Title

Evaluation of the ability of the MEESSI-AHF scale to improve decision making and prognosis in patients diagnosed with acute heart failure in the emergency department

(Version 2)

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HEALTH RESEARCH PROJECT APPLICATION REPORT

Title: Evaluation of the ability of the MEESSI-AHF scale to improve decision making and prognosis in patients diagnosed with acute heart failure in the emergency department

Clarification: This is the complete protocol granted by Instituto de Salud Carlos III (Spanish Ministry of Health), and the study that applies to Clinicaltrials.gov registry is only the Study 3 of the present protocol

BACKGROUND AND CURRENT STATUS OF THE TOPIC

Purpose of the project, background and current state of scientific-technical knowledge, national or international groups working in the specific line of the project or in related lines. International groups working in the specific line of the project or in related lines.Cite references in the following section: Most relevant bibliography.

Acute heart failure (AHF) is one of the main causes of hospitalization in Spain (1) and represents one of the greatest economic and health care burdens in any public health care system (2,3). It is associated with high in-hospital and post-discharge mortality and high readmission rates. In Spain, as in many countries with a public health system, the vast majority of patients with AHF are initially attended in hospital emergency departments (ED). Thus, AHF is one of the most frequent diagnoses in the ED; and in Western countries between 3% and 5% of hospital admissions are for AHF, mostly in cardiology and internal medicine departments. In the population over 65 years of age, it is the leading cause of hospitalization and is responsible for 2% of total health care expenditure (1-4).

However, not all patients diagnosed with AHF in the ED are hospitalized. Depending on the country, its healthcare system and the organization of its ED, between 18% and 36% of patients with AHF are discharged directly from the ED after a variable period of observation (5-7). Several studies have shown that this decision can lead to an increased risk of adverse events for the patient, either in the form of a return visit to the ED or hospitalization8 or even death (6). An important element contributing to this increase in adverse events is the lack of risk stratification of patients with AHF in the ED prior to the decision to discharge or admit them, as is done in other circumstances such as acute coronary syndrome (9) or pneumonia (10). To date, only 3 risk scales have been available to be applied to patients with AHF to aid the ED physician's decision making, two developed in Canada (EHMRG (11) and OHFRS (12)) and one in the United States (STRATIFY (13)). Their application in these countries is scarce, and they have not been implemented in Spain to date. In fact, it is possible that their application to AHF patients seen in Spanish EDs may be suboptimal. Thus, when we evaluated the discriminative capacity of the Canadian EHMRG scale in Spain, we observed that it decreased substantially (from an area under the receiver operating characteristic -COR- curve -ABC- of 0.807 in the original study to 0.741 in the Spanish population) (14). The rest of the risk stratification scales that have been described in the literature have been derived from patients hospitalized for AHF and, therefore, are not applicable in the ED where, as mentioned above, between 18%-36% of patients with AHF are discharged without hospitalization.

In this regard, our group has just derived and validated the MEESSI-AHF scale from 8,096 patients with AHF diagnosed in 34 Spanish EDs15. The MEESSI-AHF scale is thus the fourth risk scale to be applied in the ED in patients with AHF, since, like the previous three, it has been developed from the entire universe of patients diagnosed with AHF in the ED, including those admitted and discharged home without admission. The MEESSI-AHF scale stratifies risk based on the probability of death during the 30 days following diagnosis of AHF in the ED. It has a high discriminative power, the best among those published and

discussed in the previous paragraph (11-13), with an ABC COR of 0.836 in the referral cohort and 0.828 in the validation cohort. For a comparison of the main characteristics of the four currently existing scales (STRATIFY, OHFRS, EHMRG and MEESSI-AHF), see the Figure included in the appendix.

The MEESSI-AHF scale proposes a clinical classification into four risk groups: low, medium, high and very high, with all-cause mortalities 30 days after the index event (ED visit) estimated at around 2%, 7%, 15% and 45% for each risk group, respectively. To calculate risk, the scale uses 13 variables available during the patient's first ED visit. This calculation is also facilitated by a freely available online calculator (http://meessi-ahf.risk.score-calculator-ica-semes.portalsemes.org/). Furthermore, the development of the scale provides 7 additional mathematical models to the complete model that allow the calculation of risk even in the absence of 3 of the 13 variables that make up the MEESSI-AHF scale (Barthel index of the patient at the ED, troponin and NT-proBNP, in any combination). The MEESSI-AHF scale proposes that those patients classified as low risk would be ideal for the emergency physician to proceed to direct discharge without hospitalization, since the expected mortality in these patients during the following 30 days is very low (around 2% overall).

