Statistical Analysis Plan

SAP Version Number
1.0

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1.- INTRODUCCION

This document is the Statistical Analysis Plan (SAP) for the MIMO trial, and should be read in conjunction with the current trial protocol. This SAP details the proposed analyses and presentation of the data for the main paper(s) reporting the results for the MIMO trial. The results reported in these papers will follow the strategy set out here. The analysis will be carried out by an appropriately qualified statistician, who should ensure integrity of the data during their data cleaning processes.

2.- BACKGROUND AND RATIONALE

The complete MIMO protocol has been published previously[1]. In brief, MIdazolan versus Morphine in acute cardiogenic pulmonary edema (MIMO) Trial compared the efficacy and safety of midazolam versus morphine head-to-head using a randomized, single-blinded, multicenter design.

3.- TRIAL OBJECTIVES

3.1. Efficacy assessment

The primary end point for comparing midazolam and morphine was in-hospital all-cause mortality. The secondary end points were 30-day all-cause mortality, use of invasive mechanical ventilation and length of hospital stay (from ED arrival to final discharge, either home or due to death). The final adjudication of outcomes was performed at a local level by the principal investigator of the center because of the objectivity of the endpoints.

3.- TRIAL OBJECTIVES

3.2. Safety assessment

The reporting of adverse event was considered the main safety endpoint. A composite endpoint formed by 30-day mortality and serious adverse event.

4.- TRIAL METHODS

4.1. Trial design

MIMO is a prospective, randomized open-label blinded endpoint clinical trial comparing the use of Midazolam and Morphine in patients with acute pulmonary edema[1].

4.- TRIAL METHODS

4.2. Trial interventions

Midazolam (administered intravenously at a dosage of 1 mg, up to a maximum dose of 3 mg).

Morphine (administered intravenously at a dosage of 2-4 mg, up to a maximum dose of 8 mg).

4.- TRIAL METHODS

4.3. Randomisation

At emergency department arrival eligible patients were randomized in a 1:1 ratio to either midazolam or morphine via a password-protected encrypted website that uses a computer-generated minimization algorithm to ensure balance between the treatment groups.

4.- TRIAL METHODS

4.4. Sample size.

Power calculation was determined by retrospective analysis of the Acute Decompensated Heart Failure National Registry (ADHERE), in which among 147,362 hospitalizations, 20,782 (14.1%) received morphine and 126,580 (85.9%) did not. Patients who received morphine showed a greater mortality (13.0% vs. 2.4%)[2]. Therefore, we estimated that 136 patients (68 patients per group) were needed to have an 80% power with a two-sided type I error of 5% to detect a statistically significant difference between the two groups.

4.- TRIAL METHODS

4.5. Framework

The objective of the trial is to test the superiority of one intervention to another as well as to assess the safety.

Null Hypothesis for primary outcome and safety :

No difference in the in-hospital all-cause mortality neither in the adverse events when comparing a strategy of midazolam versus morphine in patients with acute cardiogenic pulmonary edema.

Alternative Hypothesis:

Use of midazolam versus morphine in patients with acute cardiogenic pulmonary edema is superior based in the in-hospital all-cause mortality and adverse events.

4.- TRIAL METHODS

4.6. Interim analyses and stopping guidance

A joint oversight committee comprising a Steering Committee (SC) and Data and Safety Monitoring Board (DSMB) will be responsible of the security of this clinical trial. The role of the SC is to provide the overall supervision of the trial. The SC will monitor trial progress and conduct and advice on scientific credibility. The SC will consider and act, as appropriate, upon the recommendations of the DSMB.

DSMB will be established to oversee the safety of participants in the trial. The DSMB will meet prior to the trial opening to enrolment, and then meet at least annually, or as per a timetable agreed by the DMC prior to trial commencement. Data analyses will be supplied in confidence to the DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with the trial specific charter. The interim analysis will be conducted for the primary measure of efficacy as well as safety to determine if there was strong evidence of efficacy (according to the Peto-Haybittle guidelines, with a criterion of $P<0.001$) or harm ($P<0.05$) for any arm of treatment.

