Standard Operating Procedure for Statistical Analysis of Clinical Trial Data

SOP ID Number: JBRU/SPON/S08/01

Effective Date: 22/01/2010

Version Number & Date of Authorisation: V01, 15/01/2010

Review Date: 22/01/2012

SOP eDocument kept: S:\CLINICAL_TRIALS\SOPs\EFFECTIVE_SOPs_Guides\SPONSOR SOPs\SPON_S08_SOP for analysis_V01.docx
**Revision Chronology:**

<table>
<thead>
<tr>
<th>SOP ID Number:</th>
<th>Effective Date:</th>
<th>Reason for Change:</th>
<th>Author:</th>
</tr>
</thead>
<tbody>
<tr>
<td>JBRU/SPON/S08/01</td>
<td>22/01/2010</td>
<td>New SOP</td>
<td>Rumana Omar Julie Barber Gareth Ambler</td>
</tr>
</tbody>
</table>

**ACRONYMS:**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>JBRU</td>
<td>Joint Biomedical Research Unit</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>BSG</td>
<td>Biostatistics Group</td>
</tr>
</tbody>
</table>
Standard Operating Procedure for 
Statistical Analysis of Clinical Trial Data

1. PURPOSE
This Standard Operating Procedure (SOP) has been written to describe the procedure for carrying out statistical analysis of clinical trials. This document is meant for internal use by statisticians in the JBRU Biostatistics Group.

2. JOINT UCLH/UCL BIOMEDICAL RESEARCH UNIT POLICY
All SOPs produced from the JBRU must be used in conjunction with local NHS Trust and UCL policies and procedures.

The JBRU acts as the representative of the Sponsor and will be the official name used on all SOPs.

3. BACKGROUND
Statistical analysis is performed according to the trial statistical analysis plan.

4. SCOPE OF THIS SOP
This SOP applies to any analysis of trial data which is the responsibility of the JBRU Biostatistics Group statisticians. It includes both the main trial analysis and interim analyses.

5. RESPONSIBLE PERSONNEL
The assigned trial statistician should follow this SOP.

6. PROCEDURE

6.1 Creation of trial analysis files
At the time of analysis the trial database is frozen. The data manager and statistician work together to download the data from the database into a format that is suitable for the statistical package to be used for analysis. All data are kept in a trial specific directory on limited access password protected UCL directories. Any data queries arising should be referred to the trial data manager for resolution and if necessary new corrected data files provided. The trial statistician will create annotated programs to prepare the data for analysis (including recording, labelling and scoring of data).

6.2 Analysis programs
The trial statistician is responsible for conducting the main analyses according to the trial statistical analysis plan. They are responsible for writing appropriate statistical programs to carry out these analyses with adequate explanatory annotation. Any changes made to the statistical analysis plan should be documented and justified. All analyses will be carried out using well established statistical software, in the majority of cases Stata will be used.
6.3 Guidance for commonly analyses

The guidance below provides detail of the approaches typically taken for analysis of continuous and categorical outcome data from trials along with the associated Stata code.

6.3.1 Analysis of continuous outcome- Parallel groups

The following guidelines are designed to assist in the analysis of a randomised controlled trial with two parallel groups and a numerical (continuous) outcome. The outcome is denoted by y, the binary treatment variable x (taking values 0 and 1), and baseline values of the outcome are denoted by z.

Exploratory analysis

1. Produce the following descriptive statistics for the outcome for each group separately and combined: mean, standard deviation, median, minimum, maximum, interquartile range, and count.

   `bysort x: summarize y, detail`

2. Investigate the distribution of the data using graphical methods. Transform the outcome if clinically appropriate.

   `histogram y, by(x)`
   `qnorm y if x==0`    (and x==1)
   `graph box y, over(x)`

3. Investigate the equality of the variance

   `sdtest y, by(x)`

4. Investigate the relationship between the baseline and outcome measures using graphical methods and summary statistics

Comparing means (or medians) between two groups

Determine an appropriate analysis based on the size of the groups, the distribution of the outcome, the variances and the presence or absence of baseline measures. In all cases an estimate of the treatment effect will be presented with a 95% confidence interval. Use the first appropriate analysis in the list below.

