

CONTENT

This supplement contains the following items:

1. Original protocol,
2. final protocol,
3. list of amendments
3. summary of changes.
4. Original statistical analysis plan,

**INITIAL AIRWAY MANAGEMENT IN PATIENTS WITH OUT-OF-
HOSPITAL CARDIAC ARREST: TRACHEAL INTUBATION VS.
BAG-VALVE-MASK VENTILATION.**

CAAM STUDY

V1.3 du 20/11 /2014

Project Number : P130932 Eudract N° 2014-A01109-38

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SIGNATURE PAGE

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Research will be conduct according protocol, and French laws

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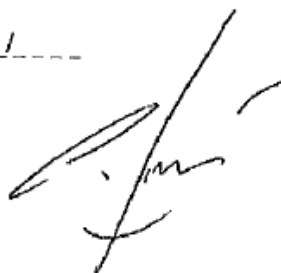
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ABBREVIATIONS

AE(s)	Adverse Events
cf.	Confer
CEC	Critical Event Committee
CI(s)	Confidence Interval(s)
CPC	Cerebral Performance Categories
CPR	Cardiopulmonary Resuscitation
e-CRF(s)	electronic -Case Report Form(s)
CRO	Clinical Research Organization
DSMB	Data Safety and Monitoring Board
e.g.	For Example
EMS	Emergency Medical Service
GCP	Good Clinical Practice
IB	Investigational Brochure
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigators Site File
NS	Not Significant
OHCA	Out-of-Hospital Cardiac Arrest
PI	Principle Investigator
QA	Quality Assurance
ROC	Resuscitation Outcome Consortium
ROSC	Return Of Spontaneous Circulation
SAE	Serious Adverse Event
SGA	Supraglottic Airway
TI	Tracheal Intubation
VAS	Visual Analogic Scale
VS	Versus

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1. SUMMARY

Title	Initial airway management in patients with out-of-hospital cardiac arrest: tracheal intubation vs. bag-valve-mask ventilation: the CAAM study
Acronym	CAAM
Coordinating Investigator	Frédéric ADNET Samu 93, hopital Avicenne Bobigny, France @ : frederic.adnet@avc.aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Primary objective	The main objective of this study is to compare the impact of two airway management techniques on the survival at 28-day with favorable neurological function of OHCA patients. The survival rate at 28-day with favorable neurological function will be compared in the TI group versus the bag-valve-mask group.
Primary endpoint	Survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less.
Secondary objectives	<ul style="list-style-type: none"> • To compare the survival rate at hospital admission and at 28-day and the neurologic outcomes in the TI group versus the bag-valve-mask group. • To estimate the immediate adverse events and serious adverse events related to the TI. • To evaluate the difficulty of intubation. • To evaluate the difficulty of ventilation with the bag-valve-mask. • To estimate the time to completion of TI. • To estimate and compare the duration of the interruption of chest compression in the TI group versus the bag-valve-mask group.
Secondary endpoint	<ul style="list-style-type: none"> • Survival at hospital admission • Survival at 28-day • Survival at hospital discharge • Neurologic outcomes assessed by modified Rankin scale score at 28-day • Rate of return of spontaneous circulation (ROSC) • Intubation difficulty assessed by Intubation difficulty Scale score • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma

	<ul style="list-style-type: none"> • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content • Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure • Ventilation difficulty with bag-valve-mask measured with a visual-analog-scale (VAS) • Han's mask ventilation classification • Difficult mask ventilation signs Time to completion of TI procedure measured from the instant that the laryngoscope blade touches the patient to the moment that the tracheal tube cuff is inflated • Duration of the interruption of chest compression during TI procedure • Duration of the interruption of chest compression during advanced CPR (from medical team's arrival to decision to stop CPR) • Duration of advanced CPR (from medical team's arrival to decision to stop CPR)
Experimental design	A multicenter prospective non-inferiority open randomized controlled trial in patients with out-of-hospital cardiac arrest carried out in physician-staffed EMS, comparing airway management by bag-valve-mask ventilation with tracheal intubation.
Population involved	We expect to enroll 2000 adult patients with out-of-hospital cardiac arrest on medical team's arrival and with a resuscitation attempted.
Inclusion criteria	<ul style="list-style-type: none"> • Age 18 years or older; • Patient with out-of-hospital cardiac arrest on medical team's arrival • Resuscitation attempted • Medical insurance
Non-inclusion criteria	<ul style="list-style-type: none"> • Massive suspected aspiration • Presence of do-not-resuscitate order • Pregnancy • Prisoners
Clinical phase	<i>III</i>
Study Centre(s)	20 study centres in 2 countries (France and Belgium)
Number of subjects :	2000 patients
Research period	Inclusion period : 24 month Duration of participation for each patient : 28 day Total study duration : 24 month and 28 day
Number of inclusions expected per centre and per month	100 patient/centre 5 patient/month/centre
Statistical analysis:	Intent-to-treat and Per Protocol analysis on non-inferiority of bag-mask ventilation over tracheal intubation.

	<p>Primary criterion: The primary ITT analysis on the primary endpoint will be carried out by calculating the 95% two-sided confidence interval (CI) (as recommended by EMEA guidelines) of the difference $\pi_{\text{bag}} - \pi_{\text{tracheal}}$. If the lower limit of this CI is higher than -0.01 then the conclusion of non inferiority will be accepted. If Necessary exact rather than asymptotic CI will be used.</p> <p>Secondary Efficacy Criteria: The secondary ITT analysis will be carried out by the chi-square test on proportions for all secondary criteria expressed as rates. The corresponding 95% confidence interval on their odds ratio and differences will also be presented.</p> <p>For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.</p> <p>Interim analyses An interim analysis will be carried out after 50% and 75% of inclusion. The only scope of these interim analyses will be to test futility and/or allow sample size recalculation (using ADDPLAN software)</p> <p>Sample size issues The sample size calculation is based on non-inferiority hypotheses using the confidence interval approach. The sample size is based on Hasegawa's study (JAMA 2013) that reported a survival rate with favorable neurological function in the bag-valve-mask group of 3% and Gueugniaud's study (NEJM 2008) of 2% survival rate with tracheal intubation. We defined a non-inferiority margin of 1%. We would need 956 patients per group for a study power of 0.8 and a type I error rate of 0.025. A total of 2,000 patients will be recruited (based on 5000 simulations using the Newcomb-Wilson score method, Statistics in Medicine 1988, 17:873-890)</p>
Funding source	Programme Hospitalier de Recherche Clinique (PHRC)
Data Safety Monitoring Board anticipated	Yes

2. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1. HYPOTHESIS FOR THE RESEARCH

Our hypothesis is that basic airway management (i.e. bag-valve-mask ventilation) is safe and may avoid the deleterious effects of tracheal intubation including interruption of chest compressions.

2.2. SCIENTIFIC BACKGROUND

Better survival of out-of-hospital cardiac arrest (OHCA) has been associated with the improvement in early access to emergency medical care, early cardiopulmonary resuscitation (CPR), rapid defibrillation, and integrated post-cardiac arrest care.^{1,2} Early advanced life support is often considered of benefit since that provides intravenous drug therapy and advanced airway management but few authors have challenged this concept.^{3,4}

Airway management in the resuscitation of cardiopulmonary arrest seeks to maintain or create an open pathway to the lungs to ensure adequate oxygenation and ventilation. Because the strategy of bag-valve-mask ventilation does not maintain an open pathway for gas exchange easily and does not protect the lungs from aspiration of gastric contents, tracheal intubation (TI) has become the “gold standard” of care in the resuscitation of OHCA. TI has been used in OHCA since the 1970s. However, recent retrospective and prospective studies have questioned the wisdom of the wide use of TI in OHCA.^{2,4-8} In the only large-scale prospective, randomized trial in 830 pediatric patients, authors found that addition of out-of-hospital TI to airway management practice did not improve survival or neurological outcome compared to bag-valve-mask ventilation alone.⁷ However, this study was limited to children and included a heterogeneous range of medical conditions beyond OHCA. A recent retrospective population based study including 649,359 patients found that TI was associated with decreased odds of neurologically favorable survival from OHCA.⁹ In this study, Hasegawa et al observed that 30-day neurologically favorable survival was higher among those who received bag-valve-mask ventilation alone (2.9% among 367,837 patients) compared with those who received tracheal intubation (1.0% among 41,972 patients).⁹ In another study, authors found that 33% (40/120) patients were alive in the group intubated after return of spontaneous circulation (ROSC) compared with 12% (69/573) in the group of patients intubated before ROSC ($p < 0.0001$).¹⁰

2.3. TRACHEAL INTUBATION

The reasons to suggest that tracheal intubation may not be the best technique for pre-hospital airway management in cardiac arrest are multi-factorial:

2.3.1. Intubation failure and implications in cardiac arrest

Failure to insert a tracheal tube during cardiac arrest has a number of implications. Most importantly, tracheal intubation during cardiac arrest can interfere with cardiopulmonary resuscitation continuity of chest compression, which can adversely influence cardiac arrest

survival.^{11,12} Multiple attempts to instrument the airway imply a period of limited ventilation whilst each attempt takes place. During OHCA, a very real concern is that intubation causes a marked pause in chest compressions.¹¹ As any intubation can lead to lengthy pauses in chest compressions it is likely that a failed intubation attempt will have a major impact on the effectiveness of resuscitation. Recent resuscitation guidelines have emphasized further the importance of effective chest compressions and minimizing any interruption in these.¹³

2.3.2. Other intubation's complications

Tracheal intubation is also associated with a number of major complications. The most important is unrecognized oesophageal intubation, rendering the patient effectively apneic until the situation is identified and rectified.¹⁴ Other complications of TI such as iatrogenic hypoxia, aspiration and bronchial intubation are also known to occur.

