Impact of ICU Triage on Long-Term Mortality in Critically Ill Elderly Patients: A Cluster-Randomized Trial

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Summary

Background:
The decision to admit or not an elderly patient to the intensive care is complex. Scientific publications are not conclusive, the benefit of admission is not clear for elderly patients and practices seem variable between centers. From 2004 to 2007, we achieved the ICE-CUB 1 study (Intensive-Care Elderly Cub-Réa, PHRC AOR 03 035) in 15 healthcare centers in France. We studied the admission process to the intensive care unit (ICU) of elderly patients presenting to the Emergency Department (ED) with a reason for admission to the ICU and their outcomes at six months. The rate of proposal for ICU admission by emergency department physicians was 25% (Garrouste et al., Crit Care Med 2009). The admission rate to the ICU was 12% and varied from 5 to 38% between centers. After adjusting for individual characteristics, the rate of ICU admission remained extremely variable: risks of being admitted to the ICU were different according to centers (median OR 2.16; 95% 1.58-3.46). In addition, the study showed that a good baseline level of autonomy, a good nutritional status and the absence of cancer indicated a good prognosis at six months. It appears therefore that elderly patients with these characteristics are good candidates for ICU admission. However, such critically ill elderly patients in the emergency department who require resuscitation-specific organ support techniques (20% of ICE-CUB patients) are effectively admitted only in 23% of cases and 32% died within six months.

The Primary Objective is to determine whether an intervention based on recommendations for systematic ICU admission of critically ill elderly patients who requiring organ support measures and presenting factors of good prognosis significantly reduces the rate of death at six months compared to standard practices.

The secondary objectives are to evaluate the impact of the intervention on:

- Hospital mortality
- ICU admission rates ad their variability between centers
- Functional status (Index of ADL), quality of life (SF-12 Health Survey) and the caregiver burden (Zarit scale) at 6 months.

Study Type: Prospective interventional cluster-randomized trial
(Randomization unit = 1 center) stratified by the annual number of ED visits and the presence or absence of a continuous monitoring unit.

Inclusion criteria: patients 75 year or over, at least one organ insufficiency requiring organ support, a preserved functional status (assessed by an Index of ADL ≥ 4), a preserved nutritional status (assessed by the physician at bedside) and free of active cancer.

Exclusion criteria: refusal to participate.

Conduct of the study:
After stratification on the type of unit, the centers will be randomized into two groups: the control group (without modification of the standard practices) and the intervention group. The intervention will consist of:

- Set up a monthly meeting for emergency department and intensive care physicians to present the ICU admission recommendations for patients included and a follow-up of these patients,
- Publishing pamphlets and posters presenting admission recommendations,
- Publishing a newsletter with follow-up on inclusion and assessment of adherence to recommendations
- Formalize a case-by-case consultation between emergency physicians and resuscitators to decide whether or not to admit patients with the inclusion criteria.

- At inclusion, the patient's assessment will encompass: illness severity (SAPS3), cognitive status (TYM score) and chronic diseases (Charlson score). During the hospital stay, the information collected will concern the services attended, the length of stay and mortality. Patients alive at six months will be interviewed about their place of life, their functional status (Index of ADL), their quality of life (SF-12 Health Survey). The "burden" of informal caregivers of elderly patients living at home will also be assessed (ZARIT scale).

Sample size:
From date of the ICE-CUB 1 study, 32% of patients with the inclusion criteria of the ICE-CUB 2 study are dead at six months. We estimate that the intervention will reduce the mortality rate of 6%. In a one-sided type one error-rate of 5%, without considering the intracluster correlation coefficient, 704 patients per group are needed to demonstrate such a difference with a power of 80%. Cluster randomization imposes inflation dependent on intraclass correlation coefficient (ICC). With an ICC of 0.01, an average of 100 patients per center, a total of 2802 patients are required, which is expected to be reached in 2 years with 20 participating centers (extrapolation based on ICE-CUB data).