5. If we have baseline measures and a relationship between y and z, we use a regression/ANCOVA based analysis.

   `regress y x z`
   `predict r, residuals`
   `qnorm r`    (normality assumption)
   `rvfplot`    (residuals vs. predicted values)
6. Where assumptions of Normality are appropriate (e.g. if we have approximately normal data (with or without transformation) or a large sample size) we use a two sample t-test.

\[ \text{ttest y, by(x) (assuming equal variances)} \]

\[ \text{ttest y, by(x) unequal (assuming unequal variances)} \]

7. If assumptions of Normality cannot be made (e.g. if we have a small sample size (n < 30) and/or non normal data), we use the Mann Whitney test.

\[ \text{ranksum y, by(x)} \]

8. If we have a large sample we might use the Normal z-test.

6.3.2 Analysis of continuous outcome- Paired groups (cross-over trial)

The following guidelines are designed to assist in the analysis of a cross-over randomised controlled trial with a numerical (continuous) outcome. The outcome is denoted by y, the binary treatment variable x (A=1, B=0), and cross-over period is denoted by period (taking values 1 and 2). Also, sequence denotes the randomisation group (AB=1, BA=2) and id the patient number. We assume the data are stored in long format (i.e. up to two rows per patient) but in order to test for the treatment effect, data will need to be organise so that each treatment is presented by a column.

No carry-over effect or treatment by period interaction is assumed. Analysis adjusting for period effect should be preferred.

Exploratory analysis

1. Produce summary statistics for each treatment/period combination

\[ \text{table sequence period, c(n y mean y sd y)} \]

2. Produce subject profile plots by plotting each subject response in the two periods

\[ \text{sort id period} \]
\[ \text{line y period if sequence==1, sav(fig1) c(L)} \]
\[ \text{line y period if sequence==2, sav(fig2) c(L)} \]
\[ \text{graph combine fig1.gph fig2.gph} \]

3. Plot the mean of each treatment for each period

\[ \text{collapse (mean) y, by(x period sequence)} \]
\[ \text{sort sequence period} \]
\[ \text{line y period if sequence==1, c(L) || line y period if sequence==2, c(L)} \]

Period adjusted analysis
4. Perform an analysis adjusting for period effect using a two sample t-test.

   reshape wide y x, i(id) j(period)
   gen diff = (y2-y1)/2
   ttest diff, by(sequence)

   (note the period adjusted treatment effect estimate and confidence interval are the
difference estimate (&CI) from the t-test divided by 2).

   The data may also be analysed using a random effects model (prior to re-shaping)

   xtreg y x period, i(id) mle

   (A non parametric approach is provided by Koch’s adaption of the Mann Whitney test
and a treatment effect estimate and confidence interval can be obtained using the
Hodges-Lehmann approach)\(^5\)

**6.3.3 Analysis of categorical outcome- Parallel groups**

The following guidelines are designed to assist in the analysis of a randomised trial
with two parallel groups and a categorical outcome. The categorical outcome is
denoted by y, the binary treatment variable x, and baseline factors for adjustment by z.

In this section we will assume that the outcome variable y is either a binary or ordinal
outcome.

The appropriate analysis will depend on the form of the categorical outcome. For all
analyses an estimate of the treatment effect will be presented with a 95% confidence
interval and P-value from an appropriate test.

**Exploratory analysis**

1. Tabulate the outcome categories by treatment group. Check if there is a need to
collapse categories of y into fewer categories.

   tabulate y x, row col

2. Check the expected frequency in each cell of y by Group

   tabulate y x, expected

**Comparing binary outcome between two groups**

**Unadjusted analysis**

**Large samples**

1. Estimates and confidence intervals for risk difference, risk ratio and odds ratio can
   be obtain using the cs command:

   cs y x, or (both variables must be coded as 0 and 1)

   This also provides a p-value from a Chi squared test.
The confidence intervals given are calculated using a normal distribution to approximate binomial. This is acceptable if samples are large i.e. \( n \cdot p \geq 5 \) and \( n \cdot (1-p) \geq 5 \).

Use of the Chi squared test to test for an association between \( y \) and \( x \) is acceptable only if 80% of the cells have expected frequencies \( \geq 5 \) and all the expected values are > 1.

**Small samples**

For small samples where the conditions specified above are not met, exact confidence intervals and tests should be reported.