Subsequently, we revalidated the MEESSI-AHF scale in a new population of 4711 AHF patients from 30 Spanish EDs. Again, the discriminative ability of the scale was very good (ABC ROC of 0.810) and, more importantly, this ability was similar and without significant differences in university and county hospitals, in EDs with different activity loads, and in those EDs that had previously participated in the original development of the scale and those that had not (unpublished data). In the latter, which was a group of 10 EDs that included patients for the first time, the ABC COR was 0.832. In total, therefore, 41 HEDs have already been involved in the MEESSI-AHF scale development project, which represents 12% of the 339 hospitals in the Spanish public health system.

Therefore, we believe that the MEESSI-AHF scale is ready to face the challenge of trying to effectively help emergency physicians in the decision-making process (discharge or admission) of patients with AHF attended in these departments. The scale could have a double positive impact on AHF patients. On the one hand, it could contribute to improving prognosis in a syndrome, that of AHF, whose prognosis has not changed over the last decades and in which attempts to find pharmacological interventions with positive results have failed (16-18). On the other hand, it could contribute to an improvement in the efficiency of the system by identifying low-risk patients who can potentially be managed on an outpatient basis, without admission, if the results obtained in them are shown to be good. Thus, a percentage of hospital admissions would be avoided.

Ideally, if the decision making made by the emergency physician in current routine clinical practice is correct, the distribution of risk groups in discharged and admitted patients should be markedly different: among the former, low-risk patients should predominate, while among the latter, low-risk patients should be scarce and medium-, high- and very-high-risk patients should predominate. However, this is currently unknown. Secondly, it is important to verify that patients who are classified as low risk by the MEESSI-AHF scale and, as recommended, are discharged, have acceptable adverse event rates, ideally within the recommended standards (19). This has not been proven either, since during the development of the MEESSI-AHF scale only 30-day mortality was used as an adverse event, and furthermore the risk was calculated globally for each risk category, without distinguishing between patients who were discharged and those who were admitted. Recently, an international consensus document has published quality standards to be achieved in the ED for patients with AHF. Specifically, it has proposed a 30-day mortality of less than 2% for patients discharged without hospitalization from the HED with the possibility of maintaining the patient under observation for a period of 24 hours (a circumstance that occurs in most Spanish HEDs), a rate of revisit to the ED for persistence or worsening of AHF during the following 7 days of less than 10% and a rate of revisit to the ED or hospitalization for the same reason at 30 days of less than 20% (19). From the clinical point of view, the low-risk patients on the MEESSI-AHF scale would be those most suitable for discharge directly from the emergency department without hospitalization. And if the results observed in them conform to these proposed standards, this scale could be an ideal instrument

to improve the management of AHF patients in the ED in daily practice based on a better selection of the patient who is in a position to be discharged directly from the ED.

However, the most important effect to demonstrate is that the application of ED risk stratification in AHF patients using the MEESSI-AHF scale can improve these adverse event rates. This requires an experimental approach, not performed so far on any other scale in this context in which we are developing the present project. Currently, the COACH trial is in its initial patient phase, in which, through a randomized clinical trial, the EHMRG scale is measuring the potential impact of its application in routine clinical practice in EDs in the province of Ontario, Canada (20) . This trial is scheduled to be completed by the end of 2019. In addition, the same group of investigators has the ACUTE study underway in which they are validating a new model of the EHMRG scale based on 7- and 30-day mortality (21). We believe that it is a priority objective to complete a similar clinical trial with the MEESSI-AHF scale so that our scale, developed in Spain, can be competitive with the EHMRG scale and, if the results are favorable, can become the scale of choice for use in the ED in Spain and, eventually, in the EDs of other countries.

Therefore, it is the set of these current challenges that have been raised in the previous paragraphs that motivate the present research project whose potential impact is expected to be great if the results are satisfactory, especially with regard to improving the prognosis of patients with AHF, through an early intervention in the ED: namely, risk stratification prior to decision making (discharge/admission) that improves the selection of patients with AHF hospitalized and discharged from the ED.

