendil : Control). Does your value imply an advantage or disadvantage for the Painendil group?

(c) Calculate a 95% confidence interval for this odds ratio.

Check your results against the output.

2) **Studying a combination of terms**

(a) Model 2 fits AGE as a covariate. Is it a statistically significant predictor?

(b) Model 3 builds on model 2 and adds SEX to the model. Using -2LogLs calculate the influence of SEX on the pain score adjusted for age.

(c) Model 4 fits AGE , SEX and DRUG. What is the odds ratio for a male patient relative to a female patient?

(d) Using the parameter estimates from Model 4, calculate the odds ratio for a male patient aged 42 receiving Painendil to a male patient aged 58 receiving Control. Write down your conclusion.

If time

3) **Fitted probabilities**

(a) Using the parameter estimates from Model 5 calculate the fitted probabilities for each age group and pain score.

(b) Compare these fitted probabilities with the observed percentages in the cross-tabulation of AGEG by PAIN shown below.

Table of ageg by pain					
ageg (Age of Patient - Grouped)	pain (Pain score at 24 hrs)				
Frequency (Row %)	None	Slight	Moderate	Severe	Total
20 – 29	25 50.00	15 30.00	7 14.00	3 6.00	50
30 – 39	21 25.30	25 30.12	31 37.35	6 7.23	83
40 – 49	11 14.67	13 17.33	29 38.67	22 29.33	75
50 – 59	2 6.25	4 12.50	6 18.75	20 62.50	32
Total	59	57	73	51	240

Appendix 1 - SAS Output

Model 1: Testing for drug effect

```
proc logistic data=popain;
  class drug (ref='Control') / param=ref order=internal;
  model pain (order=internal) = drug;
  title 'Model 1: Testing for drug effect';
run;
```

Note, the **class** statement has the option **(order = internal)** for DRUG so that DRUG will be ordered by its actual numerical values as opposed to its formatted labels, e.g. 1: Control, 2: Painendil. The options **param=ref** and **ref='Control'** mean that the parameter estimate for DRUG=Painendil is the log-odds ratio for Painendil relative to Control and this can be read off directly.

```
                        Model 1: Testing for drug effect

                             The LOGISTIC Procedure

                               Model Information

    Data Set                      WORK.POPAIN
    Response Variable             pain                  Pain score at 24 hrs
    Number of Response Levels     4
    Model                         cumulative logit
    Optimization Technique        Fisher's scoring


                    Number of Observations Read         240
                    Number of Observations Used         240


                                Response Profile

                       Ordered                       Total
                         Value     pain          Frequency

                             1     None                 59
                             2     Slight               57
                             3     Moderate             73
                             4     Severe               51

          Probabilities modeled are cumulated over the lower Ordered Values.


                            Class Level Information

                                                 Design
                       Class     Value          Variables

                       drug      Control              0
                                 Painendil            1


                           Model Convergence Status

                  Convergence criterion (GCONV=1E-8) satisfied.
```

Model 1: Testing for drug effect

Score Test for the Proportional Odds Assumption

Chi-Square	DF	Pr > ChiSq
1.9302	2	0.3809

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	667.196	661.416
SC	677.638	675.339
-2 Log L	661.196	653.416

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	7.7797	1	0.0053
Score	7.7253	1	0.0054
Wald	7.6733	1	0.0056

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
drug	1	7.6733	0.0056

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	None	1	-1.4680	0.2000	53.8807	<.0001
Intercept	Slight	1	-0.3906	0.1768	4.8813	0.0271
Intercept	Moderate	1	1.0115	0.1894	28.5123	<.0001
drug	Painendil	1	0.6501	0.2347	7.6733	0.0056

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
drug Painendil vs Control	1.916	1.209	3.035

Model 2: Fit age

```
proc logistic data=popain;
  model pain (order=internal) = age;
  title 'Model 2: Fit age';
run;
```

Model 2: Fit age

Number of Observations Read	240
Number of Observations Used	240

Response Profile

Ordered Value	pain	Total Frequency
1	None	59
2	Slight	57
3	Moderate	73
4	Severe	51

Probabilities modeled are cumulated over the lower Ordered Values.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	667.196	591.449
SC	677.638	605.371
-2 Log L	661.196	583.449

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	77.7474	1	<.0001
Score	65.5030	1	<.0001
Wald	68.2727	1	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	None	1	3.1126	0.5271	34.8715	<.0001
Intercept	Slight	1	4.4183	0.5620	61.7995	<.0001
Intercept	Moderate	1	6.1775	0.6299	96.1753	<.0001
age		1	-0.1170	0.0142	68.2727	<.0001

Model 3: Fit age and sex

```
proc logistic data=popain;
  class sex (ref='Female') / param=ref order=internal;
  model pain (order=internal) = age sex;
  title 'Model 3: Fit age and sex';
run;
```

Model 3: Fit age and sex

Number of Observations Read	240
Number of Observations Used	240

Response Profile

Ordered Value	pain	Total Frequency
1	None	59
2	Slight	57
3	Moderate	73
4	Severe	51

Probabilities modeled are cumulated over the lower Ordered Values.

