CLINICAL TRIAL PROJECT

A MULTICENTER, OPEN-LABELED, RANDOMIZED CONTROLLED TRIAL COMPARING MIDAZOLAM VERSUS MORPHINE IN ACUTE CARDIOGENIC PULMONARY EDEMA (MIMO TRIAL)

VERSION 2

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Protocol Code: MIMO/2016

EudraCT number: 2016-000884-17

Promoter and Chief Investigator

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INDEX.

A MULTICENTER, OPEN-LABELED, RANDOMIZED CONTROLLED TRIAL COMPARING MIDAZOLAM VERSUS MORPHINE IN ACUTE CARDIOGENIC PULMONARY EDEMA (MIMO TRIAL)

I. SUMMARY

1. STUDY PROMOTER: Dr. Alberto Domínguez-Rodríguez.

2. STUDY TITLE: Multicenter, open-labeled, randomized controlled trial comparing Midazolam versus Morphine in acute cardiogenic pulmonary edema "MINO trial"

3. PROTOCOL:code:
MIMO/2016
Nº EUDRACT: 2016-00884-17

4. EXECUTIVE COMMITTEE:

Dr. Alberto Domínguez-Rodríguez (Promoter) / Dr. Guillermo Burillo-Putze / Dr. Coral Suero / Dr. Pedro Abreu-González / Dr. Óscar Mirò.

5. CENTERS PARTICIPATING IN THE TRIAL:

It is foreseen that 14 national hospitals will participate in the trial.

6. **ETHICAL COMMITTEE OF INVESTIGATION WITH MEDICATIONS APPROVED BY THE TRIAL**: CEIm of the *Hospital Universitario de Canarias.*

7. PERSONS RESPONSIBLE FOR MONITORING ADVERSE EVENTS:

Dr. Ana Aldea-Perona / Dr. Patricia Rodríguez-Fortunez / Dr. Consuelo Rodríguez- Jiménez / Dr. Néstor Baez-Ferrer.

8. GROUP AND PHARMACEUTICALS:

- Study drug: MORPHINE **HYDROCHLORIDE**
- **Morphine hydrochloride**: **Presentation:** vials of 10 mg/ml (1%), 1 ml vial containing 10 mg*.

  Administration: initial i.v. dose: dilute 1 vial in 9 ml of physiological serum (1ml = 1 mg). Begin slowly administering 2-3 ml of the i.v. dilution (2-3 mg) and continue every 5 min with 1 ml (1mg) until achieving the

desired effect, the appearance of secondary effects or reaching the maximum total dose of 8 mg (8 ml).

*Other presentations of morphine hydrochloride with concentrations of 20 mg/ml should not be used.

GROUP II:

- Medication under investigation: **MIDAZOLAM HYDROCHLORIDE**
- **Midazolam: Presentation:** Midazolam injectable solution 1 mg/ml, 5 ml vial containing 5 mg**.

Administration: initial i.v. dose of 1 mg (1 ml of the vial) that should be administered in less than 30 seconds. If there is no clinical improvement the same dose can be repeated (1 mg) every 10 minutes with the same form of administration until achieving the desired effects, appearance of secondary effects or reaching the maximum total dose of 3 mg.

*Other presentations of midazolam with concentrations of 5 mg/ml should not be used.

9. TRIAL PHASE: Phase IV clinical trail

10. PRINCIPAL OBJECTIVE: Evaluate the difference in in-hospital survival of patients with acute pulmonary edema receiving the usual medical treatment after the addition of midazolam versus morphine.

11. STUDY DESIGN: Prospective, multicenter, randomized, open-label, phase IV clinical trial.

12. DISEASE OR DISORDER UNDER STUDY: Acute pulmonary edema defined as severe respiratory difficulty which worsens in supine, with clinical and radiological signs of pulmonary congestion requiring urgent treatment.

13. PRINCIPAL OUTCOME VARIABLE: In-hospital mortality.

14. STUDY POPULATION AND TOTAL NUMBER OF PATIENTS: The total number of patients is 136 with acute heart failure. Sixty-eight (68) patients will receive treatment with intravenous morphine added to standard medical therapy for this disease and will be compared with 68 patients who will receive treatment with intravenous midazolam.

15. STUDY DURATION: our study lasted 4 years and included only 111 patients during this period. Two reasons may explain this low inclusion rate: a) 667 cases were excluded because of the use of morphine by emergency medical services before emergency arrival.

16. CALENDAR AND FORESEEN FINALIZATION DATE:

INITIATION: January 2017

FINALIZATION: December 2020

II. GENERAL INFORMATION

A) IDENTIFICATION OF THE TRIAL:

- **PROTOCOL CODE**: MIMO/2016
- **EudraCT number**: 2016-000884-17.

17. TITLE: Multicenter, open-labeled, randomized controlled trial comparing Midazolam versus Morphine in acute cardiogenic pulmonary edema "MINO trial"

B) TYPE OF CLINICAL TRIAL:

Multicenter, randomized phase IV clinical trial open to the administration of midazolam versus morphine in patients with acute pulmonary edema.

Clinical trial with authorized low level of intervention medications.

C) DESCRIPTION OF THE STUDY PROTOCOL

Experimental drug: Intravenous solution of morphine hydrochloride

Mechanism of action and pharmacokineetics: Pentacyclin alkaloid. The structure of morphine is rigid and T-shaped. It is considered to be derived from phenanthrene or as a derivative of 4-phenylpiperidine. It is a powerful agonist of opioid μ receptors. From a clinical point of view, stimulation of μ receptors produces analgesia, euphoria, circulatory depression, reduction of peristaltism, myosis and dependence. Other clinical effects which may be produced by opioids include suppression of cough, hypotension and nausea/vomiting. Hypotension is due to a increase in the release of histamine and depression of the vasomotor

center of the medulla. The induction of nausea is the result of direct stimulation of

the vestibular system.