Total duration of the study: 3 years
Inclusion period: 2 years
Duration of participation for an individual patient: 6 months
Number of Healthcare Centers: 20

1. Background: the ICE-CUB 1 study

If there are guidelines for the admission of patients to the intensive care unit [1, 2], none of them takes into account the specific characteristics of the elderly patients. However, aside from the acute medical problem requiring hospitalization in intensive care, various dimensions of the health status of elderly individuals have a major influence on their prognosis in terms of mortality or functional autonomy[3]. This lack of clear guidelines for elderly patients and the fact that most elderly patients who are eligible for ICU admission may be discarded on first screening by a physician from another specialty (such as an emergency department physician) lead to significant disparities in the use of ICU in the elderly population.

In 2004-2007, with the help of PHRC funding (AOR 03 035), we conducted a first prospective study in 15 hospital centers in Ile-de-France on patients over 80 years of age, presenting to the emergency department with an indication of ICU admission, in order to determine the rate of ICU proposal by the emergency physicians, the final admission rate by intensive care physicians and to determine the criteria used by physicians to make their decisions.

The study was conducted in collaboration with the CUB-Réa network of intensive care of Ile de France, the URC-EST and the INSERM unit UMR S707. Under the responsibility of the URC-EST, clinical research assistants visited the centers once a week to monitor the inclusion (complete the observations of the clinicians, follow the hospital path of the patients included) but also distribute notebooks of observations and information sheets designed for the project in collaboration with the U707. 2646 patients were included in the study. An inclusion audit conducted at the initiative of the U707 demonstrated that 60% of the eligible patients were included in the study, which is extremely satisfactory given the difficulty to carry out prospective studies from overloaded emergency departments.

In this study, we were able to show that only 12% of the critically ill elderly patients (more than 80 years) in the emergency department are admitted to the ICU and this rate varied from 5 to 38% across centers. In a total of 8 patients included, only 2 are proposed to intensive care by emergency department physicians, and only one is finally admitted by the intensive care physicians[4]. 75% of elderly patients are not seen by an intensive care unit physician. So far, no study has been able to evaluate this number, since the triage carried out upstream of ICU admission by the emergency department physician was never taken into account in the international medical literature.

In addition, we were able to show that the decisions to admit elderly patients to the ICU, apart from the potential indication of admission, were based on age (OR/year 0.91, 95% CI 0.87-0.94), illness severity (OR/point score MPM0 1.77, 95% CI 1.51-2.08), patient's autonomy (OR/point ADL score 1.32, 95% CI 1.19-1.46), presence of active cancer (OR 0.60 95% CI 0.33-1.05), nutritional status (OR preserved nutritional status vs poor nutritional status: 0.42, 95%CI 0.20-0.82) and psychotropic drugs (OR 0.66, 95% CI 0.45-0.95).

After adjustments for all of these factors, the admission rate remained extremely variable (median OR 2.16, 95% CI 1.58-3.46). According to the emergency department in which an elderly patient consults, a patient does not have the same chance of being hospitalized in the ICU (article submitted).

Moreover, we also showed that a good baseline functional status, a good baseline nutritional status and the absence of cancer positively influenced the mortality at six months of all the candidates for the ICU admission, irrespective of the admission to the ICU (6-month mortality of 31% for individuals with these characteristics versus 62% for others). Approximately half (46%, n=1,227) of the patients in the ICE-CUB 1 study arrived to the emergency department with life-threatening conditions requiring the use of organ-support techniques specific to the ICU setting (Table 1).

204 **Table 1**. Critical conditions requiring organ support (data from the ICE-CUB 1
205 study).