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HYPOTHESIS

The application in routine clinical practice in Spanish hospital emergency departments (ED) of the MEESSI-AHF scale, which stratifies the risk of patients with acute heart failure (AHF), to assist in the decision to admit the patient to hospital or to discharge the patient directly from the ED, contributes:

1.- To the improvement of the results obtained in the globality of patients with AHF attended in the emergency department in terms of reconsultation to the emergency department, need for rehospitalization and mortality.

2.- Improvement of the results in the subgroup of patients discharged directly from the emergency department, in terms of reconsultation to the emergency department, need for hospitalization and mortality after discharge from the emergency department.

3- Improving the selection of patients to be admitted to the hospital, limiting the admission of low-risk patients, who can be kept under observation in the emergency department for 12-24 hours and discharged without hospitalization.

4- Improving efficiency in the use of hospitalization resources.

OBJECTIVES

1.- To determine the distribution in risk categories according to the MEESSI-AHF scale of AHF patients currently admitted to the hospital from the ED and of patients discharged directly from the ED without admission.

2.-To investigate whether the outcomes obtained in patients classified as low risk by the MEESSI-AHF scale and who are currently discharged directly from the ED are close to internationally recommended standards, especially in terms of reconsultation to the ED, need for hospitalization or mortality during the 7 and 30 days following discharge.

3.- To prospectively evaluate whether ED risk stratification in patients with AHF, using the MEESSI-AHF scale, is able to:

3.A.- Improve short- and long-term outcomes in these patients, both overall and in the subgroup of patients discharged from the ED without hospitalization.

3.B.- Improve the efficiency of the system.

METHODOLOGY SECTION

Design, study subjects, variables, data collection and analysis, and limitations of the study.

The fulfillment of objectives 1 and 2 will be carried out by means of a single study (STUDY 1) of non-interventional design, with consecutive inclusion of patients in 16 Spanish HEDs, and with a 1-year cohort follow-up. In response to objective 3, two different studies have been designed. The first (STUDY 2) consists of a quasi-experimental before/after study comparing the results obtained in patients with AHF attended in 10 Spanish EDs before and after the implementation of the MEESSI-AHF scale to stratify the risk of patients with AHF in the ED before the decision to admit or discharge them. The second (STUDY 3) will consist of a multicenter, randomized, open-label, clinical trial comparing the effect of risk stratification of AHF patients in the emergency department using the MEESSI-AHF scale prior to the decision to admit or discharge the patient.

Ethical aspects: The three studies will be carried out in compliance with the Declaration of Helsinki on research in human beings, the Research Ethics Committees will have been approved and all patients will sign Informed Consent prior to their inclusion in the studies.

STUDY 1

Design: Descriptive, multicenter, non-interventional, with consecutive inclusion of patients and 1-year cohort follow-up.

Study Subjects: All patients older than 14 years who consulted in the 16 participating EDs for symptoms and signs compatible with AHF following the Framinham criteria (Ho et al. Circulation 1993; 88:107-15) will be consecutively included and the diagnosis will be verified by determination of natriuretic peptides (BNP or NT-proBNP) (Ponikowski et al. Eur Heart J. 2016;37:2129-200). Failure to confirm clinical suspicion by natriuretic peptide (because it is not determined or is not above the values considered diagnostic) or if the patient presents an episode of AHF in the context of ST-segment elevation acute coronary syndrome (STEMI) will be exclusion criteria, as in most of these cases the patient is transferred to the cardiac hemodynamics unit with minimal ED intervention.

Variables: As independent variables, more than 40 variables will be collected (see appendix) that a priori can potentially be related to the clinical evolution of patients (demographics, personal history, usual chronic treatment at home, baseline functional status and in the acute episode, clinical, analytical and ECG variables of the patient on arrival at the ED, and treatment and management in the ED, including the final destination of the patient after care -discharge/admission-) that are commonly used by the group in their work (Chest 2017; 152: 821-832; JACC Heart Fail 2018; 6:52-62; Eur J Heart Failure 2017; 19:1205-1209), including those necessary for the calculation of the MEESSI-AHF scale score and patient stratification (Ann Intern Med 2017; 167:698-705). As outcome variables will be collected: 1) cardiovascular and all-cause mortality during the 30 days and year of the index event (ED consultation); 2) ED reconsultation (without admission) for AHF 30 days post-discharge; 3) hospitalization for AHF 30 days post-discharge; 4) all-cause mortality 30 days post-discharge; 5) the combined variable of 2+3+4 30 days post-discharge, and 6) days alive and out of hospital during the 30 days after the index event. Follow-up will be by telephone call to the patient or family member and consultation of hospital and primary care medical records (informed consent will have been collected for this). The adjudication and validation of the event will be carried out

by the PIs of each center. Given that these are easily objectifiable variables (mortality, admission, emergency consultation), it was not considered necessary for the events to be validated by an external researcher blinded to the MEESSI-AHF application.