The cardiovascular effects of morphine are complex because of the involvement of neurogenic, cardiac and vascular factors as well as the physiological status of the person. If pulmonary ventilation is ensured, cardiovascular function resists the action of morphine. It can produce bradycardia of vagal origin, which is more notable if the administration is intravenous. It also induces hypotension due to action on the vasomotor center as well as arterial and venous vasodilatation which has repercussion on the reduction of after- and preload, respectively. Morphine induces vasodilatation of brain circulation due to the increase of pCO_2, with elevation of intracranial pressure.

Control drug: Intravenous solution of midazolam.

Mechanism of action and pharmacokinetics: Midazolam is a drug with a short depressive action on the central nervous system with sedative and anxiolytic properties. The half life of elimination is 1-12 hours, and it is rapidly metabolized in the liver to 1-hydroxyaceyl midazolam and excreted in the urine. Following intravenous administration, sedation appears in 3-5 minutes and is maximum at 5-10 minutes.

The use of morphine and its analogs is mentioned in the 2008 national guidelines on the management of heart failure (Dickstein K et al. Guidelines for Clinical Practice of the European Society of Cardiology (ESC) for the diagnosis and treatment of acute and chronic heart failure (2008) Rev Esp Cardiol. 2008;61(12):1329.e1-1329.e70) in the initial phases of treatment of patients hospitalized for acute pulmonary edema (APE), especially in cases presenting agitation, dyspnea, anxiety or chest pain. In patients with APE, morphine alleviates dyspnea and other symptoms and can favor patient cooperation during the application of non invasive ventilation. Nonetheless, the same guideline mentions that the evidence favoring the use of morphine in APE is scarce. When heart failure is a complication of ischemic cardiopathy or the patient presents bradyarrhythmias, the use of benzodiazepines is preferred to avoid the hemodynamic effects of morphine (Bosomworth J. Rural treatment of acute

cardiogenic pulmonary edema:

applying the evidence to achieve success with failure. Can J Rural Med. 2008;13:121-8 /// Ellingsrud C, Agewall S. Morphine in the treatment of acute pulmonary oedema--Why? Int J Cardiol. 2016;202:870-3.)

D) STUDY PROMOTER – CHIEF INVESTIGATOR

Dr. Alberto Domínguez-Rodríguez

Servicio de Cardiología. Hospital Universitario de Canarias. Ofra s/n, 38320 La Laguna. Tenerife.

Telephone: (922) 679040.

E-mail: adrvdg@hotmail.com

E) MONITOR AND PROMOTER CONTACT FOR PHARMACOVIGILANCE

Dr. Ana Aldea-Perona

Servicio de Farmacología clínica

Hospital Universitario de Canarias

Teléfono: (922) 67 8117

e-mail: a.aldea@gmail.com

FAX: 922 677284

F) INVESTIGATORS:

See list of investigators attached.

G) CENTERS WHERE THE CLINICAL TRIAL WILL BE PERFORMED:

Hospital Universitario de Canarias, Hospital de la Axarquia, Hospital Clínico de Barcelona, Hospital Universitario Reina Sofía de Córdoba, Hospital Universitario Reina Sofía de Murcia, Hospital General de Alicante, Hospital Clínico San Carlos de Madrid.

H) **IDENTIFICATION OF THE ETHICAL COMMITTEE OF INVESTIGATION WITH DRUGS RECIEVING A FAVORABLE REPORT FOR PERFORMING THE TRIAL:** *CEIm DEL HOSPITAL UNIVERSITARIO DE CANARIAS.*

I) FORESEEN DURATION OF THE TRIAL

Our study lasted 4 years and included only 111 patients during this period. Two reasons may explain this low inclusion rate: a) 667 cases were excluded because of the use of morphine by emergency medical services before emergency arrival.

III. JUSTIFICATION AND OBJECTIVES

Acute cardiogenic pulmonary edema is an acute severe disease requiring emergency treatment. The treatment of chronic heart failure is well defined in the guidelines and has demonstrated to improve the life expectancy of affected patients[1,2,3]. However, in the case of APE, while the currently available diuretics and vasodilators are widely used they have not been shown to reduce mortality. In addition, there are few large clinical trials on the treatment of APE in emergency departments (EDs) and the recommendations of the current guidelines are supported by only low levels of evidence[1,2]. Nonetheless, at present it is widely accepted that the first step in the treatment of APE is immediate treatment in the ED[4,5].

The current focus of treatment in patients with APE in the ED is to improve the signs and symptoms of patients, correct the volume overload, increase the perfusion of end organs and improve the hemodynamic status counteracting neurohormonal hyperactivation which constitutes the principal physiological mechanism of the disease[6]. It has been demonstrated that an energetic adequate approach to the treatment of APE is useful to improve the clinical outcomes of the patients[7].

Diuretics continue to be the cornerstone of APE treatment. The current international guidelines consider that intravenous loop diuretics are the first line treatment in patients with APE[8].

Vasodilatators together with diuretics are the drugs most commonly used for APE in the ED. These drugs reduce the preload, the afterload or both by producing arterial and venous dilatation, thereby reducing the left ventricular filling pressure and increasing the ejection volume and improving the peripheral oxygen supply[9]. International guidelines recommend the use of vasodilators in patients with APE as

an adjuvant to diuretic treatment for rapid resolution of the congestive symptoms of normotensive or hypertensive patients who do not present severe obstructive valve disease. The vasodilators most commonly used in the treatment of APE are nitroglycerine and nitroprusiate[2].

The use of morphine in the treatment of APE is uncertain. The use of opioids is contemplated in the Spanish and European guidelines[2,3] , in the initial phase of treatment of patients hospitalized for APE, especially in cases presenting agitation, dyspnea, anxiety or chest pain. In patients with APE, morphine alleviates dyspnea and other symptoms and favors patient cooperation during the application of non invasive ventilation. However, it has been described that morphine reduces the preload and the heart rate and has sedative properties. On some occasions, benzodiazepines are used to avoid the hemodynamic effects of morphine[10]. The net effect of morphine is a reduction of myocardial oxygen demand[11]. While the ESC suppports the use of opioids in the treatment of APE, the same cannot be said of the American Heart Association[12]. The guideline of the Heart Failure Society of America makes no formal recommendation with regard to morphine, but does state that it should be used with caution[1].

