Statistical Analysis Plan

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Data preparation

The first task to be able to analyze the information statistically is the extraction and export of the data from the web application to the analysis tool. In our case IBM-SPSS. The application has an export routine that translates the data into Excel format. This information will later be imported into SPSS. It should be taken into account that it is not possible to attack the database directly, so the export process entails the subsequent adaptation of the variable formats for their final treatment.

Variable names are exported with the full label and starting with a digit, which is incompatible with the SPSS variable naming format. The variable names will be adapted and shortened to the SPSS format. Descriptive labels will be provided.

Categorical variables are exported using the literal of the selected option as the value. Said variables will be coded as numeric variables, with codes labeled in correspondence with the option they represent.

Date variables are exported in literal string format. These variables will be transformed into SPSS time or date variables, as appropriate, in order to perform calculations with them (for example, wait times).

The multi-response variables are stored as a combined string that collects all the choices. The multi-response variables will be translated into individual variables for each of the individual choices made.

String variables are exported with a string length (number of characters) equal to the longest tag selected. Therefore, if the longest possible label has not been selected before in an export and is selected later, the translation rules of the corresponding variable must be redefined.

No problems are expected with the export of numeric variables.

The string variables corresponding to open response fields (for example, comments or specify) will be returned to the scientific leaders of the study for coding, so that the corresponding descriptive summary can be made.

The files will be analyzed in isolation, as they are found in the application's repository, and only the relevant fields will be merged for the crossovers of variables proposed by the researchers or those proposed in this analysis plan.

Data export validation

The LifeTrial tool for the collection and storage of clinical study information has a statistical summary tool (Statistics module). This tool allows defining, storing and displaying descriptive statistics of the fields contained in the electronic data collection notebook.

The data exported from the repository to SPSS (through its conversion to Excel) will be validated by comparing the statistics obtained directly with the LifeTrial Statistics tool with those obtained through SPSS. The descriptive statistics obtained with the Statistics tool basically consist of counts, bar graphs and descriptive statistics (mean standard deviation, minimum, maximum, etc.). For numerical variables (type = integer, type = decimal), the values of the summary statistics obtained with the Statistics tool will be compared with those

obtained with SPSS. Since the system does not offer summary statistics (mean, standard deviation) for date variables (type = date) (all the different recorded values are presented), subsets of data will be arbitrarily selected to check their exact export.

In any case, the number of valid data and missing data of the selected fields will be checked to ensure the correct export of the data.

Treatment of missing values

The statistical analysis process assumes the correct monitoring of the data entry through the electronic data collection notebook. During the data analysis phase, no queries should be made to fill in missing information or missing values.

However, during the analysis process, missing and missing values will be identified for later treatment with the research team. Extreme and out-of-range values will also be identified for later review by the research team. The necessary corrections obtained from the identification of out-of-range values or missing information and reviewed by the patient's clinical manager will be entered into the database for subsequent treatment in subsequent re-analyzes.

The initial data treatment strategy will be to assume a non-response as a completely random missing value (MCAR) and the treatment of missing values will be isolated by variable. If it is required to relate several variables in an analysis, the treatment will be "according to the pair" of variables considered (pairwaise) to minimize the impact of the lost information on the estimates obtained.

In the cases in which the analysis of several consecutive measurements is carried out or the passage of time is valued, the carrying over of the last value obtained on subsequent measurements will be assumed. For example, if a subject has not suffered an event or there is no information on this aspect (missing value) at the time of closing the database, it will be assumed that the subject's status is the same as the last measurement with valid data.

Descriptive analysis of the data

The data repository is structured in 6 tables: Inclusion, Baseline data, Procedure, Follow-up, Adverse event and Study exit. Summary information will be provided on the variables collected in each of the tables.

Regarding dates, the time elapsed between dates or waiting times will be calculated as specified by the scientific coordinators of the study.

Inclusion

The Inclusion table contains soiodemographic information about the patient, the date of inclusion in the study, and the inclusion / exclusion criteria.

Continuous variables will be described using the statistics of central tendency (mean and median), dispersion (minimum, maximum, standard deviation and interquartile range) and shape (skewness and kurtosis). The number of valid cases and the number of cases with missing values will be reported. The continuous variables in this table are: Date of inclusion, Age, Weight and Height.

The categorical variables will be described by frequencies and percentages. The number of valid cases and the number of cases with missing values will be reported. The categorical variables contained in this table are: Sex, the inclusion criteria and the exclusion criteria.

Baseline data

The Baseline Data table contains clinical information about the patient's situation at the baseline visit. Specifically, the date of the baseline visit, characteristics of AF, REDO, heart disease, risk factors, drugs, echocardiography, and lung anatomy.

Continuous variables will be described using the statistics of central tendency (mean and median), dispersion (minimum, maximum, standard deviation and interquartile range) and shape (skewness and kurtosis). The number of valid cases and the number of cases with missing values will be reported. The continuous variables in this table are: Date of the baseline visit, number of previous procedures, CHADS2 index, CHADS2DS2-VASc index, BMI, number of arrhythmic drugs, IVTDVI, IVTSVI and area and diameter of the LA dilatation.