Data collection and analysis: Data will be collected on a sheet specifically designed for this purpose, with which the 16 EDs of the participating centers are already familiar due to their previous participation in the EAHFE Registry. To answer Objective 1, the classification variable will be the patient's destination after ED attendance: discharge or admission. In all patients, the MEESSI-AHF score will be calculated retrospectively and they will be classified as low, medium, high or very high risk. The distribution of these risk categories will be compared between both groups (discharge/admission). In addition, the characteristics of low-risk patients in both groups (discharge/admission) will be compared and the propensity for a low-risk patient to be admitted to the hospital will be investigated using multiple logistic regression. The aim is to better understand the factors associated with a likely avoidable hospital admission. On the other hand, medium, high and very high risk patients will be grouped and their characteristics will be compared in both groups (discharge/admission) and the propensity for a medium, high or very high risk patient to be discharged from the emergency department will be assessed by multiple logistic regression. The aim is to better understand the factors associated with probably inappropriate discharges from the ED. For Aim 2, we will compare outcomes obtained in the group of low-risk patients discharged from the ED with published standards: 30-day post-discharge all-cause mortality <2%, 7-day post-discharge ED reconsultation for AHF <10% (this outcome variable will be calculated in this study specifically for this comparison), and 30-day post-discharge ED reconsultation or hospitalization for AHF <20% (Miró et al. Eur J Emerg Med 2017; 24:2-12).

Study limitations: 1) Center selection bias (non-randomized).

STUDY 2

Design: Quasi-experimental before/after study of the effect of implementing the MEESSI-AHF tool to stratify the risk of AHF patients in the ED. Six EDs participating in Study 1 (pre phase) will participate in the present Study 2. After the conclusion of Study 1, the professionals of the 10 EDs will be trained in the use of the MEESSI-AHF scale to stratify risk (post phase). There will be a digital tablet in a centralized location in the ED exclusively dedicated to the calculation of the MEESSI-AHF score. The calculator, which is also available online (https://semes.org/calculadora-meessi-ahf) facilitates scoring and classifies the patient into one of four risk categories: low, medium, high or very high. If the patient's classification is "low risk", the system will make the proposal that the patient can be discharged if he or she has shown improvement after the observation period in the emergency department. The ultimate decision, however, will be made by the attending physician. If the patient is not discharged, the reason for not doing so will be classified as: 1) subjective assessment of severity; 2) difficulty of out-of-hospital medical management; 3) lack of out-of-hospital social support; 4) disagreement with the physician's discharge decision, with family or patient refusal; 5) need for admission for an active medical reason not directly related to AHF; and 6) other situations (note). If the patient's classification is "Medium Risk", "High Risk" or "Very High Risk", the system will make the proposal that the patient should be admitted to the hospital. The final decision, however, will be made by the attending physician. If admission is not carried out, the reason for not admitting the patient will be classified, which may be: 1) subjective assessment of non-severity; 2) decision to limit treatment and follow-up at home; 3) disagreement with the physician's decision to admit, with the decision of the family member or the patient to be discharged; and 4) other situations (note).

Study subjects: The inclusion and exclusion criteria will be the same as for Study 1.

Variables: The independent variables will be the same as in Study 1. There will be two primary outcome variables (PROMs): PROM-1) the 1-year all-cause mortality for the overall patients included in the study (regardless of their risk category); and PROM-2) the combined variable of ED revisit, hospitalization or death at 30 days post-discharge for patients discharged directly from the ED. Secondary outcome variables will be the rest of those mentioned in Study 1. In addition, as a measure of efficiency, the percentage of

patients discharged without admission before and after the intervention with the MEESSI-AHF scale will be counted.

Sample size calculation: Presented with Study 3 (see below).

Data collection and analysis: Presented with Study 3 (see below).

Study limitations: 1) center selection bias; 2) cohort bias.