The most common adverse effects of morphine are constipation and nausea. While constipation is not especially important in the acute medical context, it has been described that 25-35% of patients report nausea with the use of morphine[13]. The European regulations recommend the addition of 10 mg of metoclopramide to counteract nausea if morphine is administered [2]. Nausea in APE is an unfavorable secondary effect due to subjective malaise and because nausea produces the release of catecholamines, and thus, increases the afterload[13].

A terrible secondary effect of morphine is respiratory depression. Morphine acts directly on opioid μ receptors located in neurons of nuclei with bulbous protuberances which participate in the function of the respiratory center. In humans it especially depresses the respiratory rate, slowing it until apnea is produced with very high doses or it favors the onset of abnormal respiratory rates. In addition, morphine produces a loss of sensitivity to CO_2 in the respiratory center while, on the other hand, maintaining sensitivity to hypoxia. The grade of respiratory depression depends on not only the dose but also the

pathway, being maximum when administered intravenously and minimum when given orally or by epidural injection[14,15].

A recent observational analysis of the ADHERE registry reported that the use of morphine is associated with a worse clinical evolution, including the need for mechanical ventilation, longer hospitalization, more admissions to an intensive care unit and greater risk-adjusted mortality[16]. It is therefore of interest to perform a prospective randomized trial to evaluate survival following the use of morphine in patients with APE.

OBJECTIVE:

1. Principal objective: Evaluate the difference in in-hospital survival of patients with acute pulmonary edema who receive the usual medial therapy and the addition of midazolam versus morphine.
2. Secondary objectives: 30-day all-cause mortality, use of invasive mechanical ventilation and length of hospital stay (from emergency department arrival to final discharge, either home or due to death). The reporting of adverse event was considered the main safety endpoint. A composite endpoint formed by 30-day mortality and serious adverse event.

IV. TYPE AND DESIGN OF THE CLINICAL TRIAL

a) Design of the clinical trial

This will be a multicenter, randomized study open to the administration of morphine in patients with a diagnosis of acute pulmonary edema requiring treatment in a hospital emergency department.

Group I: Will receive morphine hydrochloride

- **Administration:** intravenous.
- **Presentation:** 10 mg/ml (1%) vials, vial of 1 ml containing 10 mg*.
- **Dose and administration**: initial i.v. dose: dilute 1 vial in 9 ml of physiological serum (1ml = 1 mg). Begin administering 2-3 ml (2-3 mg) of the i.v. dilution slowly and continue every 5 min with 1 ml (1 mg) until

achieving the desired effects, the appearance of secondary effects or until reaching the maximum total dose of 8 mg.

- *Other presentations of morphine hydrochloride with concentrations of 20 mg/ml should not be used.

Group II: Will receive midazolam hydrochloride

- **Administration**: intravenous.
- **Presentation:** injectable 1 mg/ml solution, 5 ml vial containing 5 mg**.
- **Dose and administration:** initial i.v. dose of 1 mg (1 ml of the vial) which should be administered in at least 30 seconds. If no clinical improvement is observed the same dose (1 mg) can be repeated every 10 minutes with the route of administration until achieving the desired effects, the appearance of secondary effects or until reaching the total maximum dose of 3 mg.
- ** Other presentations of midazolam with concentrations of 5 mg/ml should not be used

In addition, both groups will receive the usual systematic treatment for acute pulmonary edema (diuretics, vasodilators and oxygen therapy).

b) Randomization procedure

At emergency department arrival eligible patients were randomized in a 1:1 ratio to either midazolam (administered intravenously at a dosage of 1 mg, up to a maximum dose of 3 mg) or morphine (administered intravenously at a dosage of 2-4 mg, up to a maximum dose of 8 mg) via a password-protected encrypted website that uses a computer-generated minimization algorithm to ensure balance between the treatment groups.

c) Blinding process

The administration of the two drugs is not blinded since the administration dose is different.

V. PATIENT SELECTION

A. INCLUSION CRITERIA

A priori all patients attending the emergency departments of the participating

hospitals with a diagnosis of acute pulmonary edema and fulfill the following conditions will be included in the study:

- ✓ Age more than 18 years
- ✓ Symptoms of anxiety and/or acute dyspnea
- ✓ Consent to participate in the study.

B. EXCLUSION CRITERIA PRIOR TO INCLUSION IN THE STUDY:

Patients with acute pulmonary edema who fulfill any of the following criteria will not be included in the study:

- ✓ Patients receiving kidney dialysis
- ✓ Severe concomitant disease with short-term prognosis.
- ✓ Inability to provide informed consent.
- ✓ Participation in another study.

C. CALCULATION OF SAMPLE SIZE

In a study of a historical cohort of patients included in the ADHERE[14] registry it has been demonstrated that the mortality of patients receiving morphine compared to those not receiving this drug was 13% versus 2.4%, respectively.

To calculate the sample size of this clinical trial we have assumed the results of the ADHERE[14]registry, and thus, for a power of 80% and accepting an alpha risk of 0.05 and a beta risk of 0.2 in one-sided contrast, 68 subjects are required for the group receiving morphine and 68 in the group with midazolam to detect statistically significant differences between two proportions, which is expected to be of 13% for group 1 and 2.4% for group 2. A 0% loss to follow-up is estimated. This sample size allows detecting statistical significance with a $p < 0.05$.

On the other hand, the participation of the patients in this study is voluntary, and they can refuse to participate or withdraw from the study whenever they so wish without this affecting future medical care. Their evolution will be evaluated in a strict and fully complete manner. After having accepted to participate, this evolution will be immediately registered throughout hospital stay and at the time of hospital discharge. The participation of patients in this study will not induce added costs. Likewise, the Principal Investigator of the study can withdraw the patient

without need for consent for any reason considered appropriate, such as an adverse effect which may place the patient at risk of additional complications, among others.

D. STUDY DURATION

Our study lasted 4 years and included only 111 patients during this period. Two reasons may explain this low inclusion rate: a) 667 cases were excluded because of the use of morphine by emergency medical services before emergency arrival

Recruitment period: January 2017.

Finalization of the study: December 2020.

