The BALANCED Anaesthesia Study
A prospective, randomised clinical trial of two levels of anaesthetic depth on patient outcome after major surgery

Protocol
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Statistical Analysis Plan

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1 TITLE

The BALANCED Anaesthesia Study. A prospective, randomised clinical trial of two levels of anaesthetic depth on patient outcome after major surgery
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2 RATIONALE

Current public perceptions are that anaesthesia is very safe and indeed in healthy patients mortality purely attributable to anaesthesia is ~1:200,000 anaesthetics. However the influence of anaesthetic technique on perioperative outcome has barely been explored. Where such trials have been performed, they have also not shown the expected results. The MASTER trial, conducted in Australia and New Zealand in the 1990's comparing major regional anaesthesia for post-operative pain relief with intravenous analgesics showed no difference in mortality in spite of strong evidence from meta-analysis. The POISE trial, a major international trial with strong Australian and New Zealand input on the role of beta-blockade in preventing myocardial infarction and death in patients with ischaemic heart disease also showed increased mortality. This was due to an unexpected increase in strokes counterbalancing the expected decrease in myocardial infarctions. These results have led to a call for more outcome studies to answer important public health questions about how we conduct anaesthesia.

3 STUDY DESIGN AND OBJECTIVES

3.1 Design

International multicentre, prospective, randomised, double blind (subjects, investigators and outcomes assessors), active control, parallel assessment, intention to treat, safety and efficacy study comparing bipsectral index (BIS) target groups 50 and 35.

3.2 Primary Objective

The primary efficacy objective is to compare one-year all-cause mortality between the randomised BIS target groups 50 and 35.

3.3 Secondary Objectives

The secondary efficacy objective is:

- To compare secondary efficacy/safety endpoints to one-year between randomised BIS target groups 50 and 35.

The secondary endpoints are:

1. **MI:** According to the 3rd Universal Definition (Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.), defined by either of:

- A typical rise of troponin OR a typical fall of an elevated troponin OR a rapid rise and fall of CK-MB, PLUS one of the following: i) ischaemic symptoms, ii) pathological Q waves, iii) ECG changes indicative of ischaemia, iv) coronary artery intervention, and/or v) new or presumed new wall motion abnormality on echo or mibi scan; OR
- Autopsy findings of MI

2. **Cardiac arrest:** Defined as a successful resuscitation from either documented or presumed ventricular fibrillation or sustained ventricular tachycardia or asystole

3. **Pulmonary embolism:** high probability VQ scan or documented on pulmonary angiogram or spiral CT, or at autopsy

4. **Stroke**: cerebral infarction or haemorrhage on CT or MRI scan, or new neurological signs (paralysis, weakness or speech difficulties) lasting more than 24 hours or leading to earlier death

5. **Sepsis:** using Centers for Disease Control and Prevention with National Healthcare Safety Network criteria: - SIRS plus infection (positive blood culture or purulence from any site)

6. **Surgical site infection**: if associated with purulent discharge and/or a positive microbial culture

7. **MI, cardiac arrest, PE and stroke:** the composite of secondary cardiac endpoints 1 to 4.

8. **Total ICU stay**: including initial ICU admission and readmission time

9. **Hospital stay**: from the start (date, time) of surgery until actual hospital discharge.

10. **Awareness:** Questioning for evidence of awareness under anaesthetic using the modified Brice questionnaire administered once in hospital, preferably on the day following surgery, and again on day 30.

11. **WHODAS score**: pre-operative, day 30 and 1 year

12. **Disability free survival**: disability-free survival up to 1 year: survival and freedom from new-onset disability, the latter defined as a 4-point or greater increase in the WHODAS score. Disability will be assessed by the participant, but if unable then we will use the proxy's report. The date of onset of new disability will be recorded.

13. **Persistent post-operative pain**: pain over the surgical site, for at least three months after surgery, that cannot be explained by other causes, such as disease recurrence or a pre-existing pain syndrome

14. **Cancer recurrence**: defined as clinical radiological or pathological evidence for recurrence of the tumour either at the local or a distant site.

15. **Adverse Events:** all adverse events collected during the study categorised by preferred term.

3.4 Exploratory Objectives

1. **Infection composite:** the composite of secondary endpoints 5 and 6 (sepsis, surgical site infection).

2. **Composite of mortality and cardiac events:** the composite of the primary endpoint (mortality) and MI, cardiac arrest, PE and stroke.

4 General Analysis Definitions

4.1 Treatment Allocation

Once all entry details are recorded and eligibility confirmed, randomisation will be performed by contacting the automated on-line randomisation service with back-up phone service. Assignment to one of the two groups will be stratified by collaborating centre-group and a unique study number assigned.

4.2 Sample size calculation

One year all-cause mortality is expected to be ~10% based on the findings of Leslie et al. and Gurman et al. The relative risk reduction in mortality in the BIS=50 group is expected to be 20%. A power analysis using p_1=0.10 and p_2=0.08 indicates that N=3250 patients are required in each group, 1-β=0.8, α=0.049. The alpha level is reduced to allow for the single interim analysis.