So, some practitioners suggested that the airway may be swiftly and successfully managed with a supraglottic airway (SGA) device, reducing both complications and interruptions in chest compressions. Since the use of SGA devices in cardiac arrest, abandoning tracheal intubation was compelling. This has been supported by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Airway Working Group in the UK, who in 2008 published 'A Critical Reassessment of Ambulance Service Airway Management in Pre-Hospital Care', which recommended that *'The majority of those managing patients' airways in the pre-hospital setting should be trained to insert a supraglottic airway device instead of a tracheal tube'*.¹⁵ However, the use of SGA devices showed worst results than with TI.^{8,16} In Wang's study that included 10,455 adult OHCA, 8,487 of these received TI and 1,968 a SGA.⁸ The survival to hospital discharge was 4.7% for TI and 3.9% for SGA. This study was a secondary analysis of data from the multi-centre 'Resuscitation Outcomes Consortium (ROC) PRIMED trial, looking at adult non-traumatic OHCA receiving successful SGA insertion of the King Laryngeal Tube™, Combitube®, and Laryngeal Mask Airway, or successful TI. In addition, a recent animal study suggests potential neurologic harm from use of these SGA devices.¹⁶

Given the recent literature, some suggests to cease advanced airway maneuvers in OHCA. However, the choice of airway management is a potential surrogate marker of other care events or the skill of the rescuer. TI can provide very effective ventilation if performed correctly. It is a highly technical skill and skill fade will occur when there is a lack of regular exposure to the procedure. While intubation is often performed by physician staffed emergency team, intubation opportunities can be sparse in some emergency medical services (EMS) systems with paramedics. Deakin et al. report that paramedics in the UK perform tracheal intubation between 1 and 4 times annually.¹⁷

Therefore, it is unclear whether advanced airway management such as TI performed by physician-staffed prehospital emergency medical services improves outcomes following OHCA compared with conventional bag-valve-mask ventilation. To date, there is no prospective, randomized study to directly assess the outcome of adult patients with cardiac arrest comparing the basic ventilation (bag-valve-mask ventilation) with TI.

This project is the first large, randomized multicenter clinical trial implicating European physician-staffed prehospital emergency medical services (EMS) that aims to compare bag-valve-mask ventilation to tracheal intubation in OHCA patients. Our hypothesis

is that basic airway management (i.e. bag-valve-mask ventilation) is safe and may avoid the deleterious effects of tracheal intubation including interruption of chest compressions. This trial will allow verifying if this hypothesis is correct with adequately trained EMS personnel who often perform tracheal intubation.

The results of this project could modify international guidelines concerning cardiac arrest management: TI could be abandoned for the benefit of the optimization of chest compression.

2.3.3. Expected patient or public health benefit

Sudden cardiac arrest accounts for 600,000 annual deaths in industrialized countries and more than 80% of sudden cardiac arrests occur outside hospital settings.¹⁸ Despite improved resuscitative efforts provided by prehospital emergency medical services (EMS) for millions of annual victims of out-of-hospital sudden death, OHCA survival remains very low.¹⁹⁻²²

Recent resuscitation guidelines on cardiac arrest have emphasized further the importance of effective chest compressions and minimizing any interruption in these. As any intubation can lead to lengthy pauses in chest compressions, it is likely that intubation attempts have a major impact on the effectiveness of resuscitation and initial airway management during OHCA with bag-valve-mask ventilation may be preferred. The understanding of which airway management approach is optimal in out-of-hospital cardiac arrest resuscitation is necessary, and those caring for patients need to know if tracheal intubation harm or help. Given the limitations of observational data, our prospective controlled study of airway management is well suited to answer these questions. We are convinced that this randomized clinical trial is urgently required in this area. Absent this investment, the emergency medical services community risks turning a blind eye and embracing ineffective or harmful airway interventions. Patients with cardiac arrest and the out-of-hospital rescuers who care for them deserve to know what is best.

The results of our clinical trial could improve the survival rate of OHCA patients due to the optimization of airway management. In addition, this study will allow clinical practices assessment of physician-staffed EMS.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The main objective of this study is to compare the impact of two airway management techniques on the survival at 28-day with favorable neurological function of OHCA patients. The survival rate at 28-day with favorable neurological function will be compared in the TI group versus the bag-valve-mask group.

3.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To compare the survival rate at hospital admission and at 28-day and the neurologic outcomes in the TI group versus the bag-valve-mask group.
- To estimate the immediate adverse events and serious adverse events related to the TI.
- To evaluate the difficulty of intubation.
- To evaluate the difficulty of ventilation with the bag-valve-mask.
- To estimate the time to completion of TI.
- To estimate and compare the duration of the interruption of chest compression in the TI group versus the bag-valve-mask group.

4. PLAN FOR THE RESEARCH

On medical team's arrival at the scene and after verification of participant's eligibility, patients will be enrolled in the study and randomly assigned to either initial bag-valve-mask ventilation or TI. After the hospital admission, all patients will be intubated whatever the initial airway management.

➤ GROUP A (experimental)

Airway management including initial bag-valve-mask ventilation by the medical team during OHCA. When standard bag-valve-mask ventilation is possible, the patient will be intubated in case of a return of spontaneous circulation. When standard bag-valve-mask ventilation is impossible or in case of massive aspiration (after randomisation), intubation of patient is the preferred alternative.

➤ GROUP B (reference)

Tracheal intubation during OHCA by the medical team: The standard intubation procedure is to use a non-stylettet tube and no sedation. When standard laryngoscopy-assisted intubation is not possible, an alternate procedure will be used based on the French consensus conference guidelines on difficult airway management.

The group A and the group B will be compared using primary and secondary criteria described below

4.1. PRIMARY AND SECONDARY ASSESSMENT CRITERIA

4.1.1. PRIMARY ENDPOINT

Survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less (see 17.3).

4.1.2. SECONDARY ENDPOINTS

The secondary endpoints of this study are:

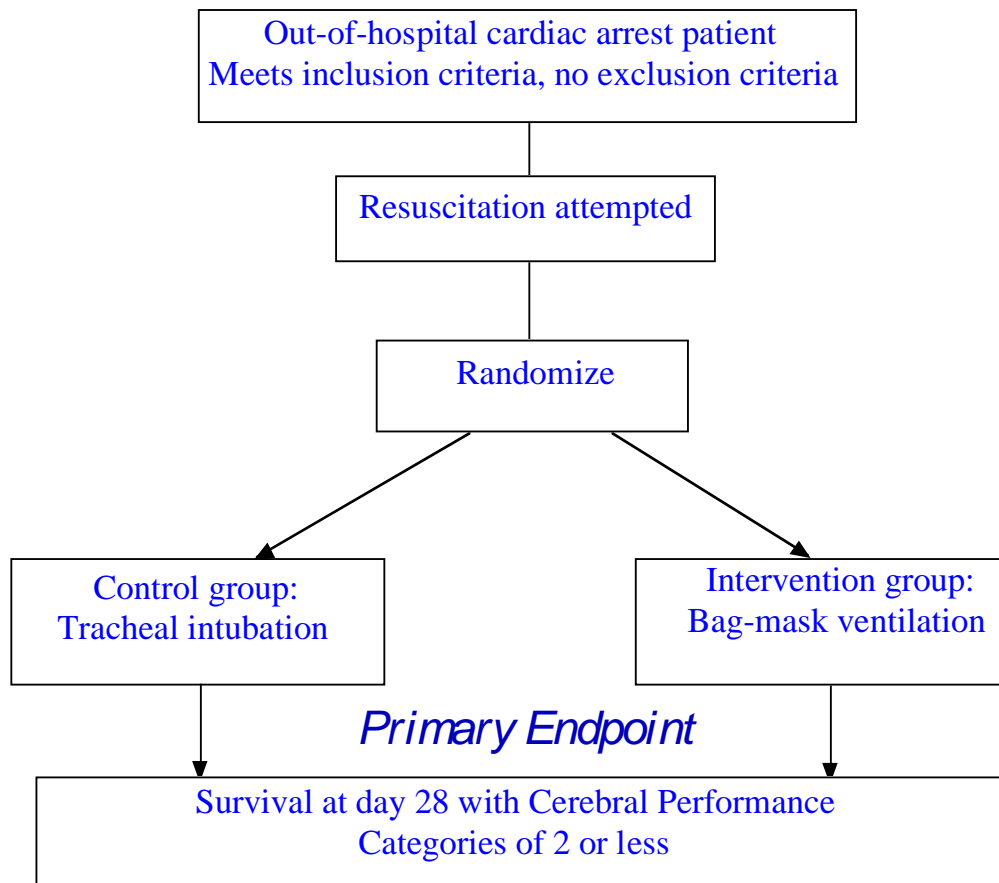
- Survival at hospital admission
- Survival at 28-day
- Survival at hospital discharge
- Neurologic outcomes assessed by modified Rankin scale score at 28-day (see 17.2)
- Rate of return of spontaneous circulation (ROSC)
- Intubation difficulty assessed by Intubation difficulty Scale score (IDS) (see 17.4)
- Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma, extubation
- Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content
- Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group)
- Ventilation difficulty with bag-valve-mask measured with a visual-analog-scale (VAS) (see 17.5)
- Time to completion of TI procedure measured from the instant that the laryngoscope blade touches the patient to the moment that the tracheal tube cuff is inflated
- Duration of the interruption of chest compression during TI procedure
- Duration of the interruption of chest compression during advanced CPR (from medical team's arrival to decision to stop CPR)
- Duration of advanced CPR (from medical team's arrival to decision to stop CPR)

4.2. DESCRIPTION OF RESEARCH METHODOLOGY

4.2.1. EXPERIMENTAL PLAN

This study is a prospective, open randomized, non-inferiority, controlled, international, multicentre, parallel-group trial evaluating the efficacy of airway management in cardiac arrest patients by comparison of bag-mask ventilation with tracheal intubation.