STUDY 3

Design: Multicenter, randomized, open clinical trial, without pharmacological intervention, in which the effect of risk stratification in the ED of patients with AHF using the MEESSI-AHF scale prior to the decision to admit or discharge will be evaluated compared to standard medical practice (without risk stratification). The 10 EDs in Study 1 that do not participate in Study 2 will participate in the study, in an attempt to limit contamination, and inclusion will be competitive. Randomization will be performed at the individual level, as the low number of participating EDs and the high heterogeneity of ED organizational models and postal care circuits make this more advisable than randomization by center. Randomization will determine the formation of the two arms of the study (1:1): patients assigned to "usual medical practice" (control group, CG) and those assigned to "risk stratification" (intervention group, IG), which will be done by means of a list provided to each center. The training of emergency professionals and the decision proposal provided by the MEESSI-AHF scale will be the same as in Study 2. The final decision on admission or discharge will depend, as in Study 2, on the emergency physician in charge of the patient, and if this decision differs from that proposed by the stratification, the reason will be stated (the same as in Study 2).

Study subjects: All patients diagnosed with AHF in the ED and who meet the inclusion and exclusion criteria mentioned in Study 1 will be eligible.

Variables: The independent variables will be the same as in Study 1 with the addition of the center and professional variables. The primary and secondary outcome variables will also be the same as in Study 2.

Sample size calculation (common with Study 2): Since the objectives of assessing the effect of the MEESSI-AHF scale on the clinical course of AHF patients in Studies 2 and 3 are the same, the necessary evaluable sample size calculation is the same for both studies, and the principles used are discussed below. On the one hand, the rate of VPR-1 in our setting is around 30% (Llorens et al. Emergencias. 2015; 27:11-22). On the other hand, patients discharged from the ED account for 30% of AHFs seen in the ED, and it is estimated that 25% of them will present the event defined by PRV-2. We intend to show that the use of the MESSI-AHF classification could have a significant impact on a decrease in both PRVs. The 6 centers of Study 2 could assess about 2000 patients in each of the phases of the development of this project. Thus, with 2027 patients, a decrease in 1-year mortality (PRV-1) from 30% to 26% could be seen as statistically significant. As 30% of patients with AHF seen in the ED are discharged, this represents about 600 patients. With 568 patients, a statistically significant decrease in the combined variable (PRV-2) from 25% to 18% can be assessed as statistically significant. With all this, with the inclusion of a little more than 4000 patients (Study 2: 2027 in pre-phase, 2027 in post phase; Study 3: 2027 in GI, 2027 in CG) we could achieve an assessment of a relative decrease as relevant of 13% for PRV-1 and 28% in PRV-2. Calculations were performed using a bilateral type I error of 5% and a statistical power of 80% using the nQuery Advisor program (Ver. 7.0).

Data collection and analysis (common with Study 2): The outcome variables in Studies 2 and 3 will be analyzed using logistic or Cox regression models, depending on whether or not it is of interest to contextualize the time of occurrence of the event studied. Specifically, in Study 2, in addition to the application of the MEESSI-AHF scale, the influence of other independent factors of interest in conjunction with the MEESSI-AHF scale will be assessed using multivariate models. In the case of Study 3, since it is a study with randomization by patient (and not stratified by center or professional), it is

proposed that the estimation of the application of MEESSI-AHF should always be adjusted by center and professional in charge of the patient. More exhaustive details of the analysis procedures for the three studies will be reflected in a Statistical Analysis Plan (SAP) agreed with the PI of the project before the closure of the different databases. It will describe in detail both the main analysis population criteria for each study and the statistical analysis of the data. Likewise, the strategy for handling missing data or loss to follow-up of patients will be elaborated.

We would like to point out that the paradigm on which the non-observational part of this research focuses, the use of MEESSI-AHF as an aid in the decision to discharge/admit patients with AHF to the ED, has non-trivial weaknesses. In the case of Study 2, the fact that the two groups (usual clinical practice, pre-phase; and use of the MEESSI-AHF scale; post phase) are not contemporaneous could have an impact on cohort bias, since part of the differences could be due to the temporal effect in the inclusion of patients. In the case of the randomized experimental design, Study 3, the main bias may come from contamination between groups. Given that the patients will be randomized, it is possible that, due to experience of use, there may be professionals who intuit the result that could occur with the MEESSI-AHF scale in patients randomized to routine clinical practice and make the discharge/admission decision in this group with a certain influence of the intervention under study (use of the risk stratification tool). It is therefore proposed that the positive conclusion of the implementation of the MEESSI-AHF scale should be based on obtaining positive results simultaneously in Studies 2 and 3. If not, a post-hoc evaluation of the studies will be necessary to assess possible biases and the impact on the results.