Class Level Information

Class	Value	Design Variables
sex	Male	1
	Female	0

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	667.196	587.078
SC	677.638	604.482
-2 Log L	661.196	577.078

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	84.1177	2	<.0001
Score	69.8479	2	<.0001
Wald	72.8086	2	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	None	1	3.5285	0.5579	40.0050	<.0001
Intercept	Slight	1	4.8806	0.5968	66.8718	<.0001
Intercept	Moderate	1	6.6374	0.6652	99.5521	<.0001
age		1	-0.1176	0.0142	68.3433	<.0001
sex	Male	1	-0.6431	0.2536	6.4287	0.0112

Model 4: Fit age, sex and drug

```
proc logistic data=popain;
  class sex (ref='Female')
        drug (ref='Control') / param=ref order=internal;
  model pain (order=internal) = age sex drug;
  title 'Model 4: Fit age, sex and drug';
run;
```

```
                         Model 4: Fit age, sex and drug

                    Number of Observations Read         240
                    Number of Observations Used         240


                                Response Profile

                       Ordered                      Total
                         Value     pain         Frequency

                             1     None                59
                             2     Slight              57
                             3     Moderate            73
                             4     Severe              51

       Probabilities modeled are cumulated over the lower Ordered Values.


                            Class Level Information

                                                Design
                       Class     Value         Variables

                       sex       Male                  1
                                 Female                0

                       drug      Control               0
                                 Painendil             1


                 Score Test for the Proportional Odds Assumption

                       Chi-Square       DF     Pr > ChiSq

                          21.0295        6         0.0018


                             Model Fit Statistics

                                                  Intercept
                                   Intercept            and
                     Criterion          Only     Covariates

                     AIC             667.196        579.940
                     SC              677.638        600.824
                     -2 Log L        661.196        567.940


                    Testing Global Null Hypothesis: BETA=0

            Test                 Chi-Square       DF     Pr > ChiSq

            Likelihood Ratio        93.2563        3         <.0001
            Score                   77.1117        3         <.0001
            Wald                    77.0909        3         <.0001
```

Model 4: Fit age, sex and drug

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
age	1	69.0338	<.0001
sex	1	6.0508	0.0139
drug	1	8.9761	0.0027

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	None	1	3.2056	0.5671	31.9584	<.0001
Intercept	Slight	1	4.5883	0.6036	57.7912	<.0001
Intercept	Moderate	1	6.3763	0.6687	90.9256	<.0001
age		1	-0.1197	0.0144	69.0338	<.0001
sex	Male	1	-0.6277	0.2552	6.0508	0.0139
drug	Painendil	1	0.7347	0.2452	8.9761	0.0027

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
age	0.887	0.863	0.913
sex Male vs Female	0.534	0.324	0.880
drug Painendil vs Control	2.085	1.289	3.371

Model 5: Fit only age as a factor

```
proc logistic data=popain;
  class ageg (ref='50 – 59') / param=ref order=internal;
  model pain (order=internal) = ageg;
  title 'Model 5: Fit only age as a factor';
run;
```

```
                        Model 5: Fit only age as a factor

                     Number of Observations Read         240
                     Number of Observations Used         240


                              Response Profile

                        Ordered                      Total
                          Value     pain         Frequency

                              1     None                59
                              2     Slight              57
                              3     Moderate            73
                              4     Severe              51

       Probabilities modeled are cumulated over the lower Ordered Values.


                           Class Level Information

                      Class     Value       Design Variables

                      ageg      20 - 29      1      0      0
                                30 - 39      0      1      0
                                40 - 49      0      0      1
                                50 - 59      0      0      0


                Score Test for the Proportional Odds Assumption

                        Chi-Square       DF     Pr > ChiSq

                            8.1957        6         0.2241


                            Model Fit Statistics

                                                 Intercept
                                   Intercept           and
                      Criterion         Only    Covariates

                      AIC            667.196       608.359
                      SC             677.638       629.243
                      -2 Log L       661.196       596.359


                     Testing Global Null Hypothesis: BETA=0

             Test                 Chi-Square       DF     Pr > ChiSq

             Likelihood Ratio        64.8370        3         <.0001
             Score                   55.4303        3         <.0001
             Wald                    59.3031        3         <.0001
```