The trial design is as follows:



4.2.2. NUMBER OF CENTRES PARTICIPATING

It is a multicentre study, with 20 participating centres: 15 in France and 5 in Belgium

4.2.3. IDENTIFICATION OF THE SUBJECTS

The subjects will be identified in the following way:

The number of the center (3 digital positions) – The order of selection of the person in the center (4 digital positions) - initial name - initial first name

This subject identification is unique and will be kept for all the duration of the research.

4.2.4. RANDOMISATION

The randomisation will be stratified by centre and, within the centres, performed in blocks to ensure balanced distribution of the treatment groups at any time.

5. PROCEDURE FOR THE RESEARCH

The study is divided in three distinct periods:

- Enrolment and out-of-hospital period;
- In-hospital period.
- Follow-up period at day 28 (+7days).

5.1. ENROLLEMENT AND OUT OF HOSPITAL PERIOD

This period starts when a given patient is randomised and finish at the time of hospital admission.

This research will take place in a context of inclusion under the emergency provisions of the law (Article L1122 -1-2 of the CSP).

Inclusion and non-inclusion criteria are first verified by physicians of the mobile intensive care units. Patients fulfilling the eligibility criteria may be randomized according to emergency clause.

In the case of cardiac arrest, it is impossible to collect a prior consent from patient or from family/relative before the inclusion. Because of the extreme emergency situation, the physicians have to act quickly and perform cardiopulmonary resuscitation. Airway management is one of the multiple urgent actions that physicians have to control to save the patient. That's why if relatives are present at the arrival of the mobile intensive care unit, it is impossible to inform them and to ask for their consent before patient management.

All patients must be enrolled according to emergency clause; in case patient out-of-hospital resuscitation succeeds a delayed consent must be collected as soon as patient condition improves.

Subjects whose consent is sought	Who informs the subject and collects their consent	When is the subject informed	When is the subject's consent collected
Patient	Investigator who participates to the study (SAMU investigator or Corresponding investigator in ICU)	As soon as he recovers and his condition improves.	Up to day 28 (+7 days), corresponding to the patient follow-up.
Legal representative (guardian designated by the law)	Investigator who participates to the study (SAMU investigator or Corresponding investigator in ICU)	in case resuscitation succeeds : after patient inclusion	Up to day 28 (+7 days), corresponding to the patient follow-up

During the out-of-hospital phase, patients will be resuscitated according to international recommendations.¹³

On arrival, physicians of the mobile intensive care units initiate airway management according to the randomized group (i.e. intubation or bag-mask-ventilation). Patients are transported to the hospital only if they are successfully resuscitated at the scene, which approximately corresponds to 20% to 23% of total enrolled patients^{20,23}. In this case, patients enrolled in the bag-mask-ventilation group are intubated and mechanically ventilated before transportation to the hospital.

In case the patient resuscitation succeeds, as soon as he recovers and his condition improves a delayed consent will be asked for further participation to the study.

As we are in the case of an extreme emergency situation, it is possible that patients under guardianship are included.

Because of an alteration of corporal or mental capacities, these patients have a legal representative (guardian) designated by the guardianship judge. The condition of a patient under guardianship makes him incapable to express his consent. According to the law (art. L1122-2 and L1121-8 of the Public Health code), it belongs to the legal representative (guardian designated by the law) to give his consent for a further participation to the research and the collection and the exploitation of the data.

Data collected during this period will be:

- Medical history (previous cardiovascular, neurologic, metabolic or haematologic disease)
- Characteristic of patient (demographic data, baseline information)
- Factors associated with difficult mask ventilation and/or difficult intubation
- Aetiology of cardiac arrest
- Time of collapse
- Duration of basic resuscitation
- Duration of advanced resuscitation
- Number of shock delivered
- Drug administration (name, quantity)
- Return of spontaneous circulation
- Intubation difficulty Scale score (IDS) (see 17.4)
- Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve (see 17.5)
- Han's mask ventilation classification (see 17.6)
- Difficult mask ventilation signs
- Survival to hospital admission
- Serious adverse events
- Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content
- Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group)

5.2. IN-HOSPITAL PERIOD

This period starts after randomization at the time of hospital admission and finish Up to patient discharge from hospital.

No procedures or treatments are added for the research during the hospitalization. The patient is followed-up at the intensive care unit and hospital ward according to the routine care (according to standard procedures).

If the patient condition improves during his hospitalization, the investigator has to inform him about his enrolment into the study. If the patient agrees to continue to participate to the study, the investigator has to collect a delayed consent.

If the patient is under guardianship, the investigator has to inform his legal representative (guardian designated by the law) about his enrolment into the study.

According to the law (art. L1122-2 and L1121-8 of the Public Health code), it belongs to the legal representative (guardian designated by the law) to give his consent for a further participation to the research and the collection and the exploitation of the data.

Data collected during this period will be:

- Death from any cause
- Primary cause of death

5.3. FOLLOW-UP PERIOD AT DAY 28 (+7 DAYS)

The patient's vital status will be established 28 day after randomisation.

The 28 day follow-up will be performed in the window 28 + 7 days, but give the status at 28 days will be done by clinic appointment or by contact (phone or mail) with the patient, a family member, the legal representative, the family physician or in the hospital if the patient is still hospitalized.

This follow-up is ideally completed on day 28, but may be postponed up to 7 days. If done later, than at the actual day the **vital status should be given for day 28**. It may NOT be given for an earlier date unless the patient died before day 28 (even so it will be recorded that the patient is dead at day 28).

During his participation to the study (up to follow-up at day 28 (+ 7 days)), if the patient condition improves, the investigator have to inform him about his enrolment into the study. If the patient agrees to continue to participate to the study, the investigator has to collect a delayed consent.

Also, if the patient is under guardianship, the investigator has to inform his legal representative (guardian designated by the law) about his enrolment into the study.

According to the law (art. L1122-2 and L1121-8 of the Public Health code), it belongs to the legal representative (guardian designated by the law) to give his consent for a further participation to the research and the collection and the exploitation of the data.

Only 3% to 5% of total patients admitted to the hospital will be able to sign a delayed consent.²⁰⁻²³

Data collected during this period will be:

- Death from any cause
- Primary cause of death
- Cerebral Performance Categories (CPC) Scale at day 28 (see 17.3)
- Modified Rankin scale score at day 28 (see 17.2)

5.4. EXPECTED LENGTH OF PARTICIPATION AND DESCRIPTION OF THE CHRONOLOGY AND DURATION OF THE RESEARCH

Inclusion period:	24 Months
Follow-up period:	Day 28 (+7 days)
Total research period:	24 month and 28 day

5.5. TABLE OR DIAGRAM SUMMARISING THE CHRONOLOGY OF THE RESEARCH

	Enrolment and out of hospital period	In-hospital	28-day follow-up
Medical history (previous cardiovascular, neurologic, metabolic or haematologic disease)	X		
Demographic data	X		
Baseline information	X		
Inclusion - exclusion criteria	X		
Inclusion according to emergency clause	X		
Informed consent	X	X	X
Randomisation	X		
Study airway management administration	X		
Intubation Difficulty Scale (IDS)	X		
Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve	X		
Cerebral Performance Categories scale (CPC)			X
Modified Rankin Scale (mRS)			X
Serious Adverse Events (SAEs)	X		
Mortality	X	X	X

5.6. DISTINCTION BETWEEN CARE AND RESEARCH

Procedures and treatments carried out as part of the research	Procedures and treatments associated with care	Procedures and treatments added because of the research
Medical history	X	
Demographic data	X	
Baseline information	X	
Inclusion - exclusion criteria		X
Inclusion according to emergency clause		X
Informed consent		X
Randomisation		X
Study airway management administration	X	
Intubation Difficulty Scale (IDS)		X
Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve		X
Cerebral Performance Categories scale (CPC)		X
Modified Rankin Scale (mRS)		X
Serious Adverse Events (SAEs)		X
Mortality		X

5.7. TERMINATION RULES

5.7.1. CRITERIA AND METHODS FOR THE PREMATURE TERMINATION OF PARTICIPATION TO THE RESEARCH

- Any subject can withdraw from participating in the research at any time and for any reason.
- The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

If a subject leaves the research prematurely, data relating to the subject can be used unless an objection was recorded.