	N	%	ICU Admission	Hospital Mortality	Mortality at 6 months
Cardiovascular					
Cardiogenic shock	44	3,6	25,0%	53,5%	70,4%
Hemorrhagic shock	12	1,0	66,7%	33,3%	66,7%
Acute hearth failure with mechanical ventilation or inotropic support	78	6,4	7,7%	18,0%	46,1%
Acute hearth failure with non-invasive ventilation	98	8,0	15,3%	25,5%	50,0%
Toxic					
Voluntary or involuntary drug intoxication	41	3,3	14,6%	5,0%	21,9%
Attempted suicide with neurologic disorders or lack of airway protection	9	0,7	22,2%	11,1%	22,2%
Surgical					
Perioperative hemodynamic or respiratory support or need for intensive monitoring	22	1,8	31,8%	40,9%	59,0%
Neurologic					
Central nervous system disorders or peripheral CNS disorder with disorder of consciousness or respiratory disorder	10	0,8	10,0%	60,0%	80,0%
Coma from intoxication	9	0,7	0,0%	44,4%	66,7%
Gastro-intestinal					
GI tract hemorrhage	57	4,6	21,0%	12,2%	33,3%
GI tract hemorrhage with circulatory collapse with coexisting diseases	31	2,5	25,8%	19,3%	35,4%
Pulmonary					
Acute respiratory failure with COPD	200	16,3	12,5%	18,0%	42,0%
Pulmonary embolism	84	6,8	9,5%	13,1%	25,0%
Acute respiratory failure with imminent tracheal intubation	30	2,4	30,0%	66,7%	76,7%
Acute respiratory failure with tracheal intubation	39	3,2	41,0%	56,4%	71,8%
Acute respiratory failure requiring non-invasive ventilation or active physiotherapy	85	6,9	22,3%	29,4%	50,6%
Severe pneumonia	136	11,1	19,8%	27,9%	51,5%
Others					
Septic shock	157	12,8	14,1%	58,5%	76,4%
Acute kidney failure with RRT	27	2,2	48,1%	33,3%	59,2%
Clinical and biologic					
Arterial pressure < 80 mmHg	58	4,7	8,6%	34,4%	56,8%
Total	*1227*		*17,9%*	*30,5%*	*51,3%*

More than 40% of these patients (n=560) had the good prognostic factors cited above. Such patients are probably as good candidates for ICU admission as younger patients. Of these patients, only 23% were actually admitted to the ICU, ranging from 8% to 53% across centers. The refusal to admit to "good candidates" resulted in a significant loss of chance.

This study, and in particular the results cited above, motivated the proposal of a new randomized prospective multicenter study aimed at establishing whether an intervention in hospitals based on recommendations for systematic ICU admission of critically ill elderly patients with factors of good prognosis (preserved baseline functional status, preserved nutritional status and free of cancer) and the organization of coordinated decisions between emergency department and intensive care physicians for each of these patients, allows to improve prognosis at six months, by increasing their chances of being admitted to the ICU.

In this study, it will be necessary to evaluate two strategies for organizing hospitals: one called «Standard Practice» (SP: the organization of the center does not change) versus a strategy of «Recommandations for the Systematic Admission of good candidates» (RSA: Recommendations for systematic ICU admissions of all good candidates), monthly information meetings, follow-up and discussion of inclusions with physicians participating to the study, concerted emergency / resuscitation decisions for all patients included). The objective is to assess whether the RSA strategy reduces mortality at six months of elderly patients in life-threatening emergencies with good prognostic factors.

2. Literature review

The international medical literature documents the rationing of health care according to the age of the patients[3,5-8]. The intensive care units account for a large part of total hospital expenditures and are under significant pressure. There are few studies on the patient process for hospitalization to the intensive care[9-18], and only two specifically concern elderly patients[4,18]. Finally, the ICE-CUB 1[4] (cited above) is the only study that correctly estimates the very low ICU admission rate of eligible elderly patients, with no other considering screening performed before and ICU admission.

Most studies show that high age is associated with refusal of admission to the intensive care unit [9,12,15,16].

For ethical and methodological reasons, there are few studies evaluating the benefit of ICU admission, especially in the elderly patients: the randomization of ICU admission is ethically questionable. The disparity of clinical situations and the heterogeneity of the patients admitted extraordinarily complicate the possible analyzes. A study of a group of eligible patients hospitalized outside of the ICU due to lack ICU bed demonstrated a benefit from ICU admission on survival at three days, but could not conclude about the effect of ICU admission on survival at 30 days[19]. In this context, the expected benefit for the elderly may appear low and disadvantage their admission. Moreover, there are no specific recommendations for the elderly, leaving the decisions entirely to the individual judgment of the physician. Concerns about the appropriate use of ICU are increasing, particularly at the end of life[20-22]. It seems essential to assess the consequences of ICU admissions and refusals of ICU admission in the elderly population.