Model 5: Fit only age as a factor

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
ageg	3	59.3031	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	None	1	-3.3079	0.4052	66.6547	<.0001
Intercept	Slight	1	-2.0611	0.3811	29.2546	<.0001
Intercept	Moderate	1	-0.3638	0.3506	1.0764	0.2995
ageg	20 - 29	1	3.3368	0.4719	50.0037	<.0001
ageg	30 - 39	1	2.3385	0.4227	30.6135	<.0001
ageg	40 - 49	1	1.3069	0.4137	9.9777	0.0016

Appendix 2 - R Output

Model 1: Testing for drug effect

```
pom.fit1 <- lrm(PAIN ~ DRUG, data=popain)
print(pom.fit1)
cat('Deviance (-2 Log L)', "\n", pom.fit1$deviance, "\n", "\n", "\n")
anova(pom.fit1)
summary(pom.fit1, DRUG='Control')
```

```
Logistic Regression Model

lrm(formula = PAIN ~ DRUG, data = popain)

Frequencies of Responses

  Severe Moderate   Slight     None
      51       73       57       59

                     Model Likelihood     Discrimination    Rank Discrim.
                        Ratio Test           Indexes          Indexes

Obs            240    LR chi2      7.78    R2       0.034    C       0.567
max |deriv| 3e-07    d.f.            1    g        0.326    Dxy     0.134
                     Pr(> chi2) 0.0053    gr       1.386    gamma   0.265
                                          gp       0.081    tau-a   0.101
                                          Brier    0.246


               Coef    S.E.   Wald Z Pr(>|Z|)
y>=Moderate     1.0115 0.1896  5.33  <0.0001
y>=Slight      -0.3906 0.1754 -2.23  0.0259
y>=None        -1.4680 0.1983 -7.40  <0.0001
DRUG=Painendil  0.6501 0.2344  2.77  0.0056


Deviance (-2 Log L)
 661.1961 653.4164


                Wald Statistics          Response: PAIN

 Factor     Chi-Square d.f. P
 DRUG       7.69       1    0.0056
 TOTAL      7.69       1    0.0056


             Effects              Response : PAIN

 Factor                   Low High Diff. Effect S.E. Lower 0.95 Upper 0.95
 DRUG - Painendil:Control 1   2    NA    0.65   0.23 0.19       1.11
  Odds Ratio              1   2    NA    1.92     NA 1.21       3.03
```

Model 2: Fit age

```
pom.fit2 <- lrm(PAIN ~ AGE, data=popain)
print(pom.fit2)
cat('Deviance (-2 Log L)', "\n", pom.fit2$deviance, "\n", "\n", "\n")
anova(pom.fit2)
```

```
Logistic Regression Model

lrm(formula = PAIN ~ AGE, data = popain)

Frequencies of Responses

  Severe Moderate   Slight     None
      51       73       57       59

                     Model Likelihood     Discrimination    Rank Discrim.
                        Ratio Test           Indexes           Indexes

Obs            240    LR chi2      77.75    R2       0.296    C       0.735
max |deriv| 3e-07    d.f.             1    g        1.329    Dxy     0.469
                     Pr(> chi2) <0.0001    gr       3.778    gamma   0.470
                                           gp       0.274    tau-a   0.351
                                           Brier    0.197


            Coef    S.E.   Wald Z Pr(>|Z|)
y>=Moderate  6.1776 0.6324  9.77  <0.0001
y>=Slight    4.4184 0.5628  7.85  <0.0001
y>=None      3.1127 0.5294  5.88  <0.0001
AGE         -0.1170 0.0142 -8.21  <0.0001


Deviance (-2 Log L)
 661.1961 583.4487


                Wald Statistics          Response: PAIN

 Factor     Chi-Square d.f. P
 AGE        67.46      1    <.0001
 TOTAL      67.46      1    <.0001
```

Model 3: Fit age and sex

```
pom.fit3 <- lrm(PAIN ~ AGE + SEX, data=popain)
print(pom.fit3)
cat('Deviance (-2 Log L)', "\n", pom.fit3$deviance, "\n", "\n", "\n")
anova(pom.fit3)
```

```
Logistic Regression Model

lrm(formula = PAIN ~ AGE + SEX, data = popain)

Frequencies of Responses

  Severe Moderate   Slight     None 
      51       73       57       59 

                     Model Likelihood     Discrimination    Rank Discrim.    
                        Ratio Test           Indexes           Indexes       

Obs            240    LR chi2      84.12    R2       0.316    C       0.746    
max |deriv| 3e-07    d.f.             2    g        1.398    Dxy     0.491    
                      Pr(> chi2) <0.0001    gr       4.046    gamma   0.492    
                                            gp       0.284    tau-a   0.368    
                                            Brier    0.195                     


            Coef    S.E.   Wald Z Pr(>|Z|)
y>=Moderate  6.6376 0.6655  9.97  <0.0001 
y>=Slight    4.8807 0.5991  8.15  <0.0001 
y>=None      3.5286 0.5598  6.30  <0.0001 
AGE         -0.1176 0.0144 -8.18  <0.0001 
SEX=Male    -0.6429 0.2562 -2.51  0.0121  


Deviance (-2 Log L) 
 661.1961 577.0785 


                Wald Statistics          Response: PAIN 

 Factor     Chi-Square d.f. P     
 AGE        66.99      1    <.0001
 SEX         6.30      1    0.0121
 TOTAL      71.62      2    <.0001
```

