Supplemental Online Content


**Trial protocol**

**Statistical analysis plan**

This supplemental material has been provided by the authors to give readers additional information about their work.
Early and comprehensive care bundle in elderly for acute heart failure: a stepped wedge cluster randomized trial

ELISABETH

MINIMAL RISKS AND CONSTRAINTS HUMAN RESEARCH STUDY

Version N°5.0 of 14/06/2019
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MINIMAL RISKS AND CONSTRAINTS HUMAN RESEARCH STUDY

Title: Early and comprehensive care bundle in elderly for acute heart failure:
a stepped wedge cluster randomized trial-ELISABETH

Version N°5-0 of 14/06/2019

The research is carried out in accordance with the current version of the protocol, with GCP and
with all statutory and regulatory requirements.

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Date: 28/8/2019
Signature:

Sponsor
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Date: 03 SEP. 2019
Signature:

The study was approved by the CPP of "SUD-OUEST & OUTRE-MER II" on 07 September 2016.
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## SUMMARY

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<th>Full title</th>
<th>Early and comprehensive care bundle in elderly for acute heart failure: the ELISABETH stepped wedge cluster randomized trial</th>
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<tr>
<td>Acronym</td>
<td>Elisabeth</td>
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<tr>
<td>Coordinating Investigator</td>
<td>Yonathan FREUND</td>
</tr>
<tr>
<td>Scientific Director</td>
<td>Alexandre MEBAZAA</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Assistance Publique-Hôpitaux de Paris</td>
</tr>
<tr>
<td>Scientific justification</td>
<td>Acute heart failure (AHF) is one of the most common diagnoses for elderly patients in the emergency department (ED), with an admission rate higher than 80% and 1-month mortality around 10%. There is scarce evidence of any clinical added value of a specific treatment to improve outcomes, and European guidelines for the management of AHF are based on moderate levels of evidence, due to the lack of randomized controlled trials. Recent reports suggest that the very early administration of full recommended therapy may decrease mortality. However, several studies highlighted that elderly patients often received suboptimal treatment: For example, less than a third of them received nitrates therapy while it is recommended. Furthermore, a recent preliminary study reported that only 50% of them are assessed for precipitating factors – although it has been reported that precipitating factors are independently associated with mortality. Our hypothesis is that an early care bundle that comprises early and comprehensive management of symptoms, along with prompt detection and treatment of precipitating factors should improve AHF outcome in elderly patients.</td>
</tr>
<tr>
<td>Main objective and primary endpoint</td>
<td>Compare the efficacy of an early and comprehensive strategy in AHF elderly patients to the usual care on morbidity and mortality at 30 days. <strong>Primary endpoint:</strong> number of days alive and out of hospital at 30 days after ED visit. The experts of the European Society of Cardiology has recently considered this endpoint as relevant and adapted (see p. 13).</td>
</tr>
<tr>
<td>Secondary objectives and endpoints</td>
<td>To evaluate the effect of AHF management on early morbidity and mortality. <strong>Secondary endpoints:</strong> • 30-day cardiovascular death • 30-day all causes death • Hospital readmission at 30 days • Length of stay in hospital • Changes of more than 2 fold in creatinine level from inclusion to day 30 or to discharge whichever comes first.</td>
</tr>
<tr>
<td>Design of the study</td>
<td>Stepped wedge randomised trial (see p. 14) The 15 participating centers will first be assigned to the “control period” for 4 weeks. Then, every 2 weeks, one center will be randomized to switch to the “intervention period”. After 32 weeks, all centers will then be in the “intervention group” for the last 12-week period of the trial. The inclusions will be stopped once the balance between the two groups is reached.</td>
</tr>
<tr>
<td>Population of study participants</td>
<td>Patients aged ≥75 years</td>
</tr>
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<td>----------------------------------</td>
<td>------------------------</td>
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<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Patients aged 75 years and older admitted to the emergency department with a diagnosis of AHF determined by the emergency physician, based on the presence of:</td>
</tr>
<tr>
<td></td>
<td>• at least one of the following symptoms: acute, or worsening of dyspnea, orthopnea</td>
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<td></td>
<td>• One or more of the followings: pulmonary rales, peripheral edema, a chest radiograph or transthoracic echocardiography showing pulmonary vascular congestion signs, increased natriuretic peptides (BNP or NT-pro-BNP).</td>
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<td></td>
<td>• Patients affiliated to French social security (“AME excepted”)</td>
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<td></td>
<td>• Written informed consent signed by the patient / the trustworthy person / family member / close relative, or inclusion in case of emergency and written informed consent will been signed by the patient (if need be by trustworthy person, family member or close relative) as soon as possible(article L1122-1-2 of the French Public Health Code)</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Patients are excluded if they have any of the followings:</td>
</tr>
<tr>
<td></td>
<td>• other obvious cause of acute illness (severe sepsis, ST elevation Myocardial infarction)</td>
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<tr>
<td></td>
<td>• systolic blood pressure less than 100mmHg</td>
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<td></td>
<td>• severe mitral or aortic stenosis, or severe aortic regurgitation</td>
</tr>
<tr>
<td></td>
<td>• known chronic kidney injury on dialysis</td>
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<td></td>
<td>• Time from ED entrance to inclusion &gt; 6h</td>
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<tr>
<td></td>
<td>• Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom</td>
</tr>
<tr>
<td><strong>Interventions or product under investigation</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>Comparator arm</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>Other interventions added by the study</strong></td>
<td>The intervention will not test any particular drug or medical disposal, but rather the application of the international guidelines (ESC, EUSEM, AHA) through the implementation of a protocol of care. The care bundle of early care with a checklist that includes the following checklist:</td>
</tr>
<tr>
<td></td>
<td>- Detection and treatment of AHF precipitating factors (infection, acute coronary syndrome or atrial fibrillation)</td>
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<td></td>
<td>- Treatment of congestion, including a protocol of nitrates titration, and low dose furosemide, as recommended by international guidelines</td>
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<td></td>
<td>- Non-invasive ventilation if indicated, as recommended by international guidelines</td>
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<tr>
<td></td>
<td>- Preventive low molecular weight heparin, as recommended by international guidelines</td>
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<tr>
<td></td>
<td>During the control period, the standard of care will be treatment as usual, left at the discretion of the treating emergency physician</td>
</tr>
<tr>
<td><strong>Expected benefits for the participants and for society</strong></td>
<td>We anticipate a reduction in length of hospitalisation and rate of readmission. The intervention is aimed at increasing the number of days alive and at home in the first month</td>
</tr>
</tbody>
</table>
after inclusion. This benefit for the patient should be associated with a reduction in the allocation of hospital resource.

**Minimal risks and constraints added by the study**

Minimal risk, as only recommended treatments will be administered

The intervention will not test any particular drug or medical disposal, but rather the application of the international guidelines (ESC, EUSEM, AHA) through the implementation of a protocol of care.