So far, the dimensions to be taken into account for a comprehensive assessment of the elderly are widely described in the literature (the consequences of a health problem can be aggravated by social problems or geriatric symptoms[23], such as falls, reduced mobility, loss of appetite or weight, and general fragility[24]).

Variables that have a positive effect on the survival of elderly hospital patients are also well documented[25] and similar to the variables associated with the long-term good prognosis in the ICE-CUB 1 study (see above, data not yet published). It is therefore possible to identify a group of elderly patients with a good prognosis in a situation that justifies the specificity of resuscitation care and for which refusal of admission could be detrimental.

Objectives

The primary objective is to determine whether an intervention based on recommendations for systematic ICU admission of critically ill elderly patients who requiring organ support measures and presenting factors of good prognosis significantly reduces the rate of death at six months compared to standard practices.

The secondary objectives are to evaluate the impact of the intervention on:

- Hospital mortality
- ICU admission rates and their variability between centers
- Functional status, quality of life and the caregiver burden at 6 months.

3. Outcome measures

3.1 Primary outcome

Mortality rate at 6 months after admission to the emergency department.

3.2 Secondary outcomes

- Hospital mortality
- ICU admission rate
- Decrease in functional status at 6 months (loss of autonomy in one dimension of the Index of ADL)
- Quality of life at 6 months (assessed by the SF-12 Health Survey)
- Institutionalization
- Caregiver burden at 6 months (assessed by the ZARIT scale).

4. Study design

4.1 Cluster-randomized controlled trial

As randomization of ICU is not feasible, we will test the application of a strategy to encourage the systematic ICU admission of "good candidates" to the hospital as a whole (ED and ICU). By stratified randomization taking into account the number of annual emergency visits and the presence of a continuous monitoring unit, each center will be assigned a strategy, either systematic admission recommendations for patients included, or without modification of current practice. The results observed will of course have to take account of the particularities of recruitment of the different services, resulting in great disparities in the populations of corresponding patients. Patients will be included consecutively and for each strategy. We will assess whether the admission strategy influences the admission of all elderly patients, even those not included in the study. It should be emphasized that whatever the strategy implemented in a center, the final decision of ICU admission of patient included will belong to the local medical team. Randomization will be managed by the INSERM UMR S-707 unit.

4.2 Inclusion criteria

Patients aged 75 years or over, at least one critical condition requiring organ support, a preserved baseline functional status (assessed by an Index of ADL ≥4), preserved baseline nutritional status (as assessed by the physician at bedside) and free of active cancer.

4.3 Exclusion criteria

Refusal to participate.

4.4 Inclusion criteria for centers

Voluntary centers with joint acceptance of the emergency department the intensive care unit were allowed to participate in the ICE-CUB 2 study protocol. The centers are located throughout France. Recruitment of the centers was favored by the physicians of the scientific committee: B Guidet; president of the French Society of Intensive care (SRLF), D Pateron; president of the French Society of Emergency Medicine (SFMU) and the solicitation of the ICU of Ile de France belonging to the Cub-Réa network, who participated in the ICE-CUB I study protocol. Of course, all participating departments will have to accept the

principle of implementing the intervention in their department and collecting information for all patients with inclusion criteria.

5. Conduct of the study

5.1 Implementation of the intervention and control strategies

The centers will be randomized into two groups (taking into account the size of the emergency department and the presence of a monitoring unit): the control group (without modification of the usual practices, SP) and the intervention group (RSA).

5.2 Definition and implementing of the intervention

In the intervention group (RSA), specific follow up the patients included will be performed in a monthly basis.

The RSA centers will be open by a physician belonging to the steering committee: a summary of the study, inclusion criteria and the observation booklet will be presented. Recommendations for systematic admissions will be detailed and justified. The first meeting will also present and discuss the modalities of implementation of the intervention. The objective of the intervention is therefore to encourage the physicians in the centers to admit any patient with the inclusion criteria in the intensive care unit. It will consist of: organize monthly meeting for emergency department and intensive care physicians facilitated by the clinical study physicians. Recommendations for ICU admission will be presented each month to all emergency and intensive care physicians, the inclusions and the course of the patients included will be discussed.