VI. DESCRIPTION OF THE TREATMENT

A. STUDY DRUG AND DOSE:

Experimental drug: Intravenous solution of morphine hydrochloride

Mechanism of action and pharmacokinetics: Pentacyclic alkaloid. The structure of morphine is rigid and T-shaped. It may be considered as derived from phenanthrene or as a derivative of 4-phenylpiperidine. It is a powerful agonist of opioid μ receptors. From a clinical point of view, stimulation of μ receptors produces analgesia, euphoria, circulatory depression, reduction of peristaltism, myosis and dependence. Other clinical effects which may be produced by opioids include suppression of cough, hypotension and nausea/vomiting. Hypotension is due to a increase in the release of histamine and depression of the vasomotor center of the medulla. The induction of nausea is the result of direct stimulation of the vestibular system.

The cardiovascular effects of morphine are complex because of the involvement of neurogenic, cardiac and vascular factors as well as the physiological status of the person. If pulmonary ventilation is ensured, cardiovascular function resists the action of morphine. It can produce bradycardia of vagal origin, which is more notable if the administration is intravenous. It also induces hypotension due to action on the vasomotor center as well as arterial and venous vasodilatation which has repercussion on the reduction of after- and preload, respectively. Morphine induces vasodilatation of brain circulation due to

the increase of pCO2, with elevation of intracranial pressure.

- **Presentation:** 10 mg/ml (1%) vials, vial of 1 ml containing 10 mg*.
- **Dose and administration**: initial i.v. dose: dilute 1 vial in 9 ml of physiological serum (1ml = 1 mg). Begin administering 2-3 ml (2-3 mg) of the i.v. dilution slowly and continue every 5 min with 1 ml (1 mg) until achieving the desired effects, the appearance of secondary effects or until reaching the maximum total dose of 8 mg.

B. CONTROL DRUG AND DOSE

***C.* Control drug: Intravenous solution of midazolam.**

D. Mechanism of action and pharmacokinetics: Midazolam is a drug with a short depressive action on the central nervous system with sedative and ansiolytic properties. The half life of elimination is 1-12 hours, and it is rapdily metabolized in the liver to 1-hydroxyaceyl midazolam and excreted in the urine. Following intravenous administration, sedation appears in 3-5 minutes and is maximum at 5-10 minutes.

- **Presentation:** injectable 1 mg/ml solution, 5 ml vial containing 5 mg**.
- **Dose and administration:** initial i.v. dose of 1 mg (1 ml of the vial) which should be administered in at least 30 seconds. If no clinical improvement is observed the same dose (1 mg) can be repeated every 10 minutes with the route of administration until achieving the desired effects, the appearance of secondary effects or until the total maximum dose of 3 mg is reached.

. ***C. OTHER TREATMENTS***

The patients will be treated according to the recommendations of the Spanish and European Society of Cardiology for patients with acute pulmonary edema[2].

The clinical decisions related to the therapeutic management of the patients will be left to the criteria of the attending physician.

VII. DEVELOPMENT OF THE TRIAL AND EVALUATON OF RESPONSE

At the beginning of the study informed consent will be obtained from all the patients, and the demographic data of the patients will be registered.

A. EVALUATION OF EFFICACY

The primary end point for comparing midazolam and morphine was in-hospital all-cause mortality. The secondary end points were 30-day all-cause mortality, use of invasive mechanical ventilation and length of hospital stay (from emergency department arrival to final discharge, either home or due to death). The final adjudication of outcomes was performed at a local level by the principal investigator of the center because of the objectivity of the endpoints. The reporting of adverse event was considered the main safety endpoint. A composite endpoint formed by 30-day mortality and serious adverse event.

B. STUDY FOLLOW-UP

Patients of both sexes will be included.

The design of the study is summarized in Annex I.

VIII. ADVERSE EVENTS

A. DEFINITIONS

An **adverse event** (AE) will be defined as any event that occurs during the clinical study whether it be an intercurrent or incidental disease and alters the well-being of the patient. An AE may also be considered as a laboratory abnormality. The term AE does not imply any causal relationship with the study treatment.

All the AE, including intercurrent diseases will be notified and registered as described below.

The AEs will be divided into categories of severe and non severe, which will determine the procedure to follow for the notification and reporting of the same.

An **adverse reaction** will be defined as any harmful and non intentional reaction to the drug under study, independently of the dose administered. An adverse reaction will be considered as unexpected if its nature

or severity does not correspond with the product information (Summary of Product Characteristics and the study drug file).

Diseases or medical conditions present prior to initiating the study will only be considered as AE if they worsen following the initiation of treatment.

Abnormal laboratory values or results will only be considered as AE if they cause clinical signs or symptoms or require treatment. Whenever possible, each AE will also be described based on:

1. The grade of severity (mild, moderate and severe).
2. The relationship with the study drug (suspected/not suspected).
3. The actions taken and, if relevant, the result.

Special attention should be given to withdrawal from treatment due to AE and, if adequate, perform statistical analyses.

B. SEVERE ADVERSE EVENTS OR ADVERSE REACTIONS

A severe adverse event or adverse reaction is defined as:

- Any event causing death or threatening the life of the patient.
- Any event producing permanent discapacity.
- Any event requiring or prolonging hospitalization.
- Any event involving cancer, congenital abnormalities or that is the consequence of an overdose (administration of a dose greater than stipulated).

Hospitalization occurring under the following circumstances will not be considered as severe adverse events: programmed before including the patient in the study, related to the treatment, occurs in an out-patient emergency regimen without the need for admission (provided that the previous criteria are met) or make up part of the normal treatment or monitoring of the indication studied and are not associated with worsening of the disease.

C. NON SEVERE ADVERSE EVENTS OR ADVERSE REACTIONS.

Adverse events or adverse reactions that do not pertain to any of the above mentioned categories will be classified as non severe.

D. CLASSIFICATION OF THE INTENSITY AND RELATIONSHIP WITH THE TREATMENT

Classification of intensity

Regardless of whether the adverse event is classified as severe or non severe (see previous sections), the intensity will be evaluated as mild, moderate or severe according to exclusively medical criteria.