4.3 Participant Populations

4.3.1 Intention-To-Treat Population (ITT)

The primary and secondary outcomes will initially be analysed using the full analysis set population i.e. the intention-to-treat population which includes all randomised patients undergoing induction of general anaesthesia for surgery. Sensitivity analyses will also be undertaken, as appropriate. In these analyses missing outcome data will be assigned a poor outcome.

In the event that patients withdraw (discontinue participation in the study or are lost to follow-up), information on their survival and secondary endpoint status at the time they are withdrawn will be included in the relevant endpoint analysis.

4.3.2 Per-Protocol (PP) Population

The per-protocol (PP) population will be defined as all randomised participants classified according to the actual median BIS value achieved irrespective of randomisation. Participants will be allocated to the BIS=50 group if the achieved median BIS is between 45 and 55 inclusive, and to the BIS=35 group if the achieved median BIS is between 30 and 40 inclusive. Participants who are not within these ranges will be excluded from these analyses. All primary and secondary endpoints will be compared between the two groups defined as per-protocol. In the event that patients withdraw (discontinue participation in the study or are lost to follow-up), information on their survival and secondary endpoint status at the time they are withdrawn will be included in the relevant endpoint analysis.

4.3.3 Safety Population

The safety population will be used to report the summaries of the adverse events that are not constituents of the secondary endpoints. The safety population is defined as all randomised patients who underwent induction of general anaesthesia for surgery, with groups defined as randomised.

4.4 Observational Period

The observational period for the study will be from the date of surgery to 1 year.

5 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

To summarise the randomisation process, participant demographic and baseline clinical characteristics will be summarised descriptively by randomised group. These variables will also be summarised by randomised group within the predefined study-centre groups. Summaries will include frequencies and percentages for categorical data and means, medians, ranges, standard deviations and inter-quartile ranges as appropriate for continuous data. These baseline summaries will include the following variables:

- Age
- Weight
- Sex
- Ethnicity
- ASA physical status
- Charlson score
- WHODAS score
- Cancer diagnosis
- Emergency/elective surgery
- Surgery type
- Haemoglobin
- Albumin
- Creatinine
- Surgical duration

These data will be examined for any imbalances between randomised treatments. If potentially confounding influences are identified, appropriate statistical adjustment will be used to mitigate these in sensitivity analyses and these will be reported and discussed in any reports or publications arising from the study. No formal hypothesis testing will be conducted on these baseline variables.

6 PARTICIPANT DISPOSITION

A flowchart will be produced showing the flow of participants throughout the study. The numbers of participants approached, screened and consented will be summarised. Those who are screened and consented but not randomised will also be summarised.

Any participants who are randomised but do not have surgery will be individually listed with explanation, by randomised group.

Any patients inappropriately randomised (subsequent to randomisation are found to violate inclusion/exclusion criteria) will also be individually listed with their inclusion or exclusion violations.

7 STUDY MEDICATION AND CONCOMITANT THERAPY

7.1 Compliance

To evaluate the degree of compliance with randomised BIS target, tabular summaries of achieved BIS values will be presented by randomised group.

The association between achieved target BIS value and all outcomes will be tested using exploratory analyses as outlined below.

7.2 Physiological data

Bispectral index (BIS), mean arterial pressure (MAP) and minimum alveolar concentration (MAC) of the volatile anaesthetic agent for each patient during anaesthesia will be recorded digitally whenever possible. Analysis will be from first BIS<50 after commencing anaesthesia or 5 minutes after anaesthesia induction if BIS<50 not achieved in that time period, until switch-off of volatile anaesthetic at the end of the case. Mac will not be adjusted for age.

BIS recordings will be visually inspected, obvious artefacts removed and then cleaned by removing all data when the signal quality index is less than 50%, when signal quality is available. Mean BIS for each individual patient will then be calculated.

Mean MAC during this time period will also be calculated for each patient.

Mean MAP will be calculated for each patient during this time period. In addition mean of the target MAP range will be calculated. Mean (MAP-MAP_{target}) will then be calculated to establish how well the patient has tracked.

These values will be reported in the ITT summaries as mean and standard deviation for each group

8 EFFICACY ANALYSES

8.1 Primary endpoint analyses:

The primary endpoint analysis will compare the primary endpoint, one-year mortality in the intention-to-treat population, using a Mantel-Haenszel Chi-square test, stratified by study-centre groups. The pooled estimate of the odds ratio and 95% confidence interval from this analysis will be used to summarise the statistical comparison.

