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

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Principal investigator:

Bertrand Guidet MD

Head of intensive care unit

Saint-Antoine Hospital, 184 Faubourg Saint-Antoine Street, Paris, Cedex 12

Phone: 0149282319 / Fax: 0149282692

Email: bertrand.guidet@sat.aphp.fr

Associated Research Team:

Methods and Analysis : INSERM UMR S 707

Pierre et Marie Curie Faculty of Medicine

Saint-Antoine Hospital, 27 rue Chaligny, 75571 Paris, Cedex 12

Phone: +33 (0)1 44 73 84 45 / Fax: +33 (0)1 44 73 84 62

Coordination, Monitoring: URCEST, Pr Tabassome Simon

184, Faubourg Saint-Antoine Street, 75971 Paris, cedex 12

Phone: 01 49 28 22 02 / Fax: 01 49 28 28 13

Email: urcest@chusa.jussieu.fr

Sponsor: Assistance Publique- Hôpitaux de Paris (AP-HP)

Department Clinical Research and Development (DRCD)

Carré Historique, Saint-Louis Hospital, 1 Claude Vellefaux Avenue, 75010 Paris

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60 **Summary**61
62 **Background:**

63 The decision to admit or not an elderly patient to the intensive care is complex. Scientific
64 publications are not conclusive, the benefit of admission is not clear for elderly patients
65 and practices seem variable between centers. From 2004 to 2007, we achieved the ICE-
66 CUB 1 study (Intensive-Care Elderly Cub-Réa, PHRC AOR 03 035) in 15 healthcare
67 centers in France. We studied the admission process to the intensive care unit (ICU) of
68 elderly patients presenting to the Emergency Department (ED) with a reason for
69 admission to the ICU and their outcomes at six months. The rate of proposal for ICU
70 admission by emergency department physicians was 25% (Garrouste et al., Crit Care
71 Med 2009). The admission rate to the ICU was 12% and varied from 5 to 38% between
72 centers. After adjusting for individual characteristics, the rate of ICU admission remained
73 extremely variable: risks of being admitted to the ICU were different according to centers
74 (median OR 2.16; 95% 1.58-3.46). In addition, the study showed that a good baseline
75 level of autonomy, a good nutritional status and the absence of cancer indicated a good
76 prognosis at six months. It appears therefore that elderly patients with these
77 characteristics are good candidates for ICU admission. However, such critically ill elderly
78 patients in the emergency department who require resuscitation-specific organ support
79 techniques (20% of ICE-CUB patients) are effectively admitted only in 23% of cases and
80 32% died within six months.

81
82 **The Primary Objective** is to determine whether an intervention based on
83 recommendations for systematic ICU admission of critically ill elderly patients who
84 requiring organ support measures and presenting factors of good prognosis significantly
85 reduces the rate of death at six months compared to standard practices.

86
87 **The secondary objectives** are to evaluate the impact of the intervention on:

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

92
93 **Study Type: Prospective interventional cluster-randomized trial**

94 (Randomization unit = 1 center) stratified by the annual number of ED visits and the
95 presence or absence of a continuous monitoring unit.

96
97 **Inclusion criteria:** patients 75 year or over, at least one organ insufficiency requiring
98 organ support, a preserved functional status (assessed by an Index of ADL ≥ 4), a
99 preserved nutritional status (assessed by the physician at bedside) and free of active
100 cancer.

101
102 **Exclusion criteria:** refusal to participate.

103
104 **Conduct of the study:**

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

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

116

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

124

125 **Sample size:**

126 From date of the ICE-CUB 1 study, 32% of patients with the inclusion criteria of the ICE-
127 CUB 2 study are dead at six months. We estimate that the intervention will reduce the
128 mortality rate of 6%. In a one-sided type one error-rate of 5%, without considering the
129 intracluster correlation coefficient, 704 patients per group are needed to demonstrate
130 such a difference with a power of 80%. Cluster randomization imposes inflation
131 dependent on intraclass correlation coefficient (ICC). With an ICC of 0.01, an average of
132 100 patients per center, a total of 2802 patients are required, which is expected to be
133 reached in 2 years with 20 participating centers (extrapolation based on ICE-CUB data).