- ***Mild***: Does not impede routine activities

- ***Moderate***: Interferes with routine activities

- ***Severe***: Makes routine activities impossible

It should be taken into account that a severe adverse event may not necessarily be severe and that a severe adverse event is not always, by definition, severe.

All severe adverse events, regardless of their severity, will be registered as described below.

Relationship with treatment

The investigator should attempt to explain and evaluate the relationship of every adverse event with the study treatment (probable, possible, no relationship). The criteria to establish the relationship between adverse clinical reactions and the study drug include:

Probable:

An adverse event is considered to have a probable relationship with the drug if it fulfills the following 3 criteria:

1. There is a reasonable temporal relationship between administration of the drug and the presentation of the adverse event and

2. It fulfills any of the following criteria:

The adverse event is a typical example of a known adverse reaction to the drug so that:

- If treatment is continued, the adverse event will persist.

- If drug administration is discontinued, the adverse event will disappear.
- In the case of re-exposure to the drug, the adverse event will reappear.

3. In the case of another explanation for the adverse event (concomitant treatment, intercurrent disease), this explanation is less probable as a cause of the adverse event.

Possible:

An adverse reaction is considered to possibly be related to the drug if it fulfills the two following criteria:

1. There is a reasonable temporal relationship between the administration of the drug and the adverse event.

2. None of the criteria established in previous point 2 (probable) are met or there is another alternative more plausible explanation for the adverse event.

No relationship:

An adverse event will be classified as having no relationship with the drug if it fulfills any of the following requisites:

1. There is no reasonable temporal relationship between administration of the drug and the onset of the adverse reaction.

2. A causal relationship between the drug and the adverse event is not plausible from a biological point of view.

3. There is a more plausible alternative explanation for the appearance of the adverse event.

E. MONITORING, NOTIFICATION AND REGISTRATION OF THE ADVERSE EVENTS AND ADVERSE REACTIONS.

Monitoring

All the patients presenting adverse events related or not to the study drug will be monitored until the disappearance of the symptoms, laboratory abnormalities have returned to the baseline values or until there is a satisfactory explanation for the changes observed.

Actions to carry out in response to an adverse event

The measures to be taken on the appearance of an adverse event are described on a numerical scale from 0 to 5 covering different possibilities. One or more possibility should be selected.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to adverse events.

Notification and registration:

Adverse events which develop during the trial will be classified as severe and non severe because this classification will determine the procedure to follow for the notification and registration of these events.

Diseases or medical conditions present prior to initiating the study treatment will only be considered as adverse events if they worsen after beginning the treatment.

Abnormal laboratory values or test results will only be considered as adverse events if they cause clinical signs or symptoms or require treatment. Whenever possible, each adverse event will also be described based on:

- Duration (date of initiation and finalization)
- The grade of severity (mild, moderate and severe).
- The relationship with the study drug (suspect/ not suspected).
- The action(s) taken, and, if relevant, the result.
- Special attention should be given to the withdrawal of treatment due to adverse events and, if appropriate, statistical analyses will be performed.

Severe and unexpected adverse events and adverse reactions:

All severe adverse events must be reported within 24 hours to the Chief Investigator of the study, Dr. Alberto Domínguez-Rodríguez, at the email address adrvdg@hotmail.com. The initial communication will be followed by a detailed written report.

In the initial reporting and in that of the follow-up, each study subject will be identified by a specific code number.

In the case of death of a study participant, the investigator will provide the promoter and the Ethical Committees of Clinical Investigation involved with all the complementary information requested.

The Coordinator will notify the Spanish Agency of Medication and Health Care Products and the Center of Pharmacovigilance of Canarias (authority of the Autonomous Community), of all suspicions of a severe adverse reaction and, in turn, unexpected adverse events associated with the study drug during the trial. The maximum notification time will be of 15 days from the time the Promoter was notified of the suspicion of an adverse reaction. If the suspected and unexpected adverse event leads to the death of the subject or threatens the life of the participant, the Promoter will inform the Spanish Agency of Medication and Health Care Products within a maximum time of 7 days from the time at which the Promoter is made aware of the case. This information will be completed as far as possible within the following 8 days.

The Coordinator will maintain a detailed registry of all the adverse events reported by the investigators. These registries will be presented to the Spanish Agency of Medication and Health Care Products upon request.

The periodic safety report will be presented annually to the Spanish Agency of Medication and Health Care Products and the Center of Pharmacovigilance of the Canarias (competent organ of the Autonomous Community) and to the CEIm involved in the study until the end of the trial and whenever requested by the health care authorities or the ethical committees involved in the study.

The Coordinator will continuously evaluate the safety of the study drug using all the information available. Likewise, any relevant information involving the safety of the study drug will be reported without delay to the Spanish Agency of Medication and Health Care Products and the Center of Pharmacovigilance of

Canarias (competent organ of the Autonomous Community) and to the CEIm.

The investigators will also be informed about any subject related to the safety of the study drug and the risk/benefit ratio.

Non severe adverse events or adverse reactions:

These events will be reported in the “adverse events” sheet of the “Data Collection Notebook” and it will not be necessary to follow any special notification procedure. Nonetheless, these adverse events or adverse reactions will be reported in the periodic safety report.

F. CONTACT ADDRESSES FOR THE NOTIFICATION OF ADVERSE EVENTS.

All investigators will notify the Chief-Investigator (Dr.Alberto Domínguez-Rodríguez) of severe adverse events within 24 hours:

adrvdg@hotmail.com

Telephone number: 922679040
Fax number: 922677284

The coordinator will report all suspicions of severe and unexpected adverse reactions to the health care authorities according to the previously established times and procedures.

Notification to the Spanish Agency of Medications will be made using the FAX number +34 918 225 076.

Notification to the corresponding Center of Pharmacovigilance can be made by fax or by post.

IX. ETHICAL ASPECTS

The trial will be performed according to the principles of the Declaration of Helsinki adopted by the 18th World Medical Assembly, Helsinki, Finland in 1964 and amended in Tokyo (1975), Venecia (1983), Hong Kong (1989), South Africa

(1996), Edinburg (2000), Washington (2002), Tokyo (2004), Seoul (2008)and Brazil (2013); the Norms of Good Clinical Practice of the International Harmonization Conference (CPMP/ICH/135/95) and the laws and regulation prevailing in Europe and Spain.