Supportive analysis of the primary endpoint will compare randomised groups using a stratified log-rank test with results summarised using Kaplan-Meier curves and hazard ratios in which withdrawn participants will be censored at the last date that they are confirmed to be event-free.
A two-tailed p-value < 0.049 will be taken to indicate statistical significance. The primary endpoint will be analysed using the full analysis set i.e. using those individuals who have confirmed outcome status, with groups designated as randomised on the intention-to-treat basis. Sensitivity analyses will also be undertaken with those missing outcome data assigned a poor outcome.

8.2 Secondary efficacy analyses:

The differences between randomised groups will be analysed using stratified Mantel-Haenszel Chi-square tests, stratified by study-centre group and general linear models, as appropriate to the form of the secondary endpoint. The occurrence of MI, cardiac arrest, PE, stroke, cardiac composite, surgical site infection, sepsis, infection composite, awareness, persistent post-operative pain and cancer recurrence within one year post-surgery will be analysed using stratified Mantel-Haenszel Chi-square tests. Supportive analysis of these secondary endpoints will compare randomised groups using a stratified log-rank test with results summarised using Kaplan-Meier curves in which withdrawn participants will be censored at the last date they are confirmed to be event-free. Sensitivity analyses will also be undertaken for these secondary endpoints with those missing outcome data assigned a poor outcome.

ICU stay, hospital stay, days disability-free and alive within one-year post-surgery and WHODAS scores at 30 days and 1 year will be analysed using general linear models with study-centre group and randomised treatment as

fixed factors. If the data do not meet assumptions for parametric analyses, the data will be log-transformed and if this does not achieve adequate normality then the groups will be compared using the Mann-Whitney U non-parametric tests.
The endpoints; infection composite (the composite of secondary endpoints sepsis, surgical site infection) and composite of mortality and cardiac events (mortality MI, cardiac arrest, PE and stroke) will be compared between randomised groups using stratified Mantel-Haenszel Chi-square tests and using a stratified log-rank test with results summarised using Kaplan-Meier curves in which withdrawn participants will be censored at the last date they are confirmed to be event-free.

Standard descriptive statistics including frequencies, percentages, means, medians and ranges will be used to describe the levels for the secondary endpoints. The differences between randomised groups for the secondary endpoints will be summarised using model derived odds ratios and mean differences with 95% confidence intervals.

8.2.1 Type I error Control for secondary efficacy analyses

The statistical testing of the secondary efficacy measures will utilize the Holm-Bonferroni method to protect the type I error rate at 5%. There are ten secondary efficacy measures including the two composite outcomes outlined above. If a composite measure shows a statistically significant difference between groups using the Holm-Bonferroni procedure then the constituents measures will be compared using the adjusted p-value to determine statistical significance.

9 CONFOUNDING

Relative hypotension associated with deep anaesthesia is suspected to be a confounding factor that may be the explanation for observed mortality difference in the published evidence to date. The BALANCED study design has attempted to mitigate these effects (via the use of vasopressors and inotropes) but achieved MAP may still confound the comparison between randomised groups. A multivariate analysis of 1 year mortality will be undertaken using Cox proportional hazards regression in which randomised group, study-centre-group, the use of vasopressors/inotropes and achieved MAP are included as covariates.

9.1 Additional analyses

- Additional analyses of efficacy endpoints will be undertaken using the PP participant population and including the intermediate BIS group 40 to 45.
- Efficacy endpoints will be summarised by randomized group within categories for age, ASA, surgery type, centre, use of vasopressors/ inotropes and anesthetic duration (quartiles). These results will be summarized using forest plots and the consistency of the difference between randomised groups tested using interaction terms within Cox-regression and general linear models as appropriate.
- Multi-variate analyses will be used to explore the independent and combined effects of randomised treatment, age, ASA, surgery type, study centre-groups, anesthetic duration, the use of inotropes, achieved MAP and achieved BIS group on the efficacy endpoints.

10 SAFETY ANALYSES

Safety analyses will be performed using the safety population as defined above. Adverse events and serious adverse events will be tabled as frequencies and percentages within Common Terminology Criteria for Adverse Events (CTCAE) preferred term and system organ class classifications by randomised group, severity class and relatedness to randomised treatment. Additionally, the incidence of adverse events (events/p-year) will be calculated and summarised by randomised group.

11 PROTOCOL VIOLATIONS

All protocol violations and deviations will be individually listed by randomised group.

12 MISSING DATA

In the event that a patient withdraws (discontinues the study or is lost to follow-up) from the study, information on their survival and secondary endpoint status at the time they are withdrawn will be included in the relevant endpoint analysis. Sensitivity analyses will also be undertaken with those missing outcome event data will be assigned a poor outcome. There will be no imputation of the ICU stay, hospital stay, days disability-free and alive within one-year post-surgery and WHODAS data at 30 days and 1 year.

13 PROCEDURE FOR AMENDMENTS TO STATISTICAL PLAN

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. Any revisions to this document prior to database lock will be made in the form of an amendment to the Statistical Analysis Plan. Any deviations or additional analyses that are performed will be summarised in the form of an addendum to the Statistical Analysis Plan. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical study report.