DSMB will perform a planned interim analysis when data from the first 50% of

enrolled patients were available. Depending of this analysis the DSMB will recommended a second analysis to review adverse events in any arm of treatment. DSMB will recommended that enrollment into the trial be continued or stopped. After this second interim analysis, the DSMB recommended that the trial be stopped due to concerns about safety. The SC concurred with this plan and was informed of the results of the interim analysis.

5.- STATISTICAL PRINCIPLES

5.1. Confidence intervals and p-values

All estimates of differences between groups will be presented with two-sided 95% confidence intervals, unless otherwise stated. P-values will be reported from two-sided tests.

5.- STATISTICAL PRINCIPLES

5.2. Adjustments for multiplicity

No correction for multiple testing will be made.

5.- STATISTICAL PRINCIPLES

5.3. Analysis populations

All primary analyses (primary and secondary outcomes including safety outcomes) will be by intention-to-treat (ITT). Participants will be analysed in the intervention group to which they were randomised, and all participants shall be included whether or not they received the allocated intervention.

5.- STATISTICAL PRINCIPLES

5.4. Handing protocol deviations and violations

A protocol deviation/violation is defined as a failure to adhere to the protocol such as errors in applying the inclusion/exclusion criteria, the incorrect intervention being given, incorrect data being collected or measured, follow-up visits outside the visit window or missed follow-up visits. We will apply a strict definition of the ITT principle and will include all participants as per the ITT population.

6.- TRIAL POPULATION

6.1. Recruitment

A flow diagram (as recommended by CONSORT[3]) will be produced to describe the participant flow through each stage of the trial. This will include information on the number (with reasons) of losses to follow-up (drop- outs and withdrawals) over the course of the trial. A template for reporting this is given in Appendix A.

6.- TRIAL POPULATION

6.2. Baseline characteristics

Categorical data were summarised by number of participants, counts and percentages. Continuous data were summarised by the number of participants, median and interquartile range. Tests of statistical significance will not be undertaken, nor confidence intervals presented[4].

7.- ANALYSIS METHODS

7.1. Data manipulations

The Trial Statistician will derive all responses from the raw data recorded in the database. We compared group differences using a chi-squared test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Risk ratios (RR) with their 95% CI were calculated for the outcome measures. The reference group was considered to be the morphine arm. Survival analysis was estimated using Kaplan-Meier tables, and the survival rate of each group was compared using the log-rank test. Although a multivariate analysis had been planned in the original statistical analysis plan, the authors decided not to carry it out due to the insufficient number of events[5]. Instead, the authors decided to run a post-hoc subgroup analysis for the primary outcome of efficacy (in-hospital mortality) and for serious adverse events in order to search for interaction in 6 key variables: sex, age (dichotomized as <80 or ≥80 years), coronary artery disease, previous episodes of heart failure, room air oximetry at emergency department arrival (dichotomized as <85 or ≥85%), and NT-proBNP (dichotomized as <5000 or ≥5000 pg/mL). Interaction was assessed using the Mantel-Haenszel test.

7.- ANALYSIS METHODS

7.2. Handling missing data

All the investigators went to great effort to record all the data in the database. Therefore, there was not missing data.

7.- ANALYSIS METHODS

7.3. Exploratory outcomes and analyses

Any data that does not form a pre-specified outcome will be presented using simple summary statistics by intervention group (i.e. numbers and percentages for binary data and means (or medians) and standard deviations (or inter-quartile ranges) for continuous normal (or non-normal) data.

8.- SAFETY DATA

The number and percentage of participants experiencing any adverse events were presented by treatment arm. All safety analyses were based on the ITT principle and included all the patients who underwent randomization.

The significance of an adverse event was used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning. The DSMB adjudicated the severity of the adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 and graded using the Common Terminology Criteria for Adverse Events version 4.03, as previously reported[6]. The MIMO trial defined the severity in the following grades:

- Grade 3 severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to adverse event.

The serious adverse events were defined with any of the degrees aforementioned. A table listing all the serious adverse events was provided.

9.- STATISTICAL SOFTWARE

Statistical analysis will be undertaken in the following statistical software packages:

- SPSS 24.0
- EPIDAT 3.1 (Area of Health Analysis and Information Systems; World Health Organization).
- Stata version 16

10.- REFERENCES

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