134

135 **Total duration of the study:** 3 years

136 **Inclusion period:** 2 years

137 **Duration of participation for an individual patient:** 6 months

138 **Number of Healthcare Centers:** 20

139

140 **1.** Background: the ICE-CUB 1 study

141

142 If there are guidelines for the admission of patients to the intensive care
143 unit ^{1, 2}, none of them takes into account the specific characteristics of the elderly
144 patients. However, aside from the acute medical problem requiring
145 hospitalization in intensive care, various dimensions of the health status of
146 elderly individuals have a major influence on their prognosis in terms of mortality
147 or functional autonomy³. This lack of clear guidelines for elderly patients and the
148 fact that most elderly patients who are eligible for ICU admission may be
149 discarded on first screening by a physician from another specialty (such as an
150 emergency department physician) lead to significant disparities in the use of ICU
151 in the elderly population.

152

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

159

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

171

172

173 In this study, we were able to show that only 12% of the critically ill elderly
174 patients (more than 80 years) in the emergency department are admitted to the
175 ICU and this rate varied from 5 to 38% across centers. In a total of 8 patients
176 included, only 2 are proposed to intensive care by emergency department
177 physicians, and only one is finally admitted by the intensive care physicians⁴.
178 75% of elderly patients are not seen by an intensive care unit physician. So far,
179 no study has been able to evaluate this number, since the triage carried out
180 upstream of ICU admission by the emergency department physician was never
181 taken into account in the international medical literature.

182

183 In addition, we were able to show that the decisions to admit elderly patients to
184 the ICU, apart from the potential indication of admission, were based on age
185 (OR/year 0.91, 95% CI 0.87-0.94), illness severity (OR/point score MPM0 1.77,
186 95% CI 1.51-2.08), patient's autonomy (OR/point ADL score 1.32, 95% CI 1.19-
187 1.46), presence of active cancer (OR 0.60 95% CI 0.33-1.05), nutritional status
188 (OR preserved nutritional status vs poor nutritional status: 0.42, 95%CI 0.20-
189 0.82) and psychotropic drugs (OR 0.66, 95% CI 0.45-0.95).

190

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

195

196 Moreover, we also showed that a good baseline functional status, a good baseline
197 nutritional status and the absence of cancer positively influenced the mortality at
198 six months of all the candidates for the ICU admission, irrespective of the
199 admission to the ICU (6-month mortality of 31% for individuals with these
200 characteristics versus 62% for others). Approximately half (46%, n=1,227) of
201 the patients in the ICE-CUB 1 study arrived to the emergency department with
202 life-threatening conditions requiring the use of organ-support techniques specific
203 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%
<i>Total</i>	<i>1227</i>		<i>17,9%</i>	<i>30,5%</i>	<i>51,3%</i>

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

211

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

221

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

231

232

233

234

235 **2.** Literature review

236

237 The international medical literature documents the rationing of health care
238 according to the age of the patients^{3,5-8}. The intensive care units account for a
239 large part of total hospital expenditures and are under significant pressure. There
240 are few studies on the patient process for hospitalization to the intensive care⁹⁻¹⁸,
241 and only two specifically concern elderly patients^{4,18}. Finally, the ICE-CUB 1⁴
242 (cited above) is the only study that correctly estimates the very low ICU
243 admission rate of eligible elderly patients, with no other considering screening
244 performed before and ICU admission.

245

246 Most studies show that high age is associated with refusal of admission to
247 the intensive care unit^{9,12,15,16}.

248

249 For ethical and methodological reasons, there are few studies evaluating
250 the benefit of ICU admission, especially in the elderly patients: the randomization
251 of ICU admission is ethically questionable. The disparity of clinical situations and
252 the heterogeneity of the patients admitted extraordinarily complicate the possible
253 analyzes. A study of a group of eligible patients hospitalized outside of the ICU
254 due to lack ICU bed demonstrated a benefit from ICU admission on survival at
255 three days, but could not conclude about the effect of ICU admission on survival
256 at 30 days¹⁹. In this context, the expected benefit for the elderly may appear low
257 and disadvantage their admission. Moreover, there are no specific
258 recommendations for the elderly, leaving the decisions entirely to the individual
259 judgment of the physician. Concerns about the appropriate use of ICU are
260 increasing, particularly at the end of life²⁰⁻²². It seems essential to assess the
261 consequences of ICU admissions and refusals of ICU admission in the elderly
262 population.

