Statistical analysis Plan

1. Database

The development of the base will be managed by the West Clinical Research Unit (URC-Ouest). The clinical database will be developed in MySQL. This database can be filled in online through a site developed in APHP. Progress, entry and connection controls will be implemented, in addition to the usual security requirements. The statistical analysis will be managed in the INSERM UMR S707 unit. We will use R and SAS V9.1 software (SAS Institute).

- Statistical analysis

The baseline characteristics of the patients (age, sex, scores, etc.) will be described by mean, median, inter-quartile interval and standard deviation for continuous variables and by frequencies with a 95% confidence interval for the qualitative variables.

We will compare mortality rates between the two strategies by adjusting for severity, autonomy, chronic diseases and nutrition status. We will use a mixed logistic regression model.

The other analyzes will concern the secondary criteria. We will compare the rates of ICU admissions and their variability in the RSA group and the SP group (gross rates and ICC values). We will also analyze the survival of patients in both groups (Cox models). The quality of life and the "burden" of caregivers of patients living at home at six months will also be compared in each group.

In addition, we will assess the impact of the implementation of the study on all ICU admissions of elderly people from the emergency departments. And the impact of this possible "contamination" on the overall mortality observed in ICU and in the hospital.

Based on data from the CUB-Réa database, we will be able to assess the volume of elderly patients included in the participating centers, the hospital mortality and the in-ICU mortality of included patients in the two years preceding the study in order to detect any change during the implementation of the study, in each of the two groups (RSA / SP).

- Sample Size Calculation

Based on the results of the ICE-CUB 1 study, 32% of patients die within six months of the emergency department visit. We hypothesize that the mortality of patients over 75 years of age will be equivalent and that the proposed intervention will reduce mortality by 6% at six months. In a unilateral situation, with a type one error rate of 5%, without taking into account the cluster effect, 704 patients per group are necessary to demonstrate such a difference with a power of 80%. Cluster randomization imposes inflation dependent on intraclass correlation coefficient (ICC). With an ICC at 0.01, an average of 100 patients per center, a total of 2802 patients are required.

Based on the data from the ICE-CUB 1 study, 560 patients over 80 years of age with factors of good prognostic and a critical conditions requiring organ support were admitted to the emergency department of 15 centers over a 1-year period. It is assumed that 560*1.5 = 840 patients over the age of 75 with the same characteristics, with an average of 56 patients per center per year. Thus, it is estimated that the number of subjects needed (n=2802) can be reached in 2 years with 20 participating centers.

- Management of the missing, unused or invalid data

The management of the missing data will be carried out according to the complexity and the frequency of the situations. The MCAR or MAR character will be evaluated according to the Little & Rubin classification (Statistical Analysis with Missing data, Wiley 1987). If the proportion of missing data is less than 0.05, a simple imputation will be used, otherwise a multiple imputation will be performed. A sensitivity analysis will be carried out if the proportion is very high.

- Management of modifications to the initial strategy analysis plan

Changes in statistical methods decided retrospectively and validated by the steering committee will be presented in an amendment to the protocol and in the analysis report of the study.

- Access to data and source documents

Persons with direct access in accordance with the applicable laws and regulations, in particular Articles L.1121-3 and R.5121-13 of the Public Health Code (investigators, quality control persons, monitors, clinical research assistants, auditors and others involved in

research) shall take all necessary precautions to ensure the confidentiality of information relating to investigational medicinal products, tests, appropriate persons and particularly as regards their identity and the results obtained. The data collected by these persons during the quality control or audits are then made anonymous.

- Quality Control and Quality Assurance

The search will be conducted according to the sponsor standard operating procedures.

The conduct of the research in the investigating centers and the management of the subjects will be done in accordance with the Helsinki Declaration and the Good Practices in force.

- Monitoring Procedures

Risk level of the study: the Clinical Research Assistants (CRA) representative of the sponsor will visit the investigating centers at the rate corresponding to the follow-up of the patients in the research protocol, to the inclusions in the different centers and to the level of risk that has been attributed to the research.

- Opening visit of each center: before inclusion, for the implementation of the protocol and acquaintance with the various participants in the research.

The principal investigator of each center as well as the other investigators including or following included patients involved in the research are engaged to receive the CRAs at regular intervals.

During these on-site visits and in accordance with the Good Clinical Practices, the following elements will be reviewed:

Compliance with protocol and defined procedures for research,

Verification of informed consent of patient

Review of source documents and comparison with data reported in the observation booklet as to accuracy, missing data, consistency of data according to the rules laid down by DRCD procedures.

Closure visit: retrieval of research documents, archiving.

- Transcription of the data in the observation booklet

The CRF will be developed by Clinical Research Unit (URC) Ouest in collaboration with the Study Coordinator. The data of the research will be entered directly by the participating physicians by means of a form accessible online or transcribed from the observation books by the Clinical Study Technicians (TEC) recruited and managed by the URC-EST for the centers of Ile-de-France and by the TEC of the centers in the provinces. These data will be centralized on a server of the University of Versailles Saint-Quentin.

The data management will be carried out by the Clinical Research Unit Ouest (URC Ouest).

All information required by the protocol must be provided in the CRF and an explanation given by the investigator for each missing data.

Clinical or para-clinical data should be transferred to the e.CRF as they are obtained.

The erroneous data detected on the e.CRF will be corrected by an investigator, who will have connected to the software with its access codes (username and password). These codes are strictly personal and confidential and are not disseminated to any third party; They help ensure data confidentiality and authenticate interventions. The access codes are associated with an electronic signature system which validates the data entered by the investigator. Each signature is time stamped and recorded in the audit trail of the search. The signed data cannot be modified, but the investigator can cancel his signature if he wants to correct a data. The cancellation of the signature is also subject to time-stamped recording.

The anonymity of the patients will be ensured by the maximum use of the numbers, the first letters of the surname and first name of the patient, on all the documents necessary for the research, or erasure by the appropriate means of the nominal data on the copies of the source documents, intended for the documentation of the search.

The file of the computerized data will be declared to the CNIL according to the procedure adapted to the case.

- Completeness of the inclusions

In order to assess the completeness of the inclusions, an audit will be carried out by randomly drawing one week in each center. A TEC and an investigating physician will visit

each center to assess the number of patients not included in this week by reviewing the emergency registry.