Validated treatment will be randomly attributed to a group of patients (List of interventions listed in the article L1122-1-2 of the French Public Health Code, and corresponding to a Minimal risks and constraints)

**Scope of the study**

Emergency care and acute heart failure

**Number of participants included**

500 patients

**Number of sites**

15 centers in France

If one center withdraw from the trial before its start, we will invite another ED to participate (2 centers are listed as willing to participate if possible)

**Schedule for the study**

- inclusion period: 44 weeks
- participation period (treatment + follow-up): 30 days
- total duration: 44 weeks and 30 days

**Number of enrolments expected per site and per month**

4

**Statistical analysis**

No interim analysis is planned. Analysis will be performed at the end of the study after data review and freezing of data base according to ITT principle and with regard to cluster level randomisation.

**Sources of monetary support**

French ministry of health
2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1 CURRENT KNOWLEDGE

Acute heart failure (AHF) is a syndrome defined as new-onset or worsening of symptoms and signs of HF, often requiring rapid escalation of therapy and hospital admission. The clinical presentation of AHF typically includes symptoms or signs related to congestion and volume overload rather than to hypoperfusion.\(^1\) Acute heart failure represents 5% of all emergency hospitalizations, and is the most common primary diagnosis in patients ≥75 years visiting the ED.\(^2,3\) The ED are the main entry to the hospital for AHF, with 64% of these admissions being subsequent to an ED visit.\(^4\) This syndrome is reportedly associated with poor outcomes, with a 80% rate of hospital admission, a median length of hospital stay of 10 days and a mortality around 10% at 30 days, and a readmission rate of 25-30% at 30 days.\(^5-7\)

Despite a high rate of morbidity and mortality, the management of AHF has not changed for several decades and most clinical studies failed to demonstrate a positive impact of new drugs on patients' prognosis.\(^8,9\) European guidelines include the use of diuretics, nitrates, oxygen and non-invasive ventilation (NIV) when indicated along with the treatment of any potential AHF triggers (precipitating factors). However, these guidelines are based on moderate levels of evidence (IB and IIaB), and high-quality randomized controlled trials data (RCT) are lacking.\(^10-12\)

In 1998 and 2000, the two cornerstones trials of Cotter et al. provided evidences of benefits associated with early vasodilator therapy with nitrates, although on a very small sample of patients (less than 200 in total).\(^13,14\) Since then, every prospective trial on AHF management failed to report a clinical significant improvement of outcomes. Equipoise remains on many questions regarding the recommended therapeutics: the optimum dose and route of administration of diuretics are not clear, the use of nitrates is also debated, and the benefit of non-invasive ventilation (NIV) is unclear.\(^15-17\)

Despite these controversies, recommendations and guidelines are published by international society (ESC, AHA, …) and constitute the basis of our understanding and standard of care.\(^10,11\) However, a large proportion of elderly patients in AHF do not receive adequate care, including low rate (30-50%) of nitrates therapy.\(^7,18,19\)

In preparation of this grant application, we conducted a preliminary analysis in 8 French EDs participating in the present ELISABETH trial. For a 7-day period, we evaluated all consecutive patients aged 75 years and older with a diagnosis of AHF in the ED. Among the 73 consecutive AHF patients, 23 patients (32%) had not been investigated for the findings of precipitating factors of AHF (namely infection, acute coronary syndrome or atrial fibrillation). Moreover, among the 50 other patients for whom precipitating factors of AHF were investigated, 17 (one third) showed evidence of precipitating factors that were not subsequently treated in the ED, although diagnosed. Regarding nitrates therapy, only 25 out of the 73 included patients received
recommended treatment. In total, only 18 elderly ED patients (23%) were managed according to the existing guidelines (Freund et al. 2017 manuscript under preparation).

The lack of solid evidence regarding the efficacy of full recommended therapeutic management of AHFS on outcomes may have been caused by four major shortcomings that we will address in the present ELISABETH trial:

1) The previous RCTs did not include in their protocol of care the systematic early assessment for precipitating factors, and subsequent treatment.\(^8,15,20,21\) The main reported triggers are acute coronary syndrome (ACS), infection, and atrial fibrillation.\(^22,23\) As the outcomes of AHF patient has been linked with the triggering factor, we make the hypothesis that early and comprehensive look up and treatment of these precipitating factors may improve the prognosis.\(^24\) A secondary analysis of the Arrigo et al. study showed that among the 15% of AHF patients with ACS, the administration of antiplatelet was associated with decreased mortality (11.4% vs 16.7%).\(^24\) Similarly, it is well established that the early introduction of antibiotics improve prognosis of infected patients.\(^25\) Along with administration of recommended treatment within the first hours of ED care, our trial will evaluate the impact of an algorithm for early detection and treatment of precipitating factors that may have contributed to the decompensation of the patient.

2) The previous RCTs only assessed the impact of single drugs, and not of a comprehensive care bundle.\(^8,9,15,20\) Due to polyfactorial causes of poor outcomes in elderly patients with AHF, we believe that an intervention that focuses only on the administration of a single drug may have a lesser effect than a care bundle. In the light of the high rate of sub-optimal care provided to elderly AHF patients, the inclusion of all aspect of the treatment seems mandatory to evaluate a therapeutic approach. To our knowledge, an intervention combining an early and multifaceted approach for AHF in the ED has never been studied.

3) The delay between ED arrival and randomization may have been too long: in recent large RCTs, this timeframe varied from 6 to > 24 hours.\(^8,20\) It has however been suggested that the introduction of decongestion treatment within hours in the ED is associated with better outcomes.\(^26,27\) Furthermore, a recent prospective study reported that early decongestion treatment with diuretics in the first hour was an independent predictor of improved in-hospital survival (Odds Ratio OR 0.39, [0.20-0.76]) \(^28\).

In the present study, nitrates and loop diuretics will be given within 1 hours of first medical contact in the ED.

4) Although elderly are described to most suffer of AHF, with worse outcomes, specific RCT in this frail population are lacking (ex. the recent True-AHF RCT, which evaluated the effect of ularitide infusion, excluded elderly patients).\(^8\) Thus our trial, focused on old AHFS patients, will be
to the best of our knowledge the first to evaluate the impact of an early intensive approach in this target population.

### 2.2 Hypotheses for the research

In elderly patients (≥75 years), acute heart failure (AHF) is associated with a high 30-day mortality and readmission rate. We hypothesis that a care bundle, which comprises very early and aggressive decongestion treatment along with assessment and treatment of precipitating factors will improve early outcomes for elderly patients that visits the ED with AHF.

### 2.3 Description of the population of research participants and justification for the choice of participants

Patients with AHF, aged 75 years and older, admitted to the ED. We chose to focus on elderly patients for several reasons:

- These patients have higher mortality rates due to frequent co-existing illness and comorbidities.\(^3,4\)
- Elderly patients are quite an homogenous population. They share a similarity in AHF profile, with a predominant proportion of patients with preserved ejection fraction, and similar profiles of triggers (infection in most of the cases). By contrast to younger patients (< 75 years) in AHF, who are often patients with poor left ventricular ejection fraction and require a different care pathway, mostly based on decongestion treatment, especially diuretics.\(^5,29\)
- Elderly patients are under-represented in clinical trials, and scientific evidence is often lacking, the diagnosis and management of AHF in this population is challenging.
- Elderly patients have been extensively shown to be undertreated, whilst this population would benefit as well as patients under 75.