263

264 So far, the dimensions to be taken into account for a comprehensive
265 assessment of the elderly are widely described in the literature (the
266 consequences of a health problem can be aggravated by social problems or
267 geriatric symptoms²³, such as falls, reduced mobility, loss of appetite or weight,
268 and general fragility²⁴).

269

270 Variables that have a positive effect on the survival of elderly hospital
271 patients are also well documented²⁵ and similar to the variables associated with
272 the long-term good prognosis in the ICE-CUB 1 study (see above, data not yet
273 published). It is therefore possible to identify a group of elderly patients with a
274 good prognosis in a situation that justifies the specificity of resuscitation care and
275 for which refusal of admission could be detrimental.

276

277 Objectives

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

283

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

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

288 **3.** Outcome measures

289 3.1 Primary outcome

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

291 3.2 Secondary outcomes

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

299

300 **4.** Study design

301 4.1 Cluster-randomized controlled trial

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

317 4.2 Inclusion criteria

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

322 4.3 Exclusion criteria

323 Refusal to participate.

324 4.4 Inclusion criteria for centers

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

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

335 **5.** Conduct of the study

336

337 5.1 Implementation of the intervention and control strategies

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

342 5.2 Definition and implementing of the intervention

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

345

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

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

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

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

372 5.3 Note on the general functioning on the departments

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

385 5.4 Data collection

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

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

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

411 Finally, a third part concerns the outcome of the patients six months after
412 inclusion in the emergency department, this data will also be collected by the TECs by
413 phone calls: place and way of life, functional status (Index of ADL), quality of life (SF-12
414 Health Survey²⁸), hospitalization in the previous six months. The burden of care for
415 caregivers of elderly patients living at home will also be assessed (ZARIT scale).

416 5.5 Duration of the research

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

420

421 5.6 Definitive or temporary termination rules

422 5.6.1 Of the patient's participation to the research

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

424

425 **6.** Safety Assessment

426 6.1 Description of Safety Assessment Parameters

427 6.1.1 Adverses events

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

430 6.1.2 Serious Adverses Events

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

435 6.1.3 New Fact

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

438 **No serious adverse events are expected in this research**

439 6.2 Specific Research Committees

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

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

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

448

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

451

452 **7.** Statistical Analyses

453

454 **1. Database**

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

461 7.1 Statistical analysis

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

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

469

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

475

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

480

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

486 7.2 Sample Size Calculation

487 Based on the results of the ICE-CUB 1 study, 32% of patients die within six
488 months of the emergency department visit. We hypothesize that the mortality of
489 patients over 75 years of age will be equivalent and that the proposed
490 intervention will reduce mortality by 6% at six months. In a unilateral situation,
491 with a type one error rate of 5%, without taking into account the cluster effect,
492 704 patients per group are necessary to demonstrate such a difference with a
493 power of 80%. Cluster randomization imposes inflation dependent on intraclass
494 correlation coefficient (ICC). With an ICC at 0.01, an average of 100 patients per
495 center, a total of 2802 patients are required.

496

497 Based on the data from the ICE-CUB 1 study, 560 patients over 80 years of age
498 with factors of good prognostic and a critical conditions requiring organ support
499 were admitted to the emergency department of 15 centers over a 1-year period.

500 It is assumed that $560 \times 1.5 = 840$ patients over the age of 75 with the same
501 characteristics, with an average of 56 patients per center per year. Thus, it is
502 estimated that the number of subjects needed ($n=2802$) can be reached in 2
503 years with 20 participating centers.

504 7.3 Management of the missing, unused or invalid data

505 The management of the missing data will be carried out according to the
506 complexity and the frequency of the situations. The MCAR or MAR character will
507 be evaluated according to the Little & Rubin classification (Statistical Analysis
508 with Missing data, Wiley 1987). If the proportion of missing data is less than
509 0.05, a simple imputation will be used, otherwise a multiple imputation will be
510 performed. A sensitivity analysis will be carried out if the proportion is very high.