The Coordinating Principal Investigator has presented the protocol to the pertinent Ethical Committee of Investigation of Medication and the trial has been approved. Likewise, approval from the health care authorities will be requested prior to initiation of the trial.

Patients should be adequately informed of the trial and must provide written informed consent. In particular, the following points should must be explained to the patients: Study objective, therapeutic actions and possible secondary effects, duration of the study, potential benefits, other possible therapeutic alternatives, freedom of the patient to choose to participate or not in the trial and decide to prematurely withdraw at any time without this representing any negative consequence to the patient.

All the participants in the trial, the objective and the study content will be managed with confidentiality. The clinical trial will be performed respecting the rights of the subjects and the ethical postulates affecting biomedical investigation in humans. The physical and mental of the subject will be particularly safeguarded as well as their privacy and the protection of their data according to Organic Law 15/1999, of December 13, on the Protection of Data of Personal Nature. Informed consent will be obtained and documented from each of the study subjects, being freely provided prior to inclusion in the study under the terms foreseen in Article 4 of Royal Decree 1090/2015.

X. PRACTICAL CONSIDERATIONS

RESPONSIBILITIES

A) RESPONSIBILITIES OF THE INVESTIGATOR

Approval of this protocol by the Principal Investigator and collaborating investigators will be confirmed by their corresponding signatures (Annex II).

Prior to the inclusion of a patient, the investigator should provide the

Spanish Agency of Medications and Health Care Products with the following documents (copies of which should be maintained by the investigator in the files which will include):

- Signed copy (original) of the approved protocol
- Completed and signed declaration of the investigator.
- Copy of the approval document signed by the Ethical Committee of Clinical Investigation.
- Conformity of the Director of the Center.
- Sample of informed consent document to be used.
- List of normal laboratory values of the center in question.

All the information indicated in this protocol will be carried out in accordance with the Norms of Good Clinical Practice. This includes the possibility of inspection at any time by representatives of the health care authorities. The investigators will provide their conformity with the inspection of the study documents by representatives of the health care authorities.

In addition to all the local regulations applicable, the investigator should respect the following principles:

1* Declaration of Helsinki

2* Spanish Law of Medication

3* Local norms

4* European norms of Good Clinical Practice

B) OTHER RESPONSIBILITIES OF THE COORDINATING INVESTIGATOR

All the Data Collection Notebooks and crude data will be conserved in the Work Center, under the custody of the Principal Investigator during a minimum of 10 years after study finalization. The data will be conserved while the product remains authorized. In the case of expiry of product commercialization, the final report of the trial will be conserved by the promoter during an additional 5-year period. The informed consent documents of the patients will be conserved by the investigators for an equal period of time.

DATA REGISTRY AND TREATMENT

This will be performed following the norms of Royal Decree 1090/2015, which establishes the requisites for performing clinical trials with medications.

A) REPORTING IN THE DATA COLLECTION NOTEBOOKS, SIGNATURE AND FILING

The Data Collection Notebooks will be supplied by the Promoter-Principal Investigator. These documents will be used to report all the information collected along the development of the study to the health care authorities. All the Data Collection Notebooks should be completed by machine or with capital letters in black ink. Corrections should be made by simply crossing out incorrect data with a line and writing the new data alongside. All the corrections should be initialed by the person who made them together with the date and the reason for correction.

The corrected data should not be crossed out so that it is impossible to read and neither should corrector fluid or an eraser be used.

A copy of the Data Collection Notebook of each patient can be sent to the General Pharmacy Administration before finalizing the study, when required by the health care authorities. The investigator will conserve the original notebook. Likewise, the investigator or the person designated by the investigator will be responsible for noting all the data in the Data Collection Notebooks, and will be certified by their signature and date on the opportune pages.

B) SOURCE DATA FILE

All the correspondence related to this clinical study should be conserved in the adequate files.

The registries of the patients, the source documents, the Data Collection Notebooks, the medication inventary and the correspondence between the Ethical Committee and the Promoter should be filed. The investigator should conserve the patient identification codes for a minimum of 15 years after finalization or suspension of the trial. The clinical histories of the patients and other data should be conserved during a maximum period of time allowed by the hospital, institution or private practice.

If an investigator is transferred to another center, withdraws from the investigation or retires, the responsibility of the conservation of the registries can

be transferred to another person (i.e. another investigator) who agrees to accept this responsibility. The Promoter-Principal Investigator will be notified and agree to the transfer of information.

C) DATA MANAGEMENT AND CONTROL

In addition to the Data Collection Notebooks, the investigator should maintain the remaining registries of the subjects including the dates of the revisions and the data referring to: vital signs, medical history or examinations performed, eventual adverse events and findings and all other opportune notes. All this information constitutes the "original data". All the data registered in the Data Collection Notebooks should be supported by the original data.

The Data Collection Notebooks should be adequately maintained and updated so that they always reflect the last observations of the patients included in the study.

The history of each patient should be together with the signed Informed Consent. When the study treatment has finalized, the Informed Consent should be filed with a copy of the Data Collection Notebook, which will include a note indicating where this can be found.

All the original laboratory reports should be available for review in the file of each subject. It is important for the original reports to be available for review due to the possibility of inaccuracies or confusions being produced in the transcription of the data from the original documents to the Data Collection Notebooks.

For each subject included in the study, the Data Collection Notebook should be completed in a legible form signed by the investigator. This will be done as soon as possible after finalization of the treatment. The study monitor will review the Data Collection Notebooks.

After finalization or suspension of the trial, the investigator should conserve the patient identification codes for at least 15 years. The histories of the patients and the remaining data sources should be conserved during the maximum period allowed by the hospital.

D) VERIFICATION OF THE STUDY DATA

Both the study Monitor and the health care authorities can compare the data of the Data Collection Notebooks with the source documents.

SAMPLES

A) SAMPLE MANAGEMENT AND CONSERVATION

The Pharmacy Department will supply the study samples according to normalized working procedures.