- Edit a newsletter on the adequacy of practices to systematic admission recommendations
- Publish booklets and posters presenting the recommendations for ICU admission of included patients.
- Organize a consultation between emergency and intensive care physicians and to decide whether or not to admit patients with the inclusion criteria. The emergency department physician including a patient in the study systematically calls the attending intensive care unit physician. The

intensive care unit physician evaluates the patient at bedside. The emergency and intensive care unit physician and jointly decide whether or not to admit the patient to the ICU, based in particular on the information collected for the study.

Note: In the SP group, centers recruitment and opening will usually be attended by a clinical research assistant (CRA).

5.3 Note on the general functioning on the departments

The intervention will apply to all included patients. The randomization for ICU admission at the individual patient level, although probably ethical in the absence of demonstrated benefit, seems extremely difficult and delicate to implement. We therefore decided to test a strategy of recommendation for a systematic ICU admission, encouraged by meetings of information allowing a follow-up and discussion on inclusions with an "expert" physician. We will evaluate the mortality rate, considering that the strategy is applied at the hospital level. It is therefore a question of evaluating the effectiveness of the response of the hospital to a request for admission of elderly patient identified as "good candidates" for ICU admission rather than the effectiveness of an ICU stay per se. It should also be noted that, regardless of the strategy applied, the final decision to admit or not an included patient belongs to the local medical team.

5.4 Data collection

A first part of the data concerns the general state of the patient and the process leading to the admission or refusal to the intensive care unit: date and time of arrival in the emergency department, age, sex, main diagnosis, SAPS3 score[26, 27], cognitive status (TYM score), functional status (Index of ADL), chronic diseases, place of life (home, institution, other), lifestyle (alone, couple, with other relatives), patient wishes about ICU admission, wishes of the family for ICU admission, number of ICU-beds available, emergency department and intensive care physicians opinion about ICU admission, date and time of the decision for ICU admission, the department in which the patient is transferred, date and time of transfer. We have attached particular importance to a collection of data that is simple so as not to burden the operation of the service. It should be noted, however, that the assessment of the health of the elderly is necessarily multidimensional (see III) and probably more complex than that of younger patients. It is known in particular that the different dimensions to be taken into account interact on the vital and functional prognosis. We will pay particular attention to taking into account the patient’s wishes and the evaluation of the number of ICU-bed available. Observations

made by participating physicians may be supplemented by clinical study technicians (TECs) as appropriate.

A second part concerns the patient's pathway during the whole hospitalization and can be completed by the TECs: details of the hospital route for the first three department visited, date and mode of discharge from the hospital, date of possible death during the hospital stay. Patients transferred to the ICU in a different center than the ED visited will not be included in the study. However, the results of the ICE-CUB 1 study indicate that this case is unlikely, since no patient presenting the inclusion criteria for the ICE-CUB 2 trial was transferred to another hospital immediately after being evaluated in the emergency department.

Finally, a third part concerns the outcome of the patients six months after inclusion in the emergency department, this data will also be collected by the TECs by phone calls: place and way of life, functional status (Index of ADL), quality of life (SF-12 Health Survey[28]), hospitalization in the previous six months. The burden of care for caregivers of elderly patients living at home will also be assessed (ZARIT scale).

5.5 Duration of the research

- Duration of participation for an individual patient: 6 months
- Inclusion period: 2 years
- Total duration of the study: 3 years

5.6 Definitive or temporary termination rules

5.6.1 Of the patient’s participation to the research

The patient can withdraw consent at any time for participation in this research.

6. Safety Assessment

6.1 Description of Safety Assessment Parameters

6.1.1 Adverses events

Any harmful events occurring in a person who participate to a research, whether this manifestation is linked or not to the research or the product studied.

6.1.2 Serious Adverses Events

Any event or adverse event that results in death, endangers the life of the person who participate to a research, requires hospitalization or prolongation of hospitalization, causes significant or lasting disability or handicap, or results in an anomaly or a congenital malformation.

6.1.3 New Fact

Any new safety data, which may lead to a reassessment of the benefits and risks to participate to the research.