511 7.4 Management of modifications to the initial strategy analysis plan

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

515 **8.** Access to data and source documents

516 Persons with direct access in accordance with the applicable laws and
517 regulations, in particular Articles L.1121-3 and R.5121-13 of the Public Health
518 Code (investigators, quality control persons, monitors, clinical research
519 assistants, auditors and others involved in research) shall take all necessary
520 precautions to ensure the confidentiality of information relating to investigational
521 medicinal products, tests, appropriate persons and particularly as regards their
522 identity and the results obtained. The data collected by these persons during the
523 quality control or audits are then made anonymous.

524 **9.** Quality Control and Quality Assurance

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

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

529 9.1 Monitoring Procedures

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

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

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

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

541 Compliance with protocol and defined procedures for research,

542 Verification of informed consent of patient

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

546 Closure visit: retrieval of research documents, archiving.

547 9.2 Transcription of the data in the observation booklet

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

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

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

559 Clinical or para-clinical data should be transferred to the eCRF as they are
560 obtained.

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

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

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

578 9.3 Completeness of the inclusions

579 In order to assess the completeness of the inclusions, an audit will be carried out
580 by randomly drawing one week in each center. A TEC and an investigating
581 physician will visit each center to assess the number of patients not included in
582 this week by reviewing the emergency registry.

583 **10.** Legal and ethical aspects

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

588

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

592 10.1 Legal Obligations

593 - **Role of the sponsor**

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

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

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

600 - **CNIL Declaration (National Committee on Information and 601 Liberties)**

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

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

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

611 10.2 Substantial amendment to the protocol

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

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

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

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

622 10.3 Information Sheet and Informed Consent

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

626 10.4 Final Research Report

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

636 **11.** Data processing and retention of documents and data

637 The specific documents of a research in acute care will be archived by the
638 investigator after the end of the research until 2 years after the publication.

639 This indexed archive comprises:

640 ●The successive versions of the protocol (identified by the number and
641 version date),

642 ●The mandatory notice of the CPP

643 ●Correspondence,

644 ●The list or register of inclusion,

645 ●The data collection form

646 ●All annexes specific to the research,

647 ●The final report of the research.

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

650

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

655 **12.** Scientific commitment

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

662

663 **13.** References

664

- 665 1. Consensus statement on the triage of critically ill patients. Society of
666 Critical Care Medicine Ethics Committee. *Journal of the American Medical*
667 *Association* 1994;271(15):1200-3.
- 668 2. Guidelines for intensive care unit admission, discharge, and triage. Task
669 Force of the American College of Critical Care Medicine, Society of Critical Care
670 Medicine. *Critical Care Medicine* 1999;27(3):633-8.
- 671 3. Boumendil A, Somme D, Garrouste-Orgeas M, Guidet B. Should elderly
672 patients be admitted to the intensive care unit? *Intensive Care Med*
673 2007;33(7):1252-62.
- 674 4. Garrouste-Orgeas M, Boumendil A, Pateron D, et al. Selection of ICU
675 Admission Criteria for Patients Aged 80 Years and Over and Compliance of
676 Emergency and ICU Physicians with the Selected Criteria: An Observational
677 Multicenter Prospective Study. *Crit Care Med* 2009;37(11):2919-28.
- 678 5. Boumendil A, Aegerter P, Guidet B. Treatment intensity and outcome of
679 patients aged 80 and older in intensive care units: a multicenter matched-cohort
680 study. *J Am Geriatr Soc* 2005;53(1):88-93.