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. In practice, the subject is excluded from the research.

The case report form must list the various reasons for ending participation in the research:

- Ineffective
- Adverse reaction
- Other medical problem
- Subject's personal reasons
- Explicit withdrawal of consent

5.7.2. FOLLOW-UP OF THE SUBJECTS AFTER THE PREMATURE TERMINATION OF PARTICIPATION TO THE RESEARCH

Ending a subject's participation does not affect the normal management of the subject's illness in any way.

If there are serious adverse events, the investigator must notify the sponsor and monitor the subject.

5.7.3. TERMINATING PART OR ALL OF THE RESEARCH

Premature termination of the trial may happen under the following conditions:

- Occurrence of unexpected serious adverse reactions (SUSARs) or increase of known adverse events that render the risk/benefit ratio unacceptable;
- In the case of interim analysis demonstrating the need to stop the study due to futility (see 11.3.4)
- Ethical justification;
- Recruitment rate is too low such that it is unrealistic to consider completion of the trial within period of time acceptable by the Sponsor (DRCD)
- At the request of the Marketing Authorisation Holders (MAH)
- Decision of the authorities. If the research is terminated prematurely, the decision and justification will be given by the sponsor, AP-HP, to the Competent Authority (ANSM) and to the CPP within 15 days.

6. ELIGIBILITY CRITERIA

6.1. INCLUSION CRITERIA

Patients must fulfil the following inclusion criteria:

- Age 18 years or older;
- Patient with out-of-hospital cardiac arrest on medical team's arrival
- Resuscitation attempted
- Medical insurance

6.2. NON-INCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from randomization into the study:

- Massive suspected aspiration
- Presence of do-not-resuscitate order
- Pregnancy
- Prisoners

6.3. RECRUITMENT METHODS

We expect to enroll 2000 adult patient with out-of-hospital cardiac arrest on medical team's arrival and with a resuscitation attempted.

	Number of subjects
Total number of subjects chosen	2000
Number of centres	20
Inclusion period (months)	24 months
Number of subjects/centre	100
Number of subjects/centre/month	5

7. ASSESSMENT OF EFFICACY

Efficacy will be evaluated by using clinically relevant outcome variable as endpoints.

7.1. DESCRIPTION OF PARAMETERS FOR ASSESSING EFFICACY

7.1.1. MEDICAL HISTORY AND PHYSICAL EXAMINATION

Medical history data will be assessed in out-of-hospital and hospital setting, which will include information on previous cardiovascular, neurologic, metabolic or hematologic disease and physical examination of the patient.

7.1.2. INTUBATION DIFFICULTY SCALE (IDS)

The intubation Difficulty Scale (IDS) is a quantitative measure which allows the assessment of the complexity of intubation. It is based on seven parameters known to be associated with difficult intubation : number of supplementary attempts, number of supplementary operators, number and type (in chronologic order) of alternative techniques used, laryngoscopic grade, subjective lifting force, the use of external laryngeal manipulation, and mobility or position of the vocal cords^{21,24}

7.1.3. VISUAL-ANALOG-SCALE (VAS)

The bag-valve mask ventilation difficulty is directly evaluated by the investigator using a Visual Analog Scale (VAS). It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured.

7.1.4. MODIFIED RANKIN SCALE (MRS)

At 28 day, the mRS will be determined to evaluate the degree of disability or dependence in their daily activities.

7.1.5. CPC SCALE

At 28 day, the Cerebral Performance Categories scale will be determined to assess neurologic outcome following cardiac arrest.

7.1.6. RESUSCITATION PROCEDURE OTHER THAN AIRWAY MANAGEMENT

Resuscitation procedures will be performed in accordance with international guidelines¹³. In case of ROSC, patients included in the bag-mask ventilation group will be intubated with or without sedation.

7.2. ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE PARAMETERS FOR ASSESSING EFFICACY

Information about the medical history, physical examination and resuscitation procedure other than airway management are requested for the routine care (not added for the research). However, the IDS, VAS, mRS and the primary endpoint CPC scale are used in the context of this trial, for the assessment of the neurologic function at day 28. No circuit is established specially for the research.

8. SPECIFIC RESEARCH COMMITTEES

Two independent committees, the Steering Committee and the Executive Committee, supervise and support the conduct of the study.

8.1. STEERING COMMITTEE

The Steering Committee is composed of the Study Chairman, Co-chairman, the Coordinating Investigators, and the Principal Investigators acting as representatives /coordinators for each one of the participating countries.

The Steering Committee will meet periodically to assess the progress, provide scientific input, and address policy issues and operational aspects of the protocol.

At the end of the trial, the Steering Committee will meet in a closed session to discuss the trial results.

8.2. EXECUTIVE COMMITTEE

The Executive Committee is composed of the Study Chairman, the Co –chairman, Coordinating Investigators, sponsor and clinical research unit representative.

The executive committee gives scientific input on the protocol and possible amendments as well as on the “state of the art” and any on-going development during the study, which could have consequences for the performance of the study. The Executive Committee is responsible for proposing actions which need to be discussed and approved by the Steering Committee.

When the results of the study become available, the Executive Committee will provide a publication policy and provide advice on the interpretation of the results and the eventual impact on current therapy.

8.3. ADHERENCE TO PROTOCOL

The rules set out in the protocol should be well known by all persons involved in the study. This is of particular importance for the site personnel and can be achieved by sufficient training of the staff and a well-defined procedure for delegation and authorisation of different tasks to various staff members. This training and authorisation process at any site is the responsibility of the investigator.

9. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

9.1. PROCEDURES IN PLACE FOR RECORDING AND REPORTING ADVERSE EVENTS

9.1.1. DEFINITIONS

According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012):

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**

Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- **Unexpected adverse reaction**

An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product

According to the notice to sponsors of clinical trials for medications (ANSM):

- **New safety issue**

Any new information regarding safety:

- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

9.1.2. THE INVESTIGATOR'S ROLES (ART R1123-54 OF THE FRENCH PUBLIC HEALTH CODE)

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see section N° 9.1.2.1).

These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see section 9.1.3).

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events

All serious and non-serious adverse events must be reported in the CRF.

9.1.2.1. SERIOUS ADVERSE EVENTS THAT DO NOT REQUIRE THE INVESTIGATOR TO IMMEDIATELY NOTIFY THE SPONSOR

Normal and natural evolution of the pathology:

Despite improved resuscitative efforts provided by prehospital emergency medical services (EMS), survival to out of hospital cardiac arrest remains very low.

That's why in this study we consider that death is a serious adverse event to record only in the "adverse event" section of the case report form (e-CRF).

Complications related to airway management:

Airway management in the tracheal intubation group includes tracheal intubation by the medical team during OHCA.

Airway management in the bag-valve-mask group includes initial bag-valve-mask ventilation by the medical team during OHCA. The patient will be intubated in case of a return of spontaneous circulation (ROSC).

Known complications related to intubation or bag-mask ventilation that will be recorded only in the "adverse event" section of the e-CRF are:

- ◆ **Tracheal intubation group**

- Aspiration during tube insertion

- Mainstem intubation

- Esophageal intubation

- Dental trauma

- ◆ **Bag-valve-mask group**

- Aspiration during bag-mask ventilation

- Vomiting during intubation after ROSC

- Desaturation during intubation after ROSC

- Hypotension during intubation after ROSC

- Aspiration during tube insertion after ROSC

- Bronchospasm and/or laryngospasm during intubation after ROSC)

- Mainstem intubation after ROSC

Esophageal intubation after ROSC
Dental trauma during intubation after ROSC

Special circumstances

Following hospitalizations don't require immediately notification to sponsor; they have to be recorded only in the "adverse event" section of the case report form.

- Hospitalization for a pre-existing pathology
 - Hospitalization for a medical or surgical treatment planned before the participation to this study
 - Admission for social or administrative reasons
 - Admission to the Emergency Department(<12 hours)

9.1.2.2.SERIOUS ADVERSE EVENTS THAT REQUIRE THE INVESTIGATOR TO IMMEDIATELY NOTIFY THE SPONSOR

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 9.1.2.1 as not requiring notification:

- 1- Death
- 2- Life threatening situation
- 3- Requiring hospitalisation or prolonging hospitalisation
- 4- Persistent or significant disability or incapacity
- 5- Congenital abnormality or birth defect
- 6- Or any other adverse event considered "medically significant"

The serious adverse event related to the research and which is expected is: failure to insert the device for intubation.

9.1.3. PROCEDURES AND DEADLINES FOR NOTIFYING THE SPONSOR

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE (see Appendix 17.7). The report must be signed by the investigator.

Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor **via fax** only to the Vigilance Division, fax No. **+33 (0)1 46 99 02 17** and to the **Clinical Research Unit fax N° +33 (0)1.40.05.49.74**.

For studies using e-CRF:

- the investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form found in Appendix 17.7. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must comply with all requests from the sponsor for additional information. For all questions relating to the notification of an adverse event, the Vigilance Division can be contacted via email: pharmacovigilance@adds.com

9.1.4. PERIOD FOR NOTIFYING THE SPONSOR

The investigator must report all SAE that occur in research subjects:

- At the end of the prehospital medical management

9.1.5. THE SPONSOR'S ROLES

The sponsor, represented by its Vigilance Division, continuously assesses the safety of each experimental medication throughout the research.