### 2.4 Interventions and products which will be performed or used as standard

No specific drug or medical disposal will be investigated per se. The present trial will evaluate the efficacy of administration of full optimaltherapy (being furosemide, isosorbidedinitrate, LMWH, antibiotics, antiplatelets…) as recommended by current guidelines See section 6 below.

### 2.5 Interventions added for the research

The intervention will not test any particular drug or medical disposal, but rather the application of the international guidelines (ESC, EUSEM, AHA) through the implementation of a protocol of care. The care bundle of early care with a checklist that includes the following checklist:

- Detection and treatment of AHF precipitating factors (infection, acute coronary syndrome or atrial fibrillation)
- Treatment of congestion, including a protocol of nitrates titration, and low dose furosemide, as recommended by international guidelines
- Non-invasive ventilation if indicated, as recommended by international guidelines
- Preventive low molecular weight heparin, as recommended by international guidelines

2.6 Summary of the known and foreseeable benefits and risks for the participants

Despite a small improvement in outcomes of elderly admitted for AHF within the past decades, its morbidity and mortality remains severe with a 10% rate of 30-day mortality, and 25-30% of early readmission rate.\(^6,7,18,29\) In the majority of cases, treatment can be initiated in the ED. However, many studies showed that a majority of these patients are still not getting recommended therapies in the ED – either for AHF *per se*, or for precipitating factors of AHF, especially acute coronary syndrome or infection.\(^7,16,18\)

In this context, there is an urgent need of multidisciplinary management program of patients with AHF in the ED and following ED to ensure better results and adherence.\(^30\) The great outcome improvement provided by early treatment in the ED have long been established in other settings (e.g., sepsis, myocardial infarction). Unfortunately, AHF has not been considered with this regard until recently. Some reports suggest the importance of time to introduce therapy in AHF. Data derived from ADHERE registry indicate that early treatment (<6h) in emergency departments would bear a positive impact by decreasing in-hospital mortality and morbidity rates (unadjusted OR for in-hospital mortality 0.77, adjusted OR 0.87 (95%CI [0.76 – 0.96]).\(^28\) Very recently, in their large prospective observational study, Matsue et al. reported a significant decreased mortality of AHF following the initiation of decongestion therapy within 1 hour in the ED (OR for in-hospital mortality of 0.39 (IC 95% [0.20-0.76]).\(^28\)

As expressed by Januzzi and Felker in a recent editorial “the failure of novel therapies for AHF requires us to make better use of what we already have. A systematic approach would allow an optimal management of acute HF, and in turn could finally improve outcomes.”\(^31\) If our hypothesis is confirmed, our trial of early intensive care bundle will be the first RCT showing a significant reduction in short term morbidity and mortality in elderly AHF, similarly to what was achieved for sepsis (with a 15% absolute reduction of in-hospital mortality).\(^32,33\)

Lastly, it can be stressed that the observed high rate of deviation to the guidelines may be caused in part by their low level of evidence of these last one. A positive outcome of the execution of a care bundle based on these recommendations would increase physician’s adherence, and patients’ outcomes.

3 OBJECTIVES OF THE RESEARCH
3.1 Main objective of the research
To compare the efficacy of an early and comprehensive management strategy of AHF in elderly patients to the usual care on morbi-mortality at 30 days.

3.2 Secondary objectives
To evaluate the effect of AHF management on early morbidity and mortality.

4 DESCRIPTION OF THE RESEARCH

4.1 Primary endpoint
Our primary endpoint is:

**The number of days alive and out of hospital at 30 days after ED visit.**

This endpoint is considered as relevant by the group of experts of the European Society of Cardiology. In their consensus paper, the experts stated that although mortality should be captured, repeated hospitalizations should also be recorded. Especially in elderly patients, where the rate of readmission to the ED and rehospitalisation is elevated: up to 40% of heart failure admissions to the hospital are actually repeated admission for recurrence of symptoms within 30 days of a previous AHF event. As expressed by Zannad et al.: “Despite their importance, repeat events are ignored in the majority of clinical trials, [...]. The ‘days alive and out of hospital’ endpoint incorporates the components of days in hospital (including days of the index hospitalization and repeat hospitalizations), days alive and not in hospital, and days dead into a single measure over a defined time frame (e.g. 30 or 60 days). This endpoint was developed to address the issue of repeat hospitalizations for all causes.”

This endpoint also makes it possible to obtain information which could have some benefits from an health-economic point of view. Furthermore, this endpoint was reported to better capture the burden of mortality and hospital stay during the follow up period. As expressed by Allen et al., this endpoint has the advantage to combine mortality, length of stay, and burden of subsequent hospital stay into a single endpoint, and therefore is appropriate to capture morbidity and mortality.

Lastly, the timeframe of 30 days is recommended as a shorter timeframe would not catch recurrence and morbidity, and a longer timeframe would catch events that are more likely linked to chronic morbidity of the patients than to the AHF syndrome.

4.2 Secondary endpoints
- 30 day all-cause mortality
- 30 day cardio-vascular mortality
- Hospital readmission at 30 days
- Length of in hospital stay truncated at 30 days
- Changes of more than 2 fold in creatinine level from inclusion to day 30 or to discharge whichever comes first.

Creatinine will be measured at day 0 in the ED, and at discharge day or day 30, whichever comes first.

5 RESEARCH METHODOLOGY

5.1 Design of the study

The ELISABETH trial is designed as a stepped wedge cluster randomized trial. We decided to choose this design for the following reasons:

- As we implement a new protocol, there is a risk of contamination. An emergency physician, who would have already treated patients via the care bundle protocol, would be subsequently influenced by this trial, and could have difficulty to provide the former “standard of care”. Therefore, a randomization at the patient level or a cross-over design would induce bias through contamination. This bias was likely a reason why the recent “Guide It” trial failed to provide significant difference between control group and intervention group.39

- The present ELISABETH trial focus on a severe condition, in EDs that are often busy places, therefore the need for a randomization at the patient level could be an impediment to inclusion, and therefore limit our ability to recruit consecutive patients

- A cluster stepped-wedge design prevents contamination as centers will first be allocated to standard care, before implementing the intervention. Furthermore, a stepped wedge design would also prevent a potential “period effect” that could have resulted from a simple cluster before/after design

All the 15 participating centers will begin with a “control period” for 4 weeks. Then, every 2 weeks, one center will be randomized to switch to the “intervention period”. After 32 weeks, all centers will then be in the intervention group for a last 12-week period. The inclusions will be stopped once the balance between the two groups is reached.