2. Fishers exact test is provided by:
   
   \( \text{cs } y \times x, \text{ or exact} \)

3. Exact confidence intervals for an odds ratio can be obtained using
   
   \( \text{cc } y \times x \)

4. Confidence intervals for an a risk difference can be obtained using
   
   \( \text{rdci } y \times x \)

   (results are based on four alternative methods: Miettinen-Nurminen, Agresti-Caffo, Wallenstein and Newcombe. All are considered to give an improvement over the Wald method (cs command) for small or moderate-sized datasets.)

**Adjusted for baseline factors**

5. The treatment effect can be adjusted for baseline factors using logistic regression assuming that none of the cells is too small or empty.

   \( \text{logit } y \times x \times z, \text{ or } (z \text{ continuous}) \)

   \( \text{xi:logit } y \times i \times z, \text{ or } (z \text{ categorical}) \)

6. To adjust a risk difference estimate Binomial regression may be used.

**Comparing ordinal outcome between groups**

**Unadjusted analysis**

7. Test for differences between treatment groups using Wilcoxon Rank Sum test

   \( \text{ranksum } y, \text{ by } (x) \)

**Adjusted for baseline factors**

8. Test for differences between treatment groups using ordinal logistic regression
SOP for statistical analysis
JBRU/SPON/S08/01
Page 8 of 13

\texttt{ologit y x, or}

(\textit{Report the combined odds ratio, confidence interval})

Check proportional odds assumption

6.3.4 Analysis of categorical outcome- Paired groups (cross-over trial)

The following is designed to assist in the analysis of 2 by 2 cross-over trials with a binary outcome. The outcome is denoted by $y$, the binary treatment variable by $x$. No carry over effect or treatment by period interaction are assumed (i.e. we assume a sufficient wash out period).

Exploratory analysis

1. A tabulation of the paired responses in each group describes the data to be analysed.

$$mcc \ y_0 \ y_1$$

To use the \texttt{mcc} command that data must be in ‘wide’ form:

<table>
<thead>
<tr>
<th>ID</th>
<th>$y_0$</th>
<th>$y_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data can be converted to this format from (long format).

Long format

<table>
<thead>
<tr>
<th>ID</th>
<th>$x$</th>
<th>$y$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The code required is:

\texttt{reshape wide x, i(id) j(y)}

(Keep only the $x$ and $y$ variables before you run this command)

Analysis of categorical outcome- Paired

2. Estimates and confidence intervals for the difference and ratio of proportions and the odds ratio are provided by the \texttt{mcc} command along with a McNemars test (unadjusted for period effect).

$$mcc \ x_0 \ x_1$$
3. Estimates and confidence intervals for the difference and ratio of proportions and
the odds ratio, *adjusted for period effect* can be obtained using a random effect
model

\[ xtlogit y x \text{ period}, \quad \text{quad(30) i(ID)} \]

Period adjusted analyses can also be carried our using Prescotts test 5

### 6.3.5 Analysis of survival outcome

Let t represent the elapsed time between entry to the study and observation of an
outcome of interest. We assume t is continuous.

A clear definition of: start time, origin e.g. date of diagnosis, end time e.g. date of death
or censoring, unit of time e.g. months, status at end time e.g dead. In all analyses the
following will be presented: estimation of effect size, precision (CI or SE), number of
events and number of patients at risk.

Let Y be the censoring variable, where y=1 outcome occurred and y=0 censoring has
occurred. We assume that censoring is uninformative and that we have no competing
events. Let z1, z2, z3 ..., zi be prognostic factors that may affect survival time. Let x
represent the k treatment groups (0 to k) e.g. placebo (x=0) and control (x=1).

**Exploratory analysis**

1. Define survival parameters: survival time and censoring variables

   \[ stset t, \text{ failure(y)} \]

2. Obtain summary descriptive statistics

   \[ stdes \]

   (Produce summary of survival data, e.g. mean median, min, max)

   \[ stsum, \text{ by(x)} \]

   (Produce summary the following summary statistics: time at risk, incidence rate,
   number of subjects, and the 25th, 50th, and 75th percentiles of survival time)

   \[ stvary \]

   (Only use with multiple records datasets. It reports pattern of missing values;
   how variables within subjects vary over time)

   \[ stsl list, \text{ by(x)} \]

   (List the survivor or cumulative hazard function)

   \[ stsl generate \text{ variable_name = function_name, by(x)} \]