The categorical variables will be described by frequencies and percentages. The number of valid cases and the number of cases with missing values will be reported. The categorical variables contained in this table are: AF type, AF evolution time, Associated arrhythmias, REDO, Type of previous procedure, Heart disease, Heart disease type, Channelopathy type, Congestive Heart Failure, Arterial hypertension, Age 65-74, Age ≥ 75 years, Diabetes Mellitus, Vascular disease, Female gender, History of stroke or Transient Ischemic Accident, Pacemaker carrier, Sports, Alcohol, SAHS, CPAP, Dyslipidemia, Obesity, Antiarrhythmic drugs, Type of antiarrhythmic agents, Beta-blockers, Calcium antagonists, Anticoagulants, Type anticoagulants, NACOs Type, FE, Ventricular Dilation, AI Dilation, VPI, VPI Type, VPD, VPD Type.

Procedure

The Procedure table contains technical information about the ablation procedure.

Continuous variables will be described using the statistics of central tendency (mean and median), dispersion (minimum, maximum, standard deviation and interquartile range) and shape (skewness and kurtosis). The number of valid cases and the number of cases with missing values will be reported. The continuous variables in this table are: Procedure date, TTE (sg), Minimum temperature (ºC), Application time (sg), Reheating time (sg), No. of balloons used, Total time of applications (min), Time total LA (min), Total procedure time (min), Total fluoroscopy time (min), Time to -30 degrees (sec), Rx Dose (PDA), Wait time (min), Contrast (ml), No. of cardioversions.

The categorical variables will be described by frequencies and percentages. The number of valid cases and the number of cases with missing values will be reported. The categorical variables contained in this table are: Study No., Previous Image, Image Type, Previous TEE (Transesophageal Echocardiography), General Anesthesia, Deep Sedation, Channeled Artery, No. of Diagnostic Catheters, Location of Diagnostic Catheters, Access, Assisted Transeptal, Assisted using, Phrenic nerve monitoring technique, Base rhythm, Applications, Vein, Application number, Potential visibility, Balloon size, Pulmonary vein isolation, Auriculogram, Protamine, Z-suture, Complications, Cardioversions, Number of cardioversions, Ablation ICT, Post-procedure antiarrhythmics, Antiarrhythmic type, Post-procedure anticoagulation, NACOs type, Base rhythm, Select type of Flutter, Catheter, Sheath, Specify.

Follow-up

The Follow-up table contains clinical information related to the follow-up of the patient. At the time of writing this protocol, it is unknown whether a patient can have multiple follow-up visits.

Continuous variables will be described using the statistics of central tendency (mean and median), dispersion (minimum, maximum, standard deviation and interquartile range) and shape (skewness and kurtosis). The number of valid cases and the number of cases with missing values will be reported. The continuous variables in this table are: Date of the follow-up visit, Date of post-procedure discharge, Date of admission, Date of discharge, Number of hospital stays.

The categorical variables will be described by frequencies and percentages. The number of valid cases and the number of cases with missing values will be reported. The categorical variables contained in this table are: Follow-up visit, ECG record / Monitoring type, Recurrence 3 months post-procedure, Recurrence specification, Asymptomatic AF, Treatment, Antiarrhythmics, Antiarrhythmic type, Specify, Anticoagulants, NACOs type, REDO, Type REDO, Death, Hospital stay

Adverse event

The Adverse Event table contains clinical information regarding adverse events that occurred during patient follow-up. It is assumed that a patient may experience several (or none) adverse events during follow-up. Therefore, two types of descriptive analysis will be carried out, one using the number of patients as the unit of analysis (summarizing aspects such as the number of events per patient, maximum and minimum time between events, etc.) and another using the units of analysis as reported events (to summarize aspects such as the most frequent type of event, the most frequent level of severity, resolution of the events, etc.)

Continuous variables will be described using the statistics of central tendency (mean and median), dispersion (minimum, maximum, standard deviation and interquartile range) and shape (skewness and kurtosis). The number of valid cases and the number of cases with missing values will be reported. The continuous variables in this table are: Date of the adverse event, Date of knowledge of the EA, Date of resolution.

The categorical variables will be described by frequencies and percentages. The number of valid cases and the number of cases with missing values will be reported. The categorical variables contained in this table are: Type of event, event (s), Type of complications, event (s), Type of arrhythmia, Is the AE serious ?, Type of severity, Measures taken, Status of the event.

Study exit

The Study Exit table contains clinical information regarding the patient's study exit.

This table only contains two variables: the reason for leaving and the date of departure. Both variables will be adequately described by frequency of the reasons and the calculation, for their description and summary, of the corresponding waiting times.

Statistical models

In order to conclude on the primary objective of the study, the number and percentage of cases with absence of atrial fibrillation recurrences will be calculated after 12 months of follow-up, after the cryoablation procedure. The scientific coordinators of the study will have to determine the closing date of the database so that it has been possible to collect information from 12 months of follow-up of a sufficiently large number of patients.

The protocol defines AF recurrence as a clinically diagnosed and documented episode of AF (using ECG, Holter monitor with a duration of at least 30 seconds, or using implantable devices

or event monitoring systems). The information necessary to determine the existence of a recurrence of AF will be extracted from the Follow-up and Adverse Events tables.

The existence of differences between patients with and without recurrence in clinical variables and patient follow-up will be explored. Student's t statistics (for continuous variables) and $\chi 2$ (for categorical variables) will be used. If there are appreciable differences between the groups of patients in the clinical variables, logistic regression models will be proposed to study the multivariate effect of the variables and assess their predictive capacity.

The waiting times until the moment of recurrence of AF will be described using survival models (survival tables and Kaplan-Meier) and the existence of variables capable of predicting the differences between both groups of patients will be explored.

The necessary statistical analyzes will be approached to verify the secondary objectives based on the variables designated by the study coordinators.