<table>
<thead>
<tr>
<th>Weeks</th>
<th>1-2</th>
<th>3-4</th>
<th>5-6</th>
<th>7-8</th>
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<th>13-14</th>
<th>27-28</th>
<th>29-30</th>
<th>31-32</th>
<th>33-34</th>
<th>35-36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center 1</td>
<td>C</td>
<td>C</td>
<td>I+T</td>
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<tr>
<td>Center 2</td>
<td>C</td>
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<td>Center 3</td>
<td>C</td>
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<td>Center 4</td>
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<tr>
<td>Center 5</td>
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<td>C</td>
<td>I+T</td>
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<td>...</td>
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</tr>
<tr>
<td>Center 6</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>...</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Center 7</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>...</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Center 8</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>...</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Center 9</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>C</td>
<td>C</td>
<td>...</td>
<td>I</td>
<td>I</td>
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<tr>
<td>Center 10</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>...</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Center 11</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>C</td>
<td>C</td>
<td>...</td>
<td>I+T</td>
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<td>I</td>
</tr>
<tr>
<td>Center 12</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>...</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>
In the case where one or more centers will have to drop out of the trial, a mid-term reevaluation of the period distribution will be conducted by the steering committee in order to ensure similar repartitions of period and number of patients in each group.

This trial is comparative: intervention period vs control period. In the intervention period, patients will be treated according to the care bundle. In the control period, patients will be treated as usual (TAU) by the emergency physicians, without the aid of a care bundle.

Due to the design of the study (stepped wedge) and the intervention, there will be no blinding of the physician and the patient.

5.2 Number of participating sites

This is a multicenter trial, which involves 15 Emergency Departments in France. Patients will be recruited in the ED at the index visit.

5.3 Avoiding and reducing bias

5.3.1 Participant identification

The participants in this research will be identified as follows:

Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial

This reference number is unique and will be used for the entire duration of the study.

5.3.2 Randomization

This is a stepped wedge randomisation. All centers will be randomised for their time of intervention implementation. Randomisation will be computer generated by a biostatistician from URC-Est, independent of the study and before the study beginning.

This is an open trial.

6 PROCEDURE FOR THE RESEARCH

<table>
<thead>
<tr>
<th>Whose consent must be obtained</th>
<th>Who informs the individuals and collects their consent</th>
<th>At what point the individuals are informed</th>
<th>At what point the consent is obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>• the subject participating in the trial;</td>
<td>• one of the local investigators (emergency physician)</td>
<td>• at inclusion in the ED</td>
<td>• At inclusion D0 or as soon as his condition permits</td>
</tr>
<tr>
<td>• or the trustworthy person / family member / close</td>
<td>Principal investigator or a declared collaborating doctor who has been trained in the research (emergency)</td>
<td>• as soon as his condition permits</td>
<td>•</td>
</tr>
</tbody>
</table>

Figure 1: stepped wedge organisation and timetable of the trial

C: Control period. I: Intervention period. T: training
6.1 Schedule for the study

- inclusion period: 44 weeks
- participation period (treatment + follow-up): 30 days
- total duration: 44 weeks and 30 days

6.1.1 D0: inclusion and baseline visit

The inclusion visit takes place at day 0, during the ED index visit. Patients should be included during the first 6 hours after ED entrance.

As this is a cluster study, and the intervention consists of an application of recommended guidelines, all patients with AHF will be treated as per the care bundle according to the strategy period, whether in the study or not but their data will not be collected if patients are not included.

1. Inclusion

After having checked inclusion and exclusion criteria, the investigator will seek consent of participation.

- if the patient is able to provide his/her written informed consent: the investigator will inform the patient and obtain his/her written informed consent (for the utilization of his hospital data and 30 days follow-up).
- if the patient is unable to provide his written informed consent: the investigator will inform and obtain the consent of the trustworthy person, family member or close relative, as appropriate (Article L1122-2 of the French Public Health Code).
- if the patient is unable to provide his written informed consent and in the absence of the trustworthy person, next of kin or close relative: a procedure for inclusion in the study in emergency situation will be applied (article L1122-1-2 of the French Public Health Code). In this case, continuation-of-care consent for the study will be signed by the patient (if need be by trustworthy person, family member or close relative) as soon as possible, according to French Law (article L1122-1-2 of the French Public Health Code).

2. Baseline data

The local investigator will also collect with the help of clinical research technician the following variables at the time of the ED stay:
- Past medical history (Chronic heart failure, acute coronary syndrome, Chronic respiratory failure)
- Chronic oral intake of diuretics, nitrates, antibiotic, antiplatelet, anticoagulant.
- Baseline characteristics: heart rate, systolic and diastolic blood pressure, temperature
- ECG rhythm and signs of ischemia
- Main biological parameters if performed: haemoglobin, White blood cell count, troponin, BNP or nt-proBNP, creatinine, CRP, procalcitonin, arterial blood gas
- Treatment given in the ED in the first 4 hours:
  - Diuretics (dose and class)
  - Nitrates (dose and class)
  - Antibiotics
  - Antiplatelet or anticoagulant
  - Anti-arythmic (digoxine, cordarone)
  - Anticoagulant / LMWH
  - NIV
- Discharge disposition: home, Clinical decision unit, admission to the hospital, cardiology, admission to intensive care unit, death.

6.1.2 Follow-up visits (if discharge before 30 days)
If the patient is discharged before 30 days, the last value of creatinine measurement before discharge will be collected.

6.1.3 Research end date (D30)
The end of study visit will be at 30 days. The in-hospital mortality will be truncated at 30 days.
- If the patient is still hospitalized: the follow-up visit will consist of a hospital visit and a chart review to ascertain the primary endpoint.
- If the patient is not still hospitalized: the follow-up visit will consist of a phone interview to patient/ trustworthy person / family member / close relative. The family practitioner of the patients will be sought for information in case the patients/relatives cannot be reached.
If follow up is impossible, the investigators or CRT will contact the city hall and administrative service of his hometown to seek for possible death.

6.2 Expected length of participation, chronology and duration of the study
The maximum duration between ED arrival and enrolment will be 6 hours.
After inclusion; the care bundle (treatment period) should be completed within 4 hours.
In both periods, each subject will participate in the study for 30 days (see above).
As shown in figure 1, there will be a first period of 4 weeks where all centres will be in the control arm, then every 2 weeks one centre will change arm and switch to the “intervention” phase. After a total of 32 weeks, all centers will be in the “intervention” arm, for four more weeks. The total duration of recruitment will therefore be 36 weeks. The inclusions will be stopped once the balance between the two groups is reached. Since patients will be followed until 30 days, the total duration of the study will then be of 44 weeks and 30 days.