   (Create variables containing survivor and related functions. See help menu for
   list of functions)
**stci, by(x)**

(Compute median survival time by treatment group)

**stci, by(x)**

(Confidence intervals for means and percentiles of survival time. Use option p() for percentile, rmean for mean)

**strate variablename, by(x)**

(Tabulate rate by treatment group)

3. Produce life table

**ltable t y, by(x)**

(Displays and graphs life tables for individual-level or aggregate data. For large datasets, use the interval option to specify the intervals into which the data are to be aggregated for tabular presentation)

**Check proportionality**

4. Visually examine the raw survival plots for subgroups to check they do not cross

**sts graph, by(x)**

(Graph KM curves for each treatment group)

5. Visually examine the raw hazard plots for subgroups to check for non-parallel trends

**sts graph, by(x) hazard**

(Graph a smoothed curve of baseline hazard)

6. Use the graphs produced in Parts 4 and 5 to assess proportionality as follows:

   a. If the KM curves cross the assumption is almost certainly violated. **Go to Part 11.**

   b. If the KM curves do not cross, the assumption is probably acceptable but will need to be checked formally (see Sections 9 and 10). **Go to Part 7.**

**Comparison of survival curves- non-parametric methods**

7. Use log-rank test to compare survival curves

**sts test x, logrank**

(Logrank test for equality of survival functions)
Comparison of survival curves- semi-parametric methods

8. Use the Cox proportional hazard model below from a to b to estimate the effect of a risk factor(s) on the hazard.

   a. Unadjusted (single variable analysis)- This is equivalent to the logrank test but allows formal assessment of the PH assumption, using Schonfeld residuals and gives estimates of the treatment effect.

   \[ \text{stcox } x, \text{schoenfeld(sch*) scaledsch(sca*)} \]

   b. Adjusted for other covariates (multivariate analysis)

   \[ \text{stcox } x \ z1 \ z2 \ldots z3, \text{schoenfeld(sch*) scaledsch(sca*)} \]

9. Test the PH assumption formally after stcox command.

   \[ \text{estat phtest} \] (PH assumption global test)
   \[ \text{estat phtest, rank detail} \] (PH assumption by each variable)

10. Produce diagnostic plots after stcox command.

   \[ \text{estat phtest, plot(zi) yline(0)} \]
   (Plot a \(-\ln(-\ln(st))\) plot by level of variable)

   \[ \text{stcoxkm, by(x)} \]
   (Plot of predicted survival from Cox model with observed survival by KM)

   \[ \text{stcurve, hazard at1(x=0) at2(x=1)} \]
   (Plot estimates of the hazard or survival function at mean values of covariates. Need to specify baseline hazard in the option part)

   \[ \text{lowess scazi _t}, \]
   (Plot survival Scaled Schoenfeld residuals vs. time and look for flatness of the smooth. Flat smooth implies PH is okay)

7. REFERENCES

   2. Campbell, Machin, and Wlaters. Medical Statistics
   3. Doug Altman. Practical Statistics for Medical Research
   4. Kirkwood and Sterne. Medical Statistics
   5. Stephen Senn. Cross-Over Trials in Clinical Research

8. APPENDICES

9. TEMPLATES/LOGS ASSOCIATATED TO THIS SOP
10. SOP DISSEMINATION AND TRAINING

This SOP will be provided to all statisticians of the Biostatistics group by the SOP authors. BSG staff will be requested to read the SOP and will given an opportunity to ask specific questions. BSG statisticians will then sign the SOP training log in section 12.

11. SIGNATURE PAGE

<table>
<thead>
<tr>
<th>Author and Job Title:</th>
<th>Rumana Omar, Julie Barber, Gareth Ambler, Statisticians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Authorised by:</td>
<td>Helen Cadiou, QA Manager</td>
</tr>
<tr>
<td>Name and Job Title:</td>
<td></td>
</tr>
<tr>
<td>Signature:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
</tbody>
</table>
## 12. SOP TRAINING LOG

<table>
<thead>
<tr>
<th>Name of Staff (Capital letters)</th>
<th>Job Title: Department:</th>
<th>Training Date</th>
<th>I confirm that I understand &amp; agree to work to this SOP SIGNATURE</th>
<th>Name of Trainer (if training required)</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>