➤ Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the research procedures are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.

- The initial declaration must be made no later than 15 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.
- The follow-up declaration must be made no later than 8 days after the 7- or 15-day deadline (depending on the seriousness).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

➤ **Analysis and declaration of other safety data**

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the research, or which could altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

➤ **Annual safety report**

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report which includes, in particular:

- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

9.1.6 DATA SAFETY MONITORING BOARD

A Data and Safety Monitoring Board (DSMB) will be convened for this biomedical research. The DSMB will be established by the sponsor. Its mission is to serve as a committee for monitoring safety data. The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The members of the DSMB will be named after the research starts. During the first meeting of the DSMB, a chairman will be appointed and the members will determine their operating methods and the meeting schedule.

All missions as well as the precise operating methods of the DSMB will be described in the DSMB's charter for the research.

1- General information about the DSMB

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
 - o safety data: serious adverse reactions

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one clinician specialising in the pathology being studied and possibly a methodologist/biostatistician.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research.

2- Definition of the DSMB's mission:

- Validation of tolerance monitoring methods:
 - o nature of the evaluated parameters
 - o frequency of the evaluations, consultation schedule
- Validation of termination criteria:
 - o criteria for terminating a subject's participation for tolerance reasons
 - o criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))
- Modification of the protocol and recommendations:

In light of the analysis of tolerance data for the research, the DSMB can, when applicable: propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, etc.). Likewise the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

3- Definition of the DSMB's operating methods:

- meeting types (open session, then closed sessions) and schedule
- desired methods and format of SAE notification from the sponsor to the DSMB

The DSMB appoints its chairman at the first meeting.

The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and the CPP.

10.DATA MANAGEMENT

10.1.DATA COLLECTION METHODS

10.1.1. ENROLMENT AND OUT-OF HOSPITAL PERIOD DATA

During the enrolment and out of hospital period all requested data are collected from the SAMU data sheet and also from the CRF

Data collected during the intervention of the mobile intensive care unit are:

- Medical history (previous cardiovascular, neurologic, metabolic or haematologic disease)
- Characteristic of patient (demographic data, baseline information)
- Aetiology of cardiac arrest
- Time of collapse
- Duration of basic resuscitation
- Duration of advanced resuscitation
- Number of shock delivered
- Drug administration (name, quantity)
- Return of spontaneous circulation
- Intubation difficulty Scale score (IDS) (see 17.4)
- Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve (see 17.5)
- Survival to hospital admission
- Serious adverse events
- Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content
- Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group)

10.1.2. IN-HOSPITAL PERIOD

Data collected during in-hospital period, at ICU and then at other hospital departments, are:

- Death from any cause
- Primary cause of death

These data can be collected from patient medical record.

All collected data are entered in an eCRF.

10.1.3. FOLLOW-UP PERIOD AT DAY 28 (+7 DAYS)

Data collected during patient follow-up are:

- Death from any cause
- Primary cause of death
- Cerebral Performance Categories (CPC) Scale at day 28 (see 17.3)
- Modified Rankin scale score at day 28 (see 17.2)

The 28 day follow-up will be performed in the window 28 + 7 days, but give the status at 28 days will be done by clinic appointment or by contact (phone or mail) with the patient, a family member or the family physician or at the hospital if the patient is still hospitalized.

10.2.IDENTIFICATION OF DATA COLLECTED DIRECTLY IN THE CRFS AND THAT WILL BE CONSIDERED AS SOURCE DATA

CPC scale data, mRS, IDS and VAS are collected directly from the CRF at day 28 (+7 days).

10.3.RIGHT TO ACCESS TO SOURCE DATA AND DOCUMENTS

10.3.1. ACCESS TO DATA

In accordance with GCPs:

- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor.
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.3.2. SOURCE DOCUMENTS

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

10.3.3. DATA AND SUBJECT CONFIDENTIALITY

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).

During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialized parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown.

The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

10.4. DATA PROCESSING AND STORAGE OF DOCUMENTS AND DATA

10.4.1. RECORDING OF STUDY DATA

All subject data generated during the study will be recorded in the Case Report Form (CRF) provided by the Sponsor. CRF will be specifically designed to meet the data recording requirements of the Clinical Study Protocol. Only the investigator and co-workers authorized by him (as listed on the specific form provided by the Sponsor) will be allowed to fill in the CRF or to make corrections.

CRF will be filled in with a black ballpoint pen. Entries will be easily legible and complete. Each CRF will be signed and dated by the investigator after completion. For all laboratory data, the units or any transformation of units will be clearly defined (if not otherwise agreed).

Corrections of wrong entries will be done by crossing out the entry in such a way that it will remain legible. Correction fluids will not be allowed. The correction will then be initialed and dated by the investigator or his/her authorized delegate.

At the end of the study, the investigator will be provided with copies of the CRFs.

10.4.2. DATA PROCESSING (CNIL, THE FRENCH DATA PROTECTION AUTHORITY) IN FRANCE

The law provides for the declaration of the computerized files of personal data collected for research must be done before the actual start of research. A methodology for specific reference to processing of personal data made in biomedical research as defined by law 2004-806 of August 9, 2004 as falling within the scope of Articles L.1121-1 of the Code of Public Health was established by the CNIL in January 2006.

This methodology allows a simplified declaration procedure when the nature of the data collected in research is consistent with the list provided by the CNIL in its reference document.

When the protocol has a data quality control by a CRA represents the promoter and enters into the scope of the simplified procedure CNIL, the DRCD as promoter asked the head of the computer file commit writing on respect for the reference methodology MR06001 simplified.

10.4.3. RETENTION OF ESSENTIALS STUDY DOCUMENTS - ARCHIVING

In compliance with the ICH/GCP guidelines, the investigator will maintain all CRFs and all source documents that support the data collected from each subject, until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator as to when these documents no longer need to be retained.

The investigator will take measures to prevent accidental or premature destruction of these documents.

↳ Investigator file

The investigator is responsible for maintaining all the records, which enable the conduct of the study at the site to be fully understood, in compliance with the ICH GCP filing standard. The study documentation including all the relevant correspondence should be kept by the investigator for at least 15 years after the completion or discontinuation of the study, if no further instructions are given by the sponsor.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named patient source records and anonymous CRF data for the sponsor. The investigator must arrange for the retention of this subject identification log and signed informed consent for at least 15 years after the completion or discontinuation of the study.

The investigator file must contain:

- All protocol versions and appendices
- ANSM agreements and ethic committee opinion
- Correspondence mails
- List of inclusions
- The final research report

No study site document may be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the sponsor must be notified.

↳ Trial Master File

The Sponsor will archive the trial master files in accordance with ICH GCP and applicable regulatory requirements.

10.5. OWNERSHIP OF THE DATA

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

11. STATISTICAL ASPECTS

11.1. STATISTICAL DESIGN / MODEL

A multicentric prospective, randomized, controlled, open two-arm non inferiority study to compare two technics for airway management.

11.2. NULL AND ALTERNATIVE HYPOTHESES

The primary aim of the trial is to demonstrate non inferiority of the bagmask vs tracheal

intubation with regard to primary endpoint as the survival rate with favorable neurological function,

The null and alternative hypotheses are as follows:

$H_0: \pi_{\text{bag}} - \pi_{\text{tracheal}} \leq -0.01$ succes rate of the bag-valve – mask is inferior to tracheal intubation
versus

$H_1: \pi_{\text{bag}} - \pi_{\text{tracheal}} \geq -0.01$ succes rate of the bag-valve – mask is not inferior to tracheal intubation

In case of demonstration of non inferiority a test of difference will be carried out.

11.3. PLANNED ANALYSES

11.3.1. Populations to be analysed

Since it is a non-inferiority trial the main analysis will be based on both the intent-to-treat population (ITT) of all patients randomised (irrespective of which study treatment is given or if any study treatment is adequately received) and in per protocol analysis (PP) of all patients randomized & treated without major protocol violations/deviations.

11.3.2. Patient accountability

Disposition of patients, patient status and patients excluded from PP populations will be summarised by treatment group. Descriptive statistics for primary reason for patient's withdrawal will be also presented by treatment group as well as a list of these patients sorted by treatment group.

DROP-OUTS

Reasons for drop-outs in each treatment group will be displayed. A detailed list of drop-out patients will also be provided.

11.3.3. Baseline characteristics

Baseline characteristics will be tabulated and comparability / differences between the treatment groups will be examined by means of descriptive statistics. As recommended by CONSORT no tests will be carried on baseline variables.

11.3.4. Interim analysis

An interim analysis will be carried out after 50% and 75% of inclusion. The only scope of these interim analyses will be to test futility and/or allow sample size recalculation (using ADDPLAN software)

The sponsor delivers interim analyses reports to the Competent Authority (ANSM) and the CPP.

11.4. EFFICACY ANALYSIS

11.4.1. Main Efficacy Criterion

The primary ITT analysis on the primary endpoint will be carried out by calculating the 95% two-sided confidence interval (CI)(as recommended by EMEA guidelines) of the difference

$\pi_{\text{bag}} - \pi_{\text{tracheal}}$ If the lower limit of this CI is higher than -0.01 then the conclusion of non inferiority will be accepted. If necessary exact rather than asymptotic CI will be used.