<table>
<thead>
<tr>
<th>Maximum period between D0 and enrolment</th>
<th>6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Inclusion period</td>
<td>44 weeks</td>
</tr>
</tbody>
</table>

Duration of participation for each subject, of which:

- protocol period: 4 hours
- Follow-up period: 30 days

Total study duration: 44 weeks and 30 days
6.3 Table or diagram summarizing the chronology of the research

<table>
<thead>
<tr>
<th>Actions</th>
<th>D0 in the ED (Inclusion and Baseline visit)</th>
<th>Discharge if before D30</th>
<th>D30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion and exclusion criteria verification</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information: (patient or trustworthy person, family member or a close relative)</td>
<td>R</td>
<td>R (if emergency situation at D0)</td>
<td></td>
</tr>
<tr>
<td>Signature of the consent form (patient or trustworthy person, family member or a close relative)</td>
<td>R</td>
<td>R**</td>
<td></td>
</tr>
<tr>
<td>Past medical history</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical exam (auscultation and examination)</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological test (cf 5.2)</td>
<td>C</td>
<td>C</td>
<td>(C)*</td>
</tr>
<tr>
<td>ECG +/- echocardiography</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-Ray</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Care bundle / Treatment as usual</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED Discharge disposition</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status (in-hospital, home, dead)</td>
<td></td>
<td></td>
<td>R</td>
</tr>
</tbody>
</table>

* only if not done before, i.e. if still admitted in the hospital at D30 subsequent to ED visit.
** if not done at D0 (patient in emergency situation)
R: performed for research/ C: performed in the context of care

6.4 Distinction between standard care and research

This is an intervention study, where the intervention comprises the application of recommendations and guidelines for the management of AHF, ACS and infection. Therefore, only conventional and recommended treatments will be delivered to patients.

Control period: Acute heart failure standard therapy:
- Treatments are given at the discretion of the treating emergency physician
  - The guidelines and standard of care will be recalled to the emergency physicians at the beginning of the trial in each center when the control period will start.

Intervention period: Early intensive care bundle: The care bundle comprises a list of items to follow and tick on a handover checklist (see below-Figure 2) within 4 hours of ED management:
- a) Treatment of the congestion: (international guidelines and recommendations)\(^ {10,11}\)
  - 40mg of Intravenous (iv) furosemide (or usual daily dose) if not already given pre-hospital.
  - IV nitrates given in boluses of 3mg every 5 minutes. After one hour of bolus titration, then continuous infusion with an hourly dose of at least half of total given
during the first hour of nitrate. Blood Pressure (BP) will be monitored every 5
minutes during the titration (then hourly), and nitrates will be discontinued if BP
drops <100mmHg.

- b) Treatment of precipitating factors:
  
  o Administration of antibiotic therapy (accordingly to local guidelines amoxicillin and
  clavulanic acid in most cases) if at least two of the following: Fever > 38°C,
  leucocytes > 12 000 G/L, radiological signs suggestive of lower respiratory tract
  infection or elevated CRP or PCT,

  o Administration of dual antiplatelet therapy and transfer to cardiac intensive care
  unit if at least 2 of the followings: chest pain, ischemic signs on ECG, elevated
  troponin concentration or change in troponin concentration. These patients will be
  transferred for coronary angiography if indicated by the cardiologist, as
  recommended.40

  o In case of atrial fibrillation: administration of heparin, heart rate control strategy
  (digoxin or amiodarone as indicated) to reduce heart rate under 100 bpm, early
  admission to a cardiac intensive care unit if elevated troponin associated.

  - c) NIV if respiratory distress with hypercapnia and pH < 7.35 in absence of contra
  indication.11

  - d) Preventive LMWH if no pre-existing anticoagulation therapy.11

All treatment will be initiated in the ED, and their continuation or discontinuation will be
evaluated by the treating physician during the subsequent hospital stay.
Acute Heart Failure care bundle

<table>
<thead>
<tr>
<th>ED arrival: .....h....</th>
<th>Inclusion: .....h....</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-Ray +/- echocardiography</td>
<td>- □</td>
</tr>
<tr>
<td>ABG, BNP, troponin, WBC, CRP/PCT</td>
<td>- □</td>
</tr>
<tr>
<td>Monitoring with automatic BP set / 5min</td>
<td>- □</td>
</tr>
<tr>
<td>Nitrates in titration</td>
<td>- □</td>
</tr>
<tr>
<td>Furosemide (40mg or daily dose)</td>
<td>- □</td>
</tr>
</tbody>
</table>

To be ordered within 1h

- Temperature > 38°C
- WBC > 12,000 G/L
- Signs of LRTI on CXR
- Elevated CRP or PCT

  If ≥ 2 YES
  - IV antibiotic - □

- Chest pain
- Ischemic ECG sign
- Elevated troponin
- Change in troponin

  If ≥ 2 YES
  - Dual antiplatelet - □
  - Cardiology referral - □

- Atrial fibrillation & Heart Rate > 100

  If Yes
  - Digoxine / amio - □

- NI Ventilation if respiratory distress - □
- Low molecular weight heparin - □

**Completion of the care bundle: .....h....**

*Figure 2: example of handover sheets with checklist for AHF management*

During the intervention period, the clinical research technician, nurse, or investigator will have to fill the handover of treatment list, as reproduced below:
6.5 Biological samples

No biological sample will be stored during the trial.

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

- Age ≥ 75 years
- Admission to the emergency department with a diagnosis of AHF determined by the emergency physician, based on the presence of:
  - at least one of the following symptoms: acute, or worsening of dyspnea, orthopnea
  - one or more of the following: pulmonary rales, peripheral edema, a chest radiograph or transthoracic ultrasound showing pulmonary vascular congestion signs, increased natriuretic peptides (BNP or NT pro BNP).
  - Patients affiliated to French social security (“AME excepted”))
  - Written informed consent signed by the patient / the trustworthy person / family member / close relative, or inclusion in case of emergency and written informed consent will be signed by the patient (if need be by trustworthy person, family member or close relative) as soon as possible (article L1122-1-2 of the French Public Health Code)

7.2 Exclusion criteria

Patients are excluded if they have any of the followings:

- Other obvious cause of acute illness (severe sepsis, ST elevation Myocardial infarction)
- Systolic blood pressure less than 100mmHg
- Any contra-indication to nitrates (severe mitral or aortic stenosis, or severe aortic regurgitation)
- Known chronic kidney injury on dialysis
- Time from ED entrance to inclusion > 6h,
- Patient under legal protection measure (tutorship or curatorship) and patient deprived of freedom

### 7.3 Enrolment procedure

The 15 recruiting centers are:

<table>
<thead>
<tr>
<th>City</th>
<th>Country</th>
<th>Hospital</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paris</td>
<td>France</td>
<td>Pitié-Salpêtrière</td>
<td>Service des Urgences</td>
</tr>
<tr>
<td>Bobigny</td>
<td>France</td>
<td>Avicenne</td>
<td>Samu 93</td>
</tr>
<tr>
<td>Paris</td>
<td>France</td>
<td>Saint-Antoine</td>
<td>Service d’Accueil des Urgences</td>
</tr>
<tr>
<td>Paris</td>
<td>France</td>
<td>HEGP</td>
<td>Service d’Accueil des Urgences</td>
</tr>
<tr>
<td>Tours</td>
<td>France</td>
<td>CHU Tours</td>
<td>Département de Médecine d’Urgences</td>
</tr>
<tr>
<td>Tours</td>
<td>France</td>
<td>CHU Tours</td>
<td>Pôle Anesthésie</td>
</tr>
<tr>
<td>Nîmes</td>
<td>France</td>
<td>CHU Nîmes</td>
<td>Réanimation</td>
</tr>
<tr>
<td>Nancy</td>
<td>France</td>
<td>CHU Nancy</td>
<td>Doulleurs Urgences</td>
</tr>
<tr>
<td>Nancy</td>
<td>France</td>
<td>CHU Nancy</td>
<td>Service des Urgences / SAMU / SMUR</td>
</tr>
<tr>
<td>Toulouse</td>
<td>France</td>
<td>CHU Rangueil</td>
<td>Service des Urgences</td>
</tr>
<tr>
<td>Paris</td>
<td>France</td>
<td>Lariboisiere</td>
<td>Service des Urgences / SMUR</td>
</tr>
<tr>
<td>Paris</td>
<td>France</td>
<td>Cochin</td>
<td>Service des Urgences</td>
</tr>
<tr>
<td>Nice</td>
<td>France</td>
<td>CHU Nice</td>
<td>Service des Urgences</td>
</tr>
<tr>
<td>Creteil</td>
<td>France</td>
<td>CHU Henri Mondor</td>
<td>Service des Urgences</td>
</tr>
<tr>
<td>Boulogne</td>
<td>France</td>
<td>CHU Ambroise Paré</td>
<td>Service d’Accueil des Urgences</td>
</tr>
<tr>
<td>Paris</td>
<td>France</td>
<td>CH Saint-Joseph</td>
<td>Urgences et Lits d’Urgence</td>
</tr>
<tr>
<td>Besançon</td>
<td>France</td>
<td>CHU Besançon</td>
<td>Service d’Accueil des Urgences</td>
</tr>
</tbody>
</table>
In the case where one center withdraw from the trial before its start, we will invite another ED to participate (two centers are listed as willing to participate if possible – CHU Nantes and CHU Lyon).

Patients will be included by the emergency physicians whilst working in the ED. After a patient is suspected of AHF, the physician in charge (with the help of clinical research technician if present) will sought any exclusion criteria before seeking patient’s informed consent. To improve adherence to the bundle, after each center switches to the intervention period, a clinical research technician will be working in the ED during training period).

The present research team and its study coordinator (Y Freund) has conducted several previous studies in these 15 centers (among others) where patients were included and followed as planned: 1000 patients (30 centres) in 1 month [NCT02738164, Freund et al. JAMA 2017]; 500 patients (4 centers) in 1 year [NCT01774500 PlıosOne 2014]; 1800 patients (14 centres) in 1 year (NCT02375919, JAMA 2018); 550 patients (13 centers) in 3 months (NCT02926664,, EJEM 2018)). Each of these prospective multicenter studies coordinated by Y. Freund, the scientific director of the present ELIŠABETH trial achieved full targeted recruitment within the pre specified timeframe.

The scientific director(A Mebazaa) of the ELISABETH trial was (among other) the European chairman of the True-AHF study, a trial that recruited similar patients in some of the participating centers. The target recruitment has been completed in time (NEJM 2017). AM was also the study coordinator of a previous PHRC funded trial (Frog –ICU), which also achieved full recruitment in time (in revision, Critical Care).

<table>
<thead>
<tr>
<th>Number of subjects/site/month</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects/site</strong></td>
<td>33</td>
</tr>
<tr>
<td><strong>Enrolment period (months)</strong></td>
<td>44 weeks</td>
</tr>
<tr>
<td><strong>Number of sites</strong></td>
<td>15</td>
</tr>
<tr>
<td><strong>Total number of subjects to be included</strong></td>
<td>500</td>
</tr>
</tbody>
</table>

AHF in elderly is a common diagnosis in the ED.

In the preliminary study that assessed our potential of recruitment in 8 of the participating centers, the median number of included patients was 10 per week per center (range 6 to 13) when using the same inclusion and exclusion criteria than the present trial, the median number of included patients was 10 per week per center (range 6 to 13):
- Nancy: 13 patients / week
- Besançon: 6 patients / week
- Pitié-Salpêtrière: 11 patients / week
- Saint-Antoine: 9 patients / week
- HEGP: 6 patients / week
- Tours: 12 patients / week
- Lariboisière: 11 patients / week
- Nimes: 6 patients / week

The remaining 7 recruiting centers that will participate in the present ELISABETH trial are EDs of similar size and settings, therefore with the same recruitment potential.

**Thus, the target of 4 patients per month per site seems highly achievable.**

In the case where one center withdraw from the trial before its start, we will invite another ED to participate (two centers are listed as willing to participate if possible – CHU Nantes and CHU Lyon). In the case where one center should withdraw from the study after the beginning of the trial, the steering committee will evaluate mid-term recruitment after 16 weeks and adjust the remaining period to ensure that all groups will have the same total period length of inclusion, and similar sample size.

### 7.4 Inclusion rate

We aim to have balanced population between the two groups, especially in terms of number of patients analysed in each group. Furthermore, to avoid any period effect, centers must include their targeted number of patients throughout the whole inclusion period. Therefore, we will closely monitor the number of patient recruited in each center. The local investigator or the CRT will follow at least once every 2 weeks how many patients were included and could be analysed.

### 8 TERMINATION AND EXIT RULES

#### 8.1 Criteria and procedure for premature withdrawals and exits from the study

- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject’s best interests.

➔ Subject lost to follow-up: the subject cannot be located. The investigator must make every effort to reconnect with the subject (and record his attempts in the source file), at least to determine whether the subject is alive or dead.

If a subject exits the trial prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
The case report form must list the various reasons why the subject exited or was withdrawn from the study:

- Subject's personal reasons
- Explicit withdrawal of consent
- Lost to follow-up

8.1.1 Procedure for replacing participants

If a subject exits the trial, this will in no way affect the standard care received for his/her condition.

8.1.2 Full or partial cancellation of the study

AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

9 EFFICACY ASSESSMENT

9.1 Description of parameters for assessing efficacy endpoints

The primary endpoint (days alive and out of hospital at day 30) will be measured at the end of the 30 days follow-up period, either by hospital visit, phone interview, and medical chart review. Vital status, date of death and date of discharge will be collected.

A death during the follow-up period will correspond to 0. An ED visit will correspond to “one day” at the hospital.

For example, a patient not admitted (at day 0), with no return visit to the hospital, and alive at day 30 will have 30 days alive and out of hospital.

A patient who is admitted (at day 0) and stays 8 days in the hospital before being discharged and have no readmission and no return visit to the ED would have a “22 days alive and out of hospital at 30 days”.

A patient that is admitted and die at 13 days, either at home or in hospital will have 0.

A patient that is admitted for 10 days, discharged home for 5 days then admitted at day 16 for 15 days will have 5 days alive and out of hospital (namely day 11, 12, 13, 14 and 15).

9.2 Anticipated methods and timetable for measuring, collecting and analyzing the efficacy data

- In-hospital mortality will be obtained from hospital data base (Mediweb, Gilda, or Orbis) and phone interview with the last known ward of hospitalization of the patient. In case of transfer
to another hospital, this data will be collected either by phone interview or hospital visit if necessary.
- 30 day all-causes mortality rate: same as above for patient still in hospital at day 30, phone call to the patients, relatives, or GP if not.
- Cardiovascular related 30 day mortality. Adjudicated by an adjudication committee (see below) as to whether the death has been mainly caused by a cardiovascular issue.
- Length of stay in hospital and changes of more than 2 fold in creatinine level from hospital database (CleanWeb, MediWeb, Gilda or Orbis)
- Efficacy data will be analyzed at the end of the study after data review and freezing of data base.