The Pharmacy Department will maintain a control sheet of the samples that will be filled in as the samples are supplied to the patients.

XI. STATISTICAL ANALYSIS

Information in the final plan for statistical analysis.

XII. PUBLICATIONS

The data obtained in the clinical trial are the property of the Promoter. They will be used in conjunction by the members of the investigative team of the project and not in an individual manner. Authorization from the Promoter will be necessary for general diffusion or publication of data, information or results related to the trial. The Promoter and the Principal Investigators are obliged to publish the results, whether positive or negative, of the trial in scientific journals and include mention of the Ethical Committee of Investigation with the drugs approved for the study.

XIII. REFERENCES.

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ANNEX I: STUDY DESIGN AND PLANNING

Procedure	Selection Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Remaining admission period	Stay in ICU	Hospital stay
Clinical history	X									
Physical examination	X									
Check inclusion criteria	X									
Check exclusion criteria	X									
Informed consent	X									
Administration MORPHINE or MIDAZOLAM	X									
Collection of demographic characteristics		X	X	X	X	X	X	X		X

Collectcio n of analytical characterist ic s and ECG		X	X	X	X	X	X	X		X
Collection of in-hospital treatment	X	X	X	X	X	X	X	X		X

Collection of clinical events	X	X	X	X	X	X	X	X	X	X

* Clinical events: in-hospital mortality, need for invasive mechanical ventilation, need for cardiopulmonary resuscitation.

ANNEX II

COMMITMENT OF THE INVESTIGATOR

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States that:

They recognize and accept to participate as Principal Investigator in the clinical trial with the protocol code MIMO/2016, EudraCT number: 2016-000884-17, entiled: **Multicenter, Open-Labeled, Randomized Controlled Trial Comparing Midazolam versus Morphine in Acute Cardiogenic Pulmonary Edema (MIMO trial).**

They commit to managing and controlling each subject according to what has been established in the protocol authorized by the Ethical Committee of Clinical Investigation and by the General Pharmacy and Health Care Products Administration.

They will respect the ethical norms applicable to this type of study.

This trial will be carried out in the Emergency Department.

ANNEX III.
INVESTIGATOR MANUAL

1. Importance of acute pulmonary edema

Acute pulmonary edema is an acute and potentially severe heart disease. According to international guidelines, when patients with acute pulmonary edema arrive at the emergency department, the usual therapeutic focus is aimed at improving the signs and symptoms, correct the volume overload and improve cardiac hemodynamics increasing perfusion of the vital organs. The treatment recommended for immediately treating acute pulmonary edema is characterized by the use of intravenous diuretics, oxygen therapy and vasodilators. Although these measure alleviate the symptoms, they do not have a favorable influence on short- and long-term mortality.

Another drug that is used is morphine due to its expected anxiolytic and vasodilator effects. However, during the last decade there has been debate about the benefits and risks that accompany the use of this drug in the case of acute pulmonary edema. The retrospective ADHERE study performed in 2008 reported that the use of morphine constitutes an independent predictive variable of hospital mortality with an odds ratio of 4.8 (95%CI: 4.52-5.18, $p < 0.001$)[14].

2. Reasons that justify a clinical trial with morphine

The guidelines of the European Society of Cardiology[2] support the use of morphine for the treatment of acute pulmonary edema. However, the Heart Failure Society of America[1], does not make a formal recommendation with respect to morphine but sustains that it should be used with caution. Therefore, a prospective randomized clinical trial should be performed to evaluate the utility or not of

4. What is morphine?

It is a pentacyclic alkaloid derived from 4-phenylpiperidine. It is a powerful agonist of opioid μ receptors. From a clinical point of view, stimulation of μ receptors produces analgesia, euphoria, circulatory depression, reduction of peristaltism, myosis and dependence. Other clinical effects which may be produced by opioids include suppression of cough, hypotension and nausea/vomiting. Hypotension is due to a increase in the release of histamine and depression of the vasomotor center of the medulla. The induction of nausea is the result of direct stimulation of the vestibular system.

The cardiovascular effects of morphine are complex because of the involvement of neurogenic, cardiac and vascular factors as well as the physiological status of the person. If pulmonary ventilation is ensured, cardiovascular function resists the action of morphine. It can produce bradycardia of vagal origin, which is more notable if the administration is intravenous. It also induces hypotension due to action on the vasomotor center as well as arterial and venous vasodilatation which has repercussion on the reduction of after- and preload, respectively. Morphine induces vasodilatation of brain circulation due to the increase of pCO_2, with elevation of intracranial pressure.

In addition, morphine has a supposed anxiolytic effect which, together with the sedative effect, reduces the activity of the sympathetic nervous system.

ANNEX IV
NORMALIZED WORK PROCEDURES

I. GOOD CLINICAL PRACTICE NORMS OF THE COMMITTEE OF PHARMACEUTICAL SPECIALTIES OF THE EUROPEAN COMMUNITY (2004)

OBLIGATIONS OF THE PROMOTER, MONITOR, AND INVESTIGATOR

PROMOTER

The responsibilities of the CHIEF INVESTIGATOR are:

1. Choose the investigators after considering their adequacy and availability of the study centers and the means of these centers. Verify the qualifications of the investigators and ensure their availability along the duration of the study and verify the conformity of the investigators to carry out the study as it is established in the protocol, according to the norms of Good Clinical Practice and acceptance of the procedures of verification, audits and inspections.

2. Provide the investigator with chemical/pharmaceutical, toxicology, pharmacologic and clinical information (including previous and ongoing trials) that justify the nature, scale and duration of the study as a previous requisite for planning the trial. Inform the investigator regarding all new relevant information that emerges during the development of the study. All relevant information will be included in the investigator manual which will be complemented and/or updated by the Promoter provided that new pertinent information is available.

3. Present the notification/request to the opportune authorities (when indicated) and ensure the presentation of all the documents necessary to the Ethical Committee of Clinical Investigation and ensure the communication of all modifications or violations of the protocol as the change might affect the safety of

5. For references purposes, conserve sufficient samples of each lot together with a registry of the analyses and characteristics.