No serious adverse events are expected in this research

6.2 Specific Research Committees

A steering committee will be composed of the clinicians initiators of the project (B Guidet and M Garrouste - ICU, D Pateron - ED, C Thomas - geriatric, of the biostatistician in charge of the project, representatives of the manager and URC-EST.

It will define the general organization and conduct of the research and coordinate the information.

It will initially determine the methodology and decide in the course of research how to behave in unforeseen cases, monitor the progress of the research in particular with regard to tolerance and adverse events.

The steering committee will monitor patient inclusions and referrals in the intervention group.

7. Statistical Analyses

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).

7.1 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).

7.2 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.

7.3 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.

7.4 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.

8. 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.

9. 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.

9.1 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.

9.2 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 eCRF as they are obtained.

The erroneous data detected on the eCRF 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 timestamped 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.

9.3 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.

10. Legal and ethical aspects

L'Assistance Publique des Hôpitaux de Paris (AP-HP) is the manager of this research in accordance with the second paragraph of Article L.1121-1 of the Code of Public Health. The Department of Clinical Research and Development (DRCD) is its representative.

Before starting the search, each physician coordinator will provide the Research Manager's representative with a copy of his / her dated and signed personal resume, including his or her registration number and the ADELI number.

10.1 Legal Obligations

- **Role of the sponsor**

The sponsor is responsible for registering the study with the French Agency for the Safety of Health Products and submits the file to the opinion of the Protection Committee (chosen by the manager).

- **Submission to the CPP (Committee for the Protection of People)**

The opinion of this Committee is notified in the information sheet given to the persons concerned.

- **CNIL Declaration (National Committee on Information and Liberties)**

This research is subject to the law of 6 January 1978 relating to data processing, files and freedoms, as amended.

Before its beginning, the processing of the data collected in the research is subordinated to the Advisory Committee on the Treatment of Information in the field of Health Research (CCTIRS) and then the National Committee of Information and Liberties (CNIL). The research will be the subject of a unit statement.

Information on the rights of persons participating in this research is included in the information note.

10.2 Substantial amendment to the protocol

The DRCD must be informed of any plans to modify the protocol by the coordinating physician. Amendments should be qualified as substantial or not.

A substantive change is an amendment that may in one way or another modify the guarantees provided to included patients (change of an inclusion criteria, extension of the inclusion period, participation of new centers, etc.).

After to the beginning of the research, any substantial modification at the initiative of the manager must obtain, prior to its implementation, a favorable opinion from the CPP. In this case, if necessary, the committee ensures that new

consent is obtained from the persons participating in the research. (if a consent form is provided in the protocol)

10.3 Information Sheet and Informed Consent

An information sheet will be distributed to participating patients, summarizing the objective of the research, detailing the follow-up at six months and including a paragraph describing how to exercise the right of access.

10.4 Final Research Report

The final research report will be co-authored by the coordinator, the scientific officer and the biostatistician for this research. This report will be submitted to each of the investigators for opinion. Once a consensus has been reached, the final version must be endorsed by signature of each investigator and sent to the manager as soon as possible after the effective completion of the research. A report drawn up in accordance with the competent authority's reference plan shall be sent to the competent authority and to the PPC within one year after the end of the search, as defined as the last visit of the last included patient. This period would be 90 days if the research is stopped prematurely.

11. Data processing and retention of documents and data

The specific documents of a research in acute care will be archived by the investigator after the end of the research until 2 years after the publication. This indexed archive comprises:

- The successive versions of the protocol (identified by the number and version date),
- The mandatory notice of the CPP
- Correspondence,
- The list or register of inclusion,
- The data collection form
- All annexes specific to the research,
- The final report of the research.

The database that gave rise to the statistical analysis must also be archived by the analyst (paper or computer).

All related documents will be archived by the principal investigator for 15 years after completion of the study. These are the protocol, the possible amendments and the consents of the patients. No movement or destruction may be made without the agreement of the study sponsor.

12. Scientific commitment

Each investigator will undertake to respect the obligations of the law and carry out the research according to the B.P.C., in accordance with the terms of the declaration of Helsinki in force. To do so, a copy of the scientific commitment (document type DRCD) dated and signed by each investigator of each clinical service of a participating center will be given to the representative of the manager.

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