10 SAFETY

During this research, adverse events (serious and non-serious) do not need to be reported to the sponsor. The report must instead be made as part of the vigilance procedure applicable to the product or intervention under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device, etc.).

11 SPECIFIC COMMITTEE FOR THE STUDY

11.1 Steering Committee

Members of the committee: Pr Alexandre Mebazaa (Primary investigator, anaesthesiologist), Dr Yonathan Freund (scientific coordinator, emergency physician), Pr Saïd Laribi (emergency physician), Pr Alain Cohen-Solal (Cardiologist), Pr Jacques Bonnaert (geriatrician), Pr Tabassome Simon (clinical pharmacologist; and Methodologist), Marine Cachanado (statistician), a representant of the promotor (DRCI head office project advisor)

Missions: Define the overall structure of the study, coordinate information, review the initial methodology and oversee the trial.

The committee can be asked to adjudicate any death in the study and relate whether it is from cardiovascular cause.

Rhythm of the meeting: 1 meeting per years.

12 DATA MANAGEMENT

12.1 Data collection

Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in collaboration with URC-EST. Baseline data will be completed by the investigators with the help
of a Clinical Research Technician (CRT) of URC-Est for AP-HP centers and a local Clinical Research Technician for other centers.

12.2 Identification of data recorded directly in the CRF which will be considered as source data

After inclusion, the local investigator, emergency physician, with the help of the CRT if present, will complete the e-CRF that contains inclusion/exclusion criteria, main baseline characteristics and will complete the handover checklist (care bundle Figure 2). The outstanding variables will be collected through the review of electronic medical chart of ED visit (Urqual in most centers). Data regarding follow up, survival and hospital evolution will be collected through the review of electronic medical chart of ward hospitalization (MEDiweb), administrative software (Gilda / Orbis) or if needed physicians'/CRT phone call.

12.3 Right to access source data and documents

12.3.1 Data access

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the research and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force.

12.3.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the study. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period. That will include:
- handover checklist and treatment list
- Medical chart, laboratory test results and imaging reports from the initial (or repeated) hospitalisation

12.3.3 Data protection

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the Code de la Santé Publique - CSP (French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the research, the participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).

During and after the research, all data collected about the participants and sent to the sponsor by the investigators (or any other specialized collaborators) will be anonymized.

Under no circumstances will the names and addresses of the participants be shown.

The sponsor will ensure that each participant has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.4 Data processing and storage of research documents and data

12.4.1 Identification of the person responsible and the location for data processing

Data management will be performed by a data manager from URC-Est under the responsibility of Pr T. Simon. Statistical analysis will be performed by a biostatistician from URC-Est under the responsibility of Pr T. Simon (Pr T. Simon).

12.4.2 Data entry

Data will be entered electronically via a web browser.

12.4.3 Data processing (CNIL, the French Data Protection Authority)

This research is governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended). AP-HP, the sponsor, has signed a declaration of compliance with this "Reference Method" Adapt based on the internal procedures of the data management entity.

All personal data for this research will be processed in accordance with Chapter IX of the amended French Data Protection Act of 6 January 1978 (articles 53-61).

12.4.4 Archiving

All specific documents for Minimal Risk and Restriction research studies are to be archived by the investigator and the sponsor for 15 years after the end of the research.

This indexed archiving applies to:

- A sealed envelope for the investigator, containing one original of all information sheets and consent forms signed by all individuals at the site who participated in the research;
- A sealed envelope for the sponsor, containing one copy of all information sheets and consent forms signed by all individuals at the site who participated in the research;
- "Study" binders for the Investigator and the sponsor, containing (non-exhaustive list):
  - all successive versions of the protocol (identified by version no. and date), and its appendices
  - decisions of the CPP
  - correspondence
• the enrolment list or register
• the appendices specific to the research
• Final report
  - The case report forms

12.5 Ownership of the data
AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

13 STATISTICAL ASPECTS

13.1 Description of statistical methods to be used including the timetable for the planned interim analyses
No interim analysis is planned. Analysis will be performed at the end of the study after data review and freezing of data base.
Analyses will be performed using SAS® software (version 9.3 or updated version).
Principal analysis will be realized according to the ITT principle.
Baseline patient’s characteristics will be considered at both with the cluster (center) and patient level.
For the center level, characteristics at the beginning of the study will be described (there are no expected change between the two periods for cluster characteristics).
Baseline characteristics of patients will be described globally and according to the period.
Continuous variables will be summarized using descriptive statistics, i.e number of subjects, mean, standard deviation (s.d), median, inter quartile range, minimum and maximum. Qualitative variables will be summarized by frequency and percentage.
Number of cross-over from one group to the other group will be described.

13.2 Principal criterion analysis
The number of days alive and out of hospital will be calculated based on date of admission, vital status, date of death and date of discharge will be collected. A death during follow-up will correspond to 0. An ED visit will correspond to “one day” at the hospital.
The number of days alive and out of hospital will be analysed using a linear regression mixed model with a random effect for each cluster, considered fixed effects will be: strategy and, for the stepped wedge design, time representing each step. In case of non-normality distribution of the interest variable, a transformation could be realized.
13.3 Secondary evaluation criteria

In hospital mortality, all causes mortality at 30 days and cardiovascular mortality at 30 days will be compared between groups by using Pearson's chi-square test or Fisher exact test. If possible, generalized linear regression mixed model with Poisson distribution will be performed. If the number of events is sufficient, generalized linear regression mixed model using logit link will be performed.

The length of stay in hospital in days will be compared between the two periods by using Student t-test or Wilcoxon rank-sum test as needed. If possible, a linear regression mixed model will be performed. A random effect for each cluster will be considered and considered fixed effects will be: strategy and, for the stepped wedge design, time representing each step. In case of non-normality distribution of the interest variable, a transformation could be realized.

Percentage of patients with a change of more than 2 fold in creatinine between inclusion and 30 days will be compared between groups by using Pearson's chi-square test or Fisher exact test. If possible, generalized linear regression mixed model with Poisson distribution will be performed. If the number of events is sufficient, generalized linear regression mixed model using logit link will be performed.

Second analysis will be performed on the per protocol population.

13.4 Calculation hypotheses for the number of subjects required and the result

From our previous cohort, the mean number of days alive and out of hospital at 30 days was 14±9. To be clinically relevant, we estimate that the new approach should increase this endpoint of 3 days at least (a relative increase of 20%). With a power of 80% and alpha=5%, we need to include 283 patients. Since this study is planned as a stepped wedge cluster and after specification of following elements: 15 clusters, ICC=0.0001, the design effect is estimated at 1.609, so we need to analyze 454 patients – to take into account 10% of non-evaluable patients, it is necessary to include 500 patients -around 2 per cluster for each 2 weeks period.