The main termination rule for Study 3, of longer duration than Study 2, would be that in the analysis of PRV-2, which is done at 30 days, a significantly worse evolution is observed in patients in the IG compared to the CG. For this procedure, a specific working group will be created, which will be made up of independent professionals.

HEALTH RESEARCH PROJECT APPLICATION REPORT. WORK PLAN SECTION

Stages of development and distribution of the tasks of the entire research team, and the assignments foreseen for the technical personnel requested. Technical personnel requested. Also indicate the place/center where the project will be carried out.

Stage 0: Preparation phase of the 16 participating EDs, with detailed discussion of the protocol and the data collection notebook. Coordination of the PI with the coordinators of each of the EDs, and of the coordinators of each ED with the professionals working in the ED, will be required. Time required: 3 months (from month 0 to month 3).

Stage 1: Field phase (recruitment of patients) of Study 1 and in which the 16 EDs involved in this project will participate. In 6 of these centers, the patients included in this study will also be used in Study 2 (quasi-experimental, pre-stage). Given that the average daily inclusion rate obtained in previous studies is between 3 and 5 patients per center (we consider as a determining factor for the calculation the inclusion of 4 patients/day in the 6 centers participating in Study 2 and the need for these to reach an N of 2,027, which will constitute the patients in the pre-phase of Study 2), a period of 84.5 days will be necessary. In that period, it is estimated that the 16 centers will include over 5,000 patients. Time required: 3 months (month 4 to month 6).

Stage 2: Entry of the data from Study 1 into the database, and first analysis (corresponding to the short-term results, 30 days) of the objectives set in Study 1.

Stage 3: Study of the status of Study 1 patients one year after the index event (emergency department visit). Time needed: 2 months, 12 months after the end of Stage 1 (months 19 and 20).

Stage 4: Entry of the remaining data from Study 1 into the database, final analysis of the objectives set out in Study 1 (including long-term results). Communication of results. Time required: 4 months (months 21 to 24).

Stage 5: Preparation of the emergency professionals of the 6 centers participating in Study 2 (quasi-experimental; post-phase), with training in the use of the risk stratification calculator using the MEESSI-AHF scale. Time required: 2 months (from month 7 to month 8).

Stage 6: Field phase (patient inclusion) of Study 2 (post phase), with an approximate N of 2,027 patients (3 patients per center per day). Time required: 4 months (from month 9 to month 12).

Stage 7: Entry of the data from Study 2 (post phase) into the database, and first analysis (corresponding to the short-term results, 30 days) of the objectives set in Study 2. Time required: 6 months (from month 13 to month 18).

Stage 8: Study of the status of Study 2 patients (post phase) at one year after the index event (emergency room visit). Time required: 2 months, 12 months after the end of Stage 6 (months 25 and 26).

Stage 9: Entry of the remaining data from Study 2 into the database, final analysis of the objectives set in Study 2 (including long-term results). Communication of results. Time required: 4 months (months 27 to 30).

Stage 10: Preparation of the emergency professionals of the 10 centers participating in Study 3 (clinical trial), with training in the use of the risk stratification calculator using the MEESSI-AHF scale. Review of the inclusion and exclusion protocol, randomization procedure, and allocation arms. Time required: 3 months (month 7 to month 9).

Stage 11: Inclusion of patients in Study 3. It is planned to randomize 1-2 patients per center per day (1.5 on average), until reaching the total N (4,054 patients; 2,027 per arm). Time required: 9 months (month 10 to month 18).

Stage 12: Entry of Study 3 data into the database, and first analysis (corresponding to short-term results, 30 days) of the objectives set in Study 3. Time required: 6 months (month 19 to month 24).

Stage 13: Study of the status of Study 3 patients (post phase) one year after the index event (emergency department visit). Time required: 2 months, 12 months after the end of Stage 11 (months 31 and 32).

Stage 14: Entry of the remaining data from Study 3 into the database, final analysis of the objectives set out in Study 2 (including long-term results). Communication of results. Time required: 4 months (months 33 to 36).