- 681 6. Fairhead JF, Rothwell PM. Underinvestigation and undertreatment of
682 carotid disease in elderly patients with transient ischaemic attack and stroke:
683 comparative population based study. *Bmj* 2006;333(7567):525-7.
- 684 7. van Delden JJ, Vrakking AM, van der Heide A, van der Maas PJ. Medical
685 decision making in scarcity situations. *J Med Ethics* 2004;30(2):207-11.
- 686 8. Brockmann H. Why is less money spent on health care for the elderly than
687 for the rest of the population? Health care rationing in German hospitals. *Soc Sci*
688 *Med* 2002;55(4):593-608.
- 689 9. Azoulay E, Pochard F, Chevret S, et al. Compliance with triage to intensive
690 care recommendations. *Critical Care Medicine* 2001;29(11):2132-6.
- 691 10. Garrouste-Orgeas M, Montuclard L, Timsit JF, Misset B, Christias M, Carlet
692 J. Triage patients to the ICU: a pilot study of factors influencing admission
693 decisions and patient outcomes. *Intensive Care Medicine* 2003;29(5):774-81.
- 694 11. Garrouste-Orgeas M, Montuclard L, Timsit JF, et al. Predictors of intensive
695 care unit refusal in French intensive care units: a multiple-center study. *Crit Care*
696 *Med* 2005;33(4):750-5.
- 697 12. Joynt GM, Gomersall CD, Tan P, Lee A, Cheng CA, Wong EL. Prospective
698 evaluation of patients refused admission to an intensive care unit: triage, futility
699 and outcome. *Intensive Care Medicine* 2001;27(9):1459-65.
- 700 13. Metcalfe MA, Slogget A, McPherson K. Mortality among appropriately
701 referred patients refused admission to intensive-care units. *Lancet*
702 1997;350(9070):7-11.
- 703 14. Sprung CL, Eidelman. Triage decisions for intensive care in terminally ill
704 patients. *Intensive Care Med* 1997;23(10):1011-4.
- 705 15. Sprung CL, Geber D, Eidelman LA, et al. Evaluation of triage decisions for
706 intensive care admission. *Critical Care Medicine* 1999;27(6):1073-9.
- 707 16. Frischo-Lima P, Gurman G, Schapira A, Porath A. Rationing critical care --
708 what happens to patients who are not admitted? *Theor Surg* 1994;9(4):208-11.
- 709 17. Thiery G, Azoulay E, Darmon M, et al. Outcome of cancer patients
710 considered for intensive care unit admission: a hospital-wide prospective study. *J*
711 *Clin Oncol* 2005;23(19):4406-13.
- 712 18. Garrouste-Orgeas M, Timsit JF, Montuclard L, et al. Decision-making
713 process, outcome, and 1-year quality of life of octogenarians referred for
714 intensive care unit admission. *Intensive Care Med* 2006;32(7):1045-51.

- 715 19. Simchen E, Sprung CL, Galai N, et al. Survival of critically ill patients
716 hospitalized in and out of intensive care units under paucity of intensive care unit
717 beds. *Crit Care Med* 2004;32(8):1654-61.
- 718 20. Angus DC, Barnato AE, Linde-Zwirble WT, et al. Use of intensive care at
719 the end of life in the United States: an epidemiologic study. *Crit Care Med*
720 2004;32(3):638-43.
- 721 21. Barnato AE, McClellan MB, Kagay CR, Garber AM. Trends in inpatient
722 treatment intensity among Medicare beneficiaries at the end of life. *Health Serv*
723 *Res* 2004;39(2):363-75.
- 724 22. Sharma G, Freeman J, Zhang D, Goodwin JS. Trends in End-of-Life ICU
725 Use Among Older Adults With Advanced Lung Cancer. *Chest* 2008;133(1):72-8.
- 726 23. Fried LP. Epidemiology of aging. *Epidemiol Rev* 2000;22(1):95-106.
- 727 24. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for
728 a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56(3):M146-56.
- 729 25. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a
730 prognostic index for 1-year mortality in older adults after hospitalization. *JAMA*
731 2001;285(23):2987-94.
- 732 26. Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3--From evaluation of the
733 patient to evaluation of the intensive care unit. Part 1: Objectives, methods and
734 cohort description. *Intensive Care Med* 2005;31(10):1336-44.
- 735 27. Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3--From evaluation of the
736 patient to evaluation of the intensive care unit. Part 2: Development of a
737 prognostic model for hospital mortality at ICU admission. *Intensive Care Med*
738 2005;31(10):1345-55.
- 739 28. Haywood KL, Garratt AM, Fitzpatrick R. Quality of life in older people: a
740 structured review of generic self-assessed health instruments. *Qual Life Res*
741 2005;14(7):1651-68.
- 742
- 743