11.4.2. Secondary Efficacy Criteria

The secondary ITT analysis will be carried out by the chi-square test on proportions for all secondary criteria expressed as rates. The corresponding 95% confidence interval on their odds ratio and differences will also be presented.

For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.

11.5. SAFETY ANALYSIS

(Serious) adverse events will be tabulated per treatment group.

All (dichotomized) endpoints will be analyzed by chi-square test on proportions and the 95% confidence interval on the odds-ratio will be presented..

11.6. EXPLORATORY ANALYSES

Potentially important prognostic factors for the main and/or secondary efficacy parameters will be identified by means of multivariate logistic regression.

11.7. HANDLING OF MISSING DATA

In the intent-to-treat analysis missing data for the primary endpoint will be imputed according to the worst case principle (no success). In case of large differences between PP and ITT populations, an analysis of sensitivity using different methods for missing data replacement, including multiple imputation technique, will be carried out.

11.8. RANDOMISATION

The randomisation will be stratified by centre and, within the centres, performed in blocks to ensure balanced distribution of the treatment groups at any time.

11.9. SAMPLE SIZE ISSUES

The sample size calculation is based on non-inferiority hypotheses using the confidence interval approach. The sample size is based on Hasegawa's study (JAMA 2013) that reported a survival rate with favorable neurological function in the bag-valve-mask group of 3% and Gueugniaud's study (NEJM 2008) of 2% survival rate with tracheal intubation. We defined a non-inferiority margin of 1%. We would need 956 patients per group for a study power of 0.8 and a type I error rate of 0.025. A total of 2,000 patients will be recruited (based on 5000 simulations using the Newcomb-Wilson score method, Statistics in Medicine 1988, 17:873-890)

11.10. STATISTICAL SOFTWARE AND RESPONSIBILITY

All analyses will be made using SAS Software version 9.2 under the responsibility of Pr Eric Vicaut.

12.QUALITY CONTROL AND ASSURANCE

The biomedical research projects supported by the AP- HP are classified according to the estimated risk for persons participating in research through the classification of biomedical research to promote AP- HP A to D.

The conduct of research in the study centers and support issues will be made in accordance with the Declaration of Helsinki and Good Practices in force.

12.1.GENERAL ORGANIZATION

The promoter must ensure the safety and respect of the people who agreed to participate in research. It must establish a quality assurance system to monitor the progress of the best research in the study centers.

To this end, the mandate Clinical Research Associates (CRA) whose primary mission is to conduct regular monitoring visits to the research sites after making openings visits

The objectives of the follow-up research, as defined in the Good Clinical Practices (GCP § 5.18.1) are to verify that:

- The right to safety and protection of persons who consent to research are met,
- The data reported are accurate, complete and consistent with the source documents,
- Research is conducted in accordance with established protocol, GCP and the applicable laws and regulations in force.

12.1.1. STRATEGY FOR OPENING CENTERS

An opening visit of each center will be performed by the ARC in charge of the study before the start of inclusions, for implementation of the protocol and getting to know the various stakeholders in the biomedical research.

12.1.2. LEVEL OF CENTRE MONITORING

The choice of an appropriate level of monitoring was weighted according to the complexity, impact and research budget. To this end, the promoter in accordance with the coordinating investigator determined the logistics and impact score that yielded the monitoring level to implement this research.

12.2.QUALITY CONTROL

A Clinical Research Associate (CRA) mandate by the promoter will ensure the successful completion of the research, data collection generated by writing their documentation, recording and reporting in accordance with the Standard Operating Procedures implemented

to DRCD within and in accordance with Good Clinical Practice and the laws and regulations in force.

The investigator and his team members agree to make available during visits of quality control carried out at regular intervals by the Clinical Research. During these visits, the following items will be reviewed:

- Written consent;
- Compliance with the research protocol and procedures that are defined;
- Quality of data collected in the case report form: accuracy, missing data, data consistency with the documents 'source' (medical records, appointment books, original lab results, etc.).
- Management of the treatments used
- Verification and transmission promoter SAEs occurred in accordance with SAE grid.
- Verification of product management research through visits to the hospital pharmacy.
- For the closing Visit of each center: Clinical research associate (CRA) will regulatory study documents maintained in the center. Prepare envelopes consents for archiving.

12.3.CASE REPORT FORM

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.

This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.

When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. 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 investigator must archive a copy of the authenticated document that was delivered to the sponsor.

12.4.MANAGEMENT OF NON-COMPLIANCES

Any event occurring due to non-compliance with the protocol, standard operating procedures, good clinical practices or laws and regulations by an investigator or any other person involved in the conduct of the research should be state. Non-compliance with the promoter. At first, these statements will be reviewed and processed by the medical coordinator DRCD to take corrective or preventative actions. Then in a second time, sent to the Quality Risk Management department of DRCD for verification and analysis. These audits may be a request for information, visits or audit compliance with the investigator in charge of the concerned place of research.

12.5.AUDIT/INSPECTION

Investigators agree to accept the quality assurance audits conducted by the promoter as well as inspections by the competent authorities. All data, all documents and reports may be subject to audits and regulatory inspections can be opposed without medical confidentiality. An audit may be conducted at any time by persons authorized by the promoter of responsible and independent research. It aims to ensure the quality of research, the validity of its results and compliance with the law and regulations in force.

Those who direct and supervise research agree to comply with the requirements of the promoter and to the competent authority regarding an audit or inspection of the research. The audit can be applied at all stages of research, protocol development to publication of results and classification of data used or generated in the course of research.

12.6.PRIMARY INVESTIGATOR'S COMMITMENT TO ASSUME RESPONSIBILITY

Before starting the research, each investigator will give the sponsor's representative a copy of his/her personal curriculum vitae, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.

The investigators and their employees will sign a delegation of duties form specifying each person's role.

13.ETHICAL AND LEGAL CONSIDERATIONS

13.1.PROCEDURES FOR INFORMING AND OBTAINING CONSENT OF THE PERSONS UNDERGOING RESEARCH

Following Article L1122 -1-1 of the Code of Public Health, no biomedical research can be performed on a person without their free and informed consent. It must be collected after he was issued the information provided for in Article L . 1122-1 of the same Code.

➤ Information of the person who is willing to a research

Following Article L. 1122-1 of the Public Health Code, the person who prepared the research received prior oral and written information on biomedical research, allowing him to give free and informed consent. He is aware of full and fair way, understandable terms, objectives, risks and constraints of research, monitoring measures and security measures, treatment of personal data necessary for the purpose of research, the right to refuse to participate in the research or the possibility to withdraw consent at any time, etc... All this information must be included in a written document.

➤ **Specificity of this study for obtaining consent of the person who is part of the research**

This research will take place in a context of inclusion under the emergency provisions of the law (Article L1122 -1-2 of the CSP). Undeniably, given the inclusion and non-inclusion criteria (cardiac arrest patients), the consent of patients or relatives if present cannot be collected at baseline. **Thus the extreme emergency situation not allowing collecting the prior consent of the person or relative, the protocol provides that their consent is not necessary.** In case the resuscitation succeeds a delayed consent will be asked to the patient for further participation to the study. **The participant shall be informed about the study during his hospitalization as soon as his condition allows it.** Then, if the patient agrees he signs the delayed consent form to pursue his participation to the research and a “no objection to the use of its data” form for the possible continuation of this research will be completed.

According to the law (art. L1122-2 and L1121-8 of the Public Health code), if the patient has a legal representative (guardian designated by the law), it belongs to his guardian to give his consent for a further participation to the research and the collection and the exploitation of the data.

➤ **Notification in the medical record**

In addition, the investigator shall specify in the medical record of the person 's participation in this research , the methods of obtaining consent of the person who cannot give consent in writing (as provided by Articles L. 1122 -1-1 to L. 1122-2 of the CSP) and the terms of issue of information in order to collect. It retains the original copy of the form to obtain signed and dated consent of the individual. A copy of the Information Statement and Consent Form will be placed at the end of the study in a tamper sealed envelope containing all the consent forms. It will be archived by the promoter.

➤ **Subject Information Card**

The subject will be provided with a study information card bearing the following information:

- That he/she is participating in a clinical study.
- The name and phone number of the investigator.

13.2.SUPPORT ON RESEARCH

The management of patients included in this study was modeled on the assumption usually recommended. However, the results of acts of routine care will be used for research. Thus, a TEC will be recruited for the collection of these data in different ICUs. It will also be responsible for conducting follow tours on telephone (see section 6.3.2).

13.3.COMPENSATION FOR SUBJECTS

No patient compensation is provided in the protocol.

13.4.SUBJECT PROHIBITED FROM PARTICIPATING IN ANOTHER RESEARCH

During the period of the patient's participation, the subject may not participate in other biomedical research protocols relating to medications until after his follow-up at day 28 (+7 days)

However, patients can simultaneously participate to other non interventional trials.

13.5.ROLE OF THE SPONSOR

The Assistance Publique Hôpitaux de Paris (AP- HP) is the promoter of the research and by delegation the Department of Clinical Research and Development (DRCD) ensures missions, in accordance with Article L.1121 - 1 of the public health code. The Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any time for medical or administrative reasons, in this case, a notification will be provided to the investigator.