13.5 Anticipated level of statistical significance

All tests will be performed at 5%.

13.6 Statistical criteria for termination of the study

Not applicable.

13.7 Method for taking into account missing, unused or invalid data

Missing value for the principal criteria will be considered as failure (0 days alive and out of the hospital), whatever the period considered.
Sensitivity analyses will be performed to check the impact of replacement methods of missing values with missing data considered: 1) success (maximum days alive and out of the hospital observed in the total population of the study) in the experimental group and as failure (0 days alive and out of the hospital) in the control group; 2) failure in the experimental group and as success in the control group. Others missing data will not be replaced.

13.8 Management of modifications made to the analysis plan for the initial strategy
Modification made in analysis will be documented in the final report.

13.9 Choice of individuals to include in the analyses
ITT population: all included patients according to the period assigned by the randomization to the center, regardless of the strategy effectively received by the patient.

Per protocol population: all included patients without major protocol deviation:
- No respect of selection criteria,
- No respect of strategy assigned by randomization (cross-over for example),
- Missing value for the principal criteria,
- Other major protocol deviation identified during data review and freezing of database.

14 QUALITY CONTROL AND ASSURANCE
Every clinical study managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

14.1 General organization
The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centers.

The sponsor will establish a system for opening the research centers and may also implement a data quality control system.

The sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their initial visits.

The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:
- the research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.
14.1.1 Strategy for site opening

The strategy for opening the centers will be determined before the research begins. Opening visit will be carried out by the local investigator and at least one member of the steering committee and one member of URC-Est. ED physicians will be invited to participate in the opening session in each center. A similar visit will occur at the time of the period switch, with the presence of one member of URC-Est, one member of the steering committee and the local investigator.

14.1.2 Data quality control

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of: minimal level.

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate.

During these visits, the following elements will be reviewed:
- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)

14.2 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and must be written clearly and legibly. Any missing data must be coded.

Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.

Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.

A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The sponsor will keep the original. The investigator must keep a copy.
14.3 Management of non-compliances

Any events that occur as a result the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor. The sponsor has its own procedures for managing these non-compliances.

14.4 Audits

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

14.5 Principal Investigator's declaration of responsibility

Before starting the study, each investigator will give the sponsor's representative a signed and dated copy of his/her most recent curriculum vitae, produced within the past year, and RPPS number (RépertoirePartagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must describe any previous participation in clinical research and related training.

Each investigator will agree to comply with legislation and to conduct the study in line with regulations, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCI document) which will be sent to the sponsor's representative. The investigators and their co-workers will sign a delegation form specifying each person's role and must supply their CV.
15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing and obtaining consent from the research participants

This is a cluster stepped wedge randomised trial, in other words randomization is performed at the hospital level and concerns the switch from control period (no intervention in care) to interventional period (focus on standard care recommendations). The informed consent of the patients will be required to collect his in-hospital data in the eCRF, and the 30-day follow up.

In accordance with Article L.1122-1-1 of the Code de la Santé Publique - CSP (French Public Health Code), no Minimal Risk and Constraints research can be carried out on a person without his/her free and informed consent, obtained expressly after the person has been given the information specified in Article L.1122-1 of said Code.

The person will be given a reflection period between receiving the information and being asked to sign the consent form.

If the patient is alert and considered capable of giving consent by the physician in charge:

After screening, the emergency physician will inform the patient on the aim and details of the study.

In accordance with Article L.1122-1-1 of the French Public Health Code, no research can be carried out on a person without his/her free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent [or the consent of any other person, in the cases described in Articles L.1122-1-1 to L.1122-2 CSP] as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form The information sheet and a copy of the consent form, signed and dated by patient and by the investigator or the doctor representing the investigator, will be given to the individual.

If the person is unable to give his or her written consent:

The consent may be obtained, in descending order of priority, from a legal representative, family member or a close relative. These persons must have no connection whatsoever to the investigator or the sponsor.

In accordance with Article L.1122-1-3, since this trial focus on an emergency condition with high mortality and morbidity, the signature of the consent by the patient can be obtained after the treatment has been started. The patient's free and informed written consent will be obtained as soon as the clinical condition of the patient allow it by the investigator, or by a doctor representing the investigator.
if the patient is unable to provide his written informed consent and in the absence of the trustworthy person, next of kin or close relative: a procedure for inclusion in the study in emergency situation will be applied (article L1122-1-2 of the French Public Health Code). In this case, continuation-of-care consent for the study will be signed by the patient (if need be by trustworthy person, family member or close relative) as soon as possible, according to French Law (article L1122-1-2 of the French Public Health Code).

If the patient is a protected adult, in accordance with L.1122-2, the consent will be sought from his legal guardian. Furthermore, in case of death of the patient included in emergency situation, data collected will be used and conserved as part of research.

15.2 Prohibition of concomitant clinical studies participation and exclusion period after the study, if applicable

Whilst participating in this trial, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial. A participation in a non-interventionnal, observational study can be allowed during the trial. There is no exclusion period after the participation of the subject.

15.3 Compensation for participants

15.3.1 Reimbursement of out-of-pocket expenses
Not Applicable

15.3.2 Compensation
Not Applicable

15.4 Registration on a national register of clinical research participants
Not Applicable

15.5 Legal obligations
Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Innovation Department (DRCI) in order to conduct the study in accordance with Article L.1121-1 of the Code de la Santé Publique - CSP (French Public Health Code). AP-HP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

15.6 Request for approval from the CPP
AP-HP, as sponsor, obtains prior approval from the CPP for its Minimal Risk and Restriction research studies, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.
15.7 Informing the ANSM
The AP-HP will send the approval from the CPP and the summary of the protocol to the ANSM, for information.

15.8 Declaration of compliance with the MR 001 "Reference Method"
AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

15.9 Modifications to the study
Any substantial amendment made to the protocol must be sent to the sponsor for approval. Once approval has been received from the sponsor, it must also obtain approval from the CPP before the amendment can be implemented.

The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

15.10 Final Study report
The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority’s guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant.

16 FUNDING AND INSURANCE

16.1 Sources of monetary support
Programme Hospitalier de Recherche Clinique- PHRC 2017 (Ministère de la Santé)

16.2 Insurance
For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor’s own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participants and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. Compensation cannot be refused on the grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique - CSP (French Public Health Code).
17 PUBLICATION RULES

17.1 Mention of AP-HP affiliation for projects sponsored by AP-HP
- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- However, if the research is funded by an internal call for tenders at the AP-HP, the first affiliation must be “AP-HP”
- Each of these affiliations must be identified by an address and separated by a semicolon
- The AP-HP institution must feature under the acronym “AP-HP” first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France.

17.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text
“The sponsor was Assistance Publique – Hôpitaux de Paris (Clinical Research and Innovation Department)”

17.3 Mention of the funder in the acknowledgements of the text
The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2017 (Ministry of Health)”
This research program will be registered on the website http://clinicaltrials.gov/ (include the registration number once registered).

18 REFERENCES


10. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33(14):1787-1847. doi:10.1093/eurheartj/ehs104.