6. A registry of the quantities of the investigation products should be kept, including the lot and series numbers. The Promoter should check that the investigator establishes an adequate manipulation and conservation system in their institution and ensure safe use of the study products delivered.

7. Arrange the availability and ensure permanent training of adequately trained monitors and assisting clinical investigation personnel.

8. Designate the appropriate individuals and/or committees for the management, supervision, data management, statistical processing and writing of the trial report.

9. Together with the investigator, rapidly consider all severe adverse events and take the necessary adequate means to safeguard the interests of the study subjects and inform the pertinent authorities according to the requirements.

10. Rapidly inform the investigator of all relevant information that becomes available during the development of the trial and verify that, when necessary, the investigator(s) notify the Ethical Committee.

11. Ensure the preparation of a final global trial report that is adequate for health care registry purposes when necessary, regardless of whether the trial is completed or not. From the safety point of view, data uptakes may be necessary.

12. Provide adequate compensation and adequate treatment of the subjects in the case of lesion or death related to the study and adequate coverage (legal and economical) to the investigator, except in the case of malpractice or negligence.

13. Agree with the investigator(s) as to the assignment of responsibilities in relation to data processing, statistical analyses, result reporting and publication policy.

1. Work according to predetermined Normalized Work Procedures, visit the investigator before, during and after the study to control the fulfillment of the protocol and ensure that all the data have been correctly collected and reported and that the informed consent of the study subjects has been obtained and registered prior to their participation in the study.

2. Verify that the study center has adequate space, means (including laboratories), equipment and personnel and that during the study the appropriate number of subjects has been recruited.

3. Verify that all the personnel that will assist the investigator in the study have been adequately informed about the study and fulfill the study requisites.

4. Rapidly enable and ensure communication between the investigator and the Chief Investigator at all times.

5. Compare the data of the Data Collection Notebooks with the source documents and report any error/omission to the investigator.

6. Verify that the storage, distribution, return and documentation of the product(s) delivered during the study are adequate and correct and are in accordance with local norms.

7. Help the investigator in the case of requiring notification/request before the pertinent organisms.

8. Help the investigator report the study data and results to the Promoter.

9. Elaborate a written report after each visit (monitor report) and after all telephone calls, letters and other relevant contacts with the investigator (audit of document verification).

INVESTIGATOR

The responsibilities of the investigator are:

1. Know in detail the properties of the product(s) under investigation

3. Provide retrospective data on the values of patients who previously satisfied the inclusion criteria proposed by the study with the aim of ensuring that the study will have an adequate subject recruitment time.

4. Present an updated curriculum vitae and other credentials to the Promoter and, when necessary, to the pertinent authorities.

5. Agree with the protocol, sign it together with the Promoter and confirm in writing that the protocol has been read, understood and will be carried out as established and according to the norms of Good Clinical Practice, accepting inspections by the monitor and control procedures and being in agreement with the publication policy of the Promoter.

6. Name (if appropriate) a local study coordinator who can help in managing the study.

7. Present the notification / request to pertinent organisms, including the administration of the hospital and the Ethical Committee together with the Promoter when indicated.

8. Provide the pertinent information to all the members of the team participating in the study or in other aspects of patient treatment.

9. Obtain the informed consent from the study subjects prior to their inclusion in the study.

10. Establish a system in relation to the medical study products that ensures that these products from the Promoter are correctly received by a specific person (for example; a pharmacist) and that the delivery is registered, the study products are manipulated and stored safely and adequately, the study products are only delivered to the study subjects according to the protocol, and all the products that concordance between the registries of medication delivery and those used and returned. All possible discrepancies should be explained. The documents of

when necessary, the Ethical Committee (and the pertinent authorities when indicated) in the case of severe adverse events and take the appropriate measures to safeguard the interests of the study subjects.

14. Facilitate all the data to the Promoter / monitor and the pertinent authorities (when required) for purposes of verification /audit / inspection.

15. Sign and send the data (Data Collection Notebook), results and interpretations (analyses and reports) of the study performed in the center to the Promoter (and the pertinent authorities when indicated). These documents should also be signed by the collaborators of the investigator and those responsible for the analyses (including statistical analyses) and interpretation of the results.

16. Coordinate and sign the Final Study Report. In multicenter type studies, the signature of the Coordinator Investigator may be sufficient if established in the protocol.

17. Ensure that the confidentiality of all the information of the study subjects is respected by all the persons participating in the study as well as the information provided by the Promoter.

18. Follow the points below especially related to patient care:

1* The investigator is medically responsible for the subjects under their care during the study, and it should be assured that after the study these patients continue to receive the appropriate medical care.

2* Significant clinical alterations of laboratory values or clinical observations should be followed until the recovery of the subjects after finalizatin of the study.

3* The medical records of the patients should clearly indicate that the subject is participating in a clinical trial.

- **DOCUMENTATION FILING PROCEDURE**

All the information corresponding to this study will remain in a safe file that

Promotor and the Investigators are committed to saving the documentation during the time established in Article 43 of Royal Decree 1090/2015 regarding Clinical Trials with Medications.

III. MONITORING PROCEDURE

In the present trial the monitoring actions are designed to:

1* Ensure ethical and technical correction in the performance of the study

2* Obtain data coinciding with the real findings.

3* Have documents which in all cases allow following information from its origin so that it can be verified.

Monitoring will be carried out by Dr. Ana Aldea Perona, study monitor according to the established monitoring plan.

Additionally, the investigators will hold bimonthly meetings along the study period. The data collected in the Data Collection Notebooks will be transferred to a database elaborated in SPSS for Windows software for posterior statistical analysis. The specific study database will be operative from the introduction of the first patient in the study and will be completed the same day that information from the Data Collection Notebooks is added under the responsibility of the Principal Investigator. This will allow a new validation of the information collected in the Data Collection Notebooks in order to detect uncorrected noted values or values outside a reasonable range. The database used will include the necessary statistics to explore the data weekly and detect outliers. This wills complete the validation and verification
of the data.

IV. OTHER INFORMATION.

The regulation of the procedures of supply, registry and the dispensing destination as well as the procedure for the notification of adverse event is

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