13.6.INDEPENDENT ETHICS COMMITTEE(S) AND REGULATORY AUTHORITIES REQUIREMENTS

The study protocol, the "Participant information and consent form" document, and the list of investigators document will be submitted for review to the appropriate Independent Ethics Committee(s) by the Coordinator or the Sponsor in accordance with local regulations.

The study will not start before written approval by corresponding Ethics Committee(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the technical protocol by each contractual party involved has been obtained.

In accordance with local regulations, the investigator and/or the Sponsor will inform the Director of the Hospital involved in the study.

13.7.REQUEST FOR ANSM AUTHORIZATION

To start the study, AP-HP as a sponsor must submit an application license to the competent authority ANSM in France. The competent authority, as defined by Article L. 1123-12, speaks regarding of safety of persons who consent to biomedical research, including the safety and quality of products used in research in accordance, where appropriate, existing repositories, their condition use and safety of persons in respect of the acts and methods used and the arrangements for tracking people.

13.8.MODIFICATIONS TO THE RESEARCH

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the Ethics Committee(s) and authorisation from the competent authorities within the scope of their respective authorities.

The information sheet and the consent form can be revised if necessary; in particular if there is a substantial modification to the research or if adverse reactions occur.

13.9. FINAL REPORT OF RESEARCH

The final report of biomedical research referred to in Article R1123 - 60 of the CSP will be co-written by the coordinator and biostatistician for this research. This report will be submitted to each of the investigators for review. Once a consensus has been reached, the final version must be endorsed by the signature of each of the investigators and sent to the promoter as soon as possible after the effective end of the search. A report in the reference plane of the competent authority must be submitted to the competent authority and the CPP within one year after the end of the research, being understood as the last follow-up visit of the last included patient. This period is reported at 90 days in case of premature termination of the research.

14.FUNDING AND INSURANCE

14.1.RESEARCH BUDGET

The costs associated with this research are:

- Recruitment of staff:
 - Recruitment of physician time
 - Recruitment of a clinical study technician
- Quality control by an clinical research associate (CRA) by the promoter
- Taxes, insurance, Ethic committee (CPP)
- Data management: report forms, data-management, statistical analysis
- Miscellaneous expenses: meetings, missions coordinator, notebooks, miscellaneous items.

14.2.INSURANCE

Pursuant to Article L.1121-10 of the Code of Public Health, insurance contracts should ensure the liability of the promoter and that of all involved and cover the financial consequences of claims finding their generating cause in biomedical research.

The Promoter, subscribed for the entire duration of the research insurance covering its own liability and that of any doctor involved in the conduct of research. It also provides full compensation for damaging the search for the person who is ready and assigns, subject to proof to bear the damage is not due to his fault or that of any participant without consequences that may be the opposite of a third party or the voluntary withdrawal of the person who had originally agreed to pay for research.

The Assistance Publique-Hôpitaux de Paris (AP-HP) has taken an insurance with the company HDI-Gerling through BIOMEDIC-INSURE for the duration of the research, ensuring civil liability as well as any stakeholder (doctor or personnel involved in the conduct of research), in accordance with Article L.1121-10 of the CSP.

15.PUBLICATION RULES

The Sponsor (APHP) shall retain ownership of all case report forms, data analyses, and reports, which result from this study. All information obtained as a result of the study will be regarded as confidential, until appropriate analysis and review by the Sponsor and the Coordinator are completed.

The results of the study remain the exclusive property of the Sponsor, which will be able to freely exploit the results and forward them to other investigators and administrative authorities in various countries.

No communication or publication (irrespective of the medium used) concerning the study or its results may take place during the period of technical protocol implementation or after the end of the study without the prior, written, signed agreement of the Sponsor.

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17.ANNEXE1:

17.1.PARTICIPATING CENTERS

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17.2. MODIFIED RANKIN SCALE (MRS)

Score Description

0 No symptoms at all

1 No significant disability despite symptoms; able to carry out all usual duties and activities

2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 Moderate disability; requiring some help, but able to walk without assistance

4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 Dead

TOTAL (0–6): _____

17.3.CEREBRAL PERFORMANCE CATEGORIES SCALE (CPC SCALE)

Note: If patient is anesthetized, paralyzed, or intubated, use “as is” clinical condition to calculate scores.

CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.

CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.

CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.

CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

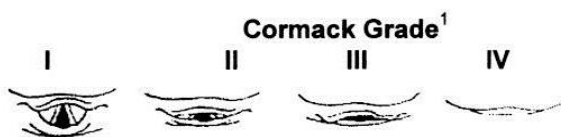
17.4. INTUBATION DIFFICULTY SCALE SCORE (IDS)

Parameter	Score
Number of Attempts >1	N ₁
Number of Operators >1	N ₂
Number of Alternative Techniques	N ₃
Cormack Grade - 1	N ₄
Lifting Force Required	
Normal	N ₅ =0
Increased	N ₅ =1
Laryngeal Pressure	
Not applied	N ₆ =0
Applied	N ₆ =1
Vocal Cord Mobility	
Abduction	N ₇ =0
Adduction	N ₇ =1
TOTAL: IDS = SUM OF SCORES	N₁-N₇

IDS Score	Degree of Difficulty
0	Easy
0 < IDS ≤ 5	Slight Difficulty
5 < IDS	Moderate to Major Difficulty
IDS = ∞	Impossible intubation

Rules for Calculating IDS Score:

N₁	Every additional attempt adds 1 pt.
N₂	Each additional operator adds 1 pt.
N₃	Each alternative technique adds 1 point: Repositioning of the patient, change of materials (blade, ET tube, addition of a stylette), change in approach (nasotracheal/orotracheal) or use of another technique (fibroscopy, intubation through a laryngeal mask).
N₄	Apply Cormack grade for 1st oral attempt. For successful blind intubation N ₄ = 0.
N₆	Sellick's maneuver adds no points.
Impossible intubation: IDS takes the value attained before abandonment of intubation attempts.	



¹ Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984;39:1105-1111.

17.5.VISUAL-ANALOG-SCALE (VAS)

The difficulty of ventilation by bag valve mask is assessed by the following Visual Analog Scale (VAS):

Was the ventilation difficult by bag valve mask?



No, not at all

Yes, extremely difficult

17.6.HAN'S MASK VENTILATION CLASSIFICATION

Classification	Description/definition
Grade 0	Ventilation by mask not attempted
Grade 1	Ventilated by mask
Grade 2	Ventilated by mask with oral airway or other adjuvant
Grade 3	Difficult mask ventilation (inadequate, unstable, or requiring two practitioners)
Grade 4	Unable to mask ventilate

Reference: Han R, Tremper KK, Kheterpal S, O'Reilly M. Grading scale for mask ventilation. *Anesthesiology* 2004;101:267.

17.7.FORM FOR REPORTING SERIOUS ADVERSE EVENTS

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)	 Form for reporting a Serious Adverse Event (SAE) occurring in a biomedical research for not health products	PART RESERVED FOR THE SPONSOR - - DRRC 20 - -
---	---	---

This form must be correctly filled out (2 pages), signed and sent immediately via fax to the Vigilance Division, fax No. +33 (0)1 46 99 02 17 and to the Clinical Research Unit fax N° +33 (0)140 05 49 74 as soon as the investigator becomes aware of the serious adverse event

Initial reporting Follow-up of a reported SAE Follow-up number |__|__|

1. Clinical trial identification	
CAAM	Date of this report : __ __ __ __ 2 0 __ __ dd mm yyyy
Sponsor's trial number : P130932	Date of investigator first learning of the SAE : __ __ __ __ 2 0 __ __ dd mm yyyy
Title: CAAM study "Initial airway management in patients with out-of-hospital cardiac arrest: tracheal intubation vs. bag-valve-mask ventilation":	Research risk : <input type="checkbox"/> A <input checked="" type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/> D
	Study design : <input type="checkbox"/> Non comparative trial <input checked="" type="checkbox"/> Comparative trial : <input type="checkbox"/> Double-blind <input type="checkbox"/> Single-blind <input checked="" type="checkbox"/> Open-label <input checked="" type="checkbox"/> Randomized <input type="checkbox"/> Non- randomized

2. Investigator centre	
Name of the centre :	Investigator (Last name/First name) :
City – post code : Country	Tél : Fax :
Department :	

3. Identification number and medical history of the patient	
Identification number : __ __ - __ __ __ - __ - __ <small style="margin-left: 20px;">center Nb. randomization No. lastname firstname initial</small>	Relevant surgical-medical/family history to facilitate the assessment of the case (attach a medical hospitalization report if required) :
Gender : <input type="checkbox"/> M <input type="checkbox"/> F	
Weight : __ __ kg Date of birth : __ __ __ __ __ mm dd mm yyyy	
Height : __ __ cm Age : __ __ years	
Date of inclusion according to emergency clause = Date of randomization : __ __ __ __ 2 0 __ __ dd mm yyyy	
Signature of the delayed consent date : __ __ __ __ 2 0 __ __ dd mm yyyy	Randomization group : <input type="checkbox"/> Bag-valve-mask ventilation <input type="checkbox"/> Tracheal ventilation