Model 4: Fit age, sex and drug

```
pom.fit4 <- lrm(PAIN ~ AGE + SEX + DRUG, data=popain)
print(pom.fit4)
cat('Deviance (-2 Log L)', "\n", pom.fit4$deviance, "\n", "\n", "\n")
anova(pom.fit4)
summary(pom.fit4, AGE=c(40,40,41), SEX='Female', DRUG='Control')
```

```
Logistic Regression Model

lrm(formula = PAIN ~ AGE + SEX + DRUG, data = popain)

Frequencies of Responses

  Severe Moderate   Slight     None
      51       73       57       59

                      Model Likelihood     Discrimination    Rank Discrim.
                         Ratio Test            Indexes          Indexes

Obs            240    LR chi2      93.26    R2        0.344    C        0.755
max |deriv| 5e-07    d.f.             3    g         1.476    Dxy      0.510
                      Pr(> chi2) <0.0001    gr        4.374    gamma    0.511
                                            gp        0.291    tau-a    0.382
                                            Brier     0.193


               Coef    S.E.   Wald Z Pr(>|Z|)
y>=Moderate     6.3768 0.6732  9.47  <0.0001
y>=Slight       4.5886 0.6100  7.52  <0.0001
y>=None         3.2060 0.5731  5.59  <0.0001
AGE            -0.1197 0.0145 -8.23  <0.0001
SEX=Male       -0.6276 0.2586 -2.43  0.0152
DRUG=Painendil  0.7346 0.2449  3.00  0.0027


Deviance (-2 Log L)
 661.1961 567.9398


                Wald Statistics          Response: PAIN

 Factor     Chi-Square d.f. P
 AGE        67.74      1    <.0001
 SEX         5.89      1    0.0152
 DRUG        9.00      1    0.0027
 TOTAL      77.20      3    <.0001


             Effects              Response : PAIN

 Factor                    Low High Diff. Effect S.E. Lower 0.95 Upper 0.95
 AGE                       40  41    1    -0.12  0.01 -0.15      -0.09
  Odds Ratio               40  41    1     0.89    NA  0.86       0.91
 SEX - Male:Female          1   2   NA    -0.63  0.26 -1.13      -0.12
  Odds Ratio                1   2   NA     0.53    NA  0.32       0.89
 DRUG - Painendil:Control  1   2   NA     0.73  0.24  0.25       1.21
  Odds Ratio                1   2   NA     2.08    NA  1.29       3.37
```

Model 5: Fit only age as a factor

```
pom.fit5 <- lrm(PAIN ~ AGEG, data=popain)
print(pom.fit5)
cat('Deviance (-2 Log L)', "\n", pom.fit5$deviance, "\n", "\n", "\n")
anova(pom.fit5)
```

```
Logistic Regression Model

lrm(formula = PAIN ~ AGEG, data = popain)

Frequencies of Responses

  Severe Moderate   Slight     None
      51       73       57       59

                     Model Likelihood     Discrimination    Rank Discrim.
                        Ratio Test           Indexes           Indexes

Obs            240    LR chi2      64.84    R2       0.253    C       0.705
max |deriv| 1e-07    d.f.             3    g        1.146    Dxy     0.411
                     Pr(> chi2) <0.0001    gr       3.145    gamma   0.552
                                           gp       0.242    tau-a   0.307
                                           Brier    0.208


             Coef    S.E.   Wald Z Pr(>|Z|)
y>=Moderate  -0.3641 0.3664 -0.99  0.3204
y>=Slight    -2.0614 0.3961 -5.20  <0.0001
y>=None      -3.3083 0.4181 -7.91  <0.0001
AGEG=20 - 29  3.3371 0.4831  6.91  <0.0001
AGEG=30 - 39  2.3389 0.4334  5.40  <0.0001
AGEG=40 - 49  1.3072 0.4285  3.05  0.0023


Deviance (-2 Log L)
 661.1961 596.3591


                Wald Statistics          Response: PAIN

 Factor     Chi-Square d.f. P
 AGEG       57.52      3    <.0001
 TOTAL      57.52      3    <.0001
```