4. Procedures and care added by the research (ex. : biopsies, MRI, blood samples ... <i>Strikethrough the box 5. if the procedures and care have not been realized</i>) :	Realisation date (dd/mm/yyyy)	Chronology	
		Before SAE occurrence	After SAE occurrence
.....	__ __ __ __ 2 0 __ __	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ __ __ __ 2 0 __ __	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ __ __ __ 2 0 __ __	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ __ __ __ 2 0 __ __	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ __ __ __ 2 0 __ __	<input type="checkbox"/>	<input type="checkbox"/>

5. Concomitant medicinal product(s) at the time of the SAE, exclude those used to treat the adverse event (fill the table below and if necessary the concomitant drug(s) appendix ⇒ Appendix attached to this form : <input type="checkbox"/> Yes <input type="checkbox"/> No						
Brand name (preferably) or International Nonproprietary Name including the pharmaceutical form and the dose	Indication	Route (1)	Daily dose	Starting date (dd/mm/yyyy)	On going (2)	Stopping date (dd/mm/yyyy)
.....	__ __ __ __ __ __	<input type="checkbox"/>	__ __ __ __ 2 0 __ __
.....	__ __ __ __ __ __	<input type="checkbox"/>	__ __ __ __ 2 0 __ __
.....	__ __ __ __ __ __	<input type="checkbox"/>	__ __ __ __ 2 0 __ __
.....	__ __ __ __ __ __	<input type="checkbox"/>	__ __ __ __ 2 0 __ __

CAAM

PART RESERVED FOR THE SPONSOR
- DRRC 20 -

Patient identification number : | | | | - | | | | | | - | | - | |
center Nb. randomization No. lastname firstname initial

(1) Route of administration : PO = oral route ; IM=intramuscular ; IV=intravenous ; SC=subcutaneous or other (specify) (2) On going at the time of the SAE

6. Serious Adverse Event [SAE]		
Diagnosis : <input type="checkbox"/> Final <input type="checkbox"/> Provisional	Body site(s) :	Symptom(s) :
Date of the first symptoms' occurrence : 2 0 Precise those symptoms :		Seriousness criteria : <input type="checkbox"/> Involved or prolonged hospitalisation : from 2 0 to 2 0 <input type="checkbox"/> on going <input type="checkbox"/> Death <input type="checkbox"/> Life-threatening <input type="checkbox"/> Involved persistence or significant disability or handicap <input type="checkbox"/> Congenital anomaly <input type="checkbox"/> Other medically significant criteria, specify :
Start date of onset of the SAE : 2 0 dd mm yyyy Time of onset : hh min <input type="checkbox"/> missing data	Delay of occurrence between the last procedure/care added by the research and the date of onset of the SAE : / dd hh min	
Has the event conducted to an interruption of the procedure/care added by the research? <input type="checkbox"/> No <input type="checkbox"/> Yes Date : 2 0 The interruption of the procedure/care added by the research has been : <input type="radio"/> Temporary <input type="radio"/> Permanent If required, date of the return to the procedure/care added by the research : 2 0 Recurrence of the SAE after this return : <input type="radio"/> No <input type="radio"/> Yes - Date : 2 0		
Has the event conducted to unblinding ? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> NA Date : 2 0		
SAE's outcome		
<input type="checkbox"/> Death : <input type="radio"/> unrelated to the SAE <input type="radio"/> related to the SAE Date : 2 0 dd mm yyyy	<input type="checkbox"/> On going : <input type="radio"/> Stable condition <input type="radio"/> Worsening <input type="radio"/> Improvement	
<input type="checkbox"/> Resolved : <input type="radio"/> without sequelae <input type="radio"/> with sequelae, specify sequelae : Date : 2 0 dd mm yyyy hh min	Symptomatic measures were taken : <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, specify :	
7. Other aetiology(ies) considered :		
<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, specify :		
8. Additional investigation(s) done :		
<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, specify :		
9. According to the investigator, the SAE is (several possible cases) :		
Related to the clinical trial : <input type="checkbox"/> Yes : <input type="radio"/> to the procedure/care of the clinical trial ; specify : Specify : <input type="checkbox"/> Certain relation <input type="checkbox"/> Probable relation <input type="checkbox"/> Possible relation <input type="checkbox"/> Unlikely relation Specify : <input type="checkbox"/> Certain relation <input type="checkbox"/> Probable relation <input type="checkbox"/> Possible relation <input type="checkbox"/> Unlikely relation <input type="checkbox"/> No : <input type="radio"/> to the disease progression : <input type="radio"/> to the pregnancy <input type="radio"/> to one (or several) concomitant medicinal product(s) administered, specify : <input type="radio"/> to an intercurrent disease, specify : <input type="radio"/> other, specify :		
Reporter Name and role : Signature :	Investigator Name : Signature :	Department stamp :



**INITIAL AIRWAY MANAGEMENT IN PATIENTS WITH
OUT-OF-HOSPITAL CARDIAC ARREST:
TRACHEAL INTUBATION VS. BAG-VALVE-MASK VENTILATION.
CAAM STUDY**

V1.4 of 22/09/2015 V2 of 22/01/2016

Project Number: P130932 Eudract N° 2014-A01109-38

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SIGNATURE PAGE**Initial airway management in patients with out-of-hospital cardiac arrest:
tracheal intubation vs. bag-valve-mask ventilation. CAAM study**Version **V1.4 of 22/09/2015 V2 of 22/01/2016****ADMINISTRATIVES REFERENCES:**

N° DRCD: P130932

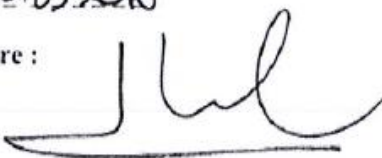


N° EudraCT: 2014-A01109-38

N° NIH (<http://www.clinicaltrials.gov>) :

CPP Ile de France X, date avis favorable : 04/11/2014

ANSM, date authorisation: 22/10/2014

Research will be conduct according protocol, and French laws

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ABBREVIATIONS

AE(s)	Adverse Events
cf.	Confer
CEC	Critical Event Committee
CI(s)	Confidence Interval(s)
CPC	Cerebral Performance Categories
CPR	Cardiopulmonary Resuscitation
e-CRF(s)	electronic -Case Report Form(s)
CRO	Clinical Research Organization
DSMB	Data Safety and Monitoring Board
e.g.	For Example
EMS	Emergency Medical Service
GCP	Good Clinical Practice
IB	Investigational Brochure
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigators Site File
NS	Not Significant
OHCA	Out-of-Hospital Cardiac Arrest
PI	Principle Investigator
QA	Quality Assurance
ROC	Resuscitation Outcome Consortium
ROSC	Return Of Spontaneous Circulation
SAE	Serious Adverse Event
SGA	Supraglottic Airway
TI	Tracheal Intubation
VAS	Visual Analogic Scale
VS	Versus

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1. SUMMARY

Title	Initial airway management in patients with out-of-hospital cardiac arrest: tracheal intubation vs. bag-valve-mask ventilation: the CAAM study
Acronym	CAAM
Coordinating Investigator	Frédéric ADNET Samu 93, hopital Avicenne Bobigny, France @ : frederic.adnet@avc.aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Primary objective	The main objective of this study is to compare the impact of two airway management techniques on the survival at 28-day with favorable neurological function of OHCA patients. The survival rate at 28-day with favorable neurological function will be compared in the TI group versus the bag-valve-mask group.
Primary endpoint	Survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less.
Secondary objectives	<ul style="list-style-type: none"> • To compare the survival rate at hospital admission and at 28-day and the neurologic outcomes in the TI group versus the bag-valve-mask group. • To estimate the immediate adverse events and serious adverse events related to the TI. • To evaluate the difficulty of intubation. • To evaluate the difficulty of ventilation with the bag-valve-mask. • To estimate the time to completion of TI. • To estimate and compare the duration of the interruption of chest compression in the TI group versus the bag-valve-mask group.
Secondary endpoints	<ul style="list-style-type: none"> • Survival at hospital admission • Survival at 28-day • Survival at hospital discharge • Neurologic outcomes assessed by modified Rankin scale score at 28-day • Rate of return of spontaneous circulation (ROSC) • Intubation difficulty assessed by Intubation difficulty Scale score • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, aspiration

	<p>pneumonia, dental trauma, extubation</p> <ul style="list-style-type: none"> • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, aspiration pneumonia • Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group) • Ventilation difficulty with bag-valve-mask measured with a visual-analog-scale (VAS) • Han's mask ventilation classification • Difficult mask ventilation signs • Time to completion of TI procedure measured from the instant that the laryngoscope blade touches the patient to the moment that the tracheal tube cuff is inflated • Duration of the interruption of chest compression during TI procedure • Duration of the interruption of chest compression during advanced CPR (from medical team's arrival to decision to stop CPR) • Duration of advanced CPR (from medical team's arrival to decision to stop CPR)
Experimental design	A multicenter prospective non-inferiority open randomized controlled trial in patients with out-of-hospital cardiac arrest carried out in physician-staffed EMS, comparing airway management by bag-valve-mask ventilation with tracheal intubation.
Population involved	We expect to enroll 2000 adult patients with out-of-hospital cardiac arrest on medical team's arrival and with a resuscitation attempted.
Inclusion criteria	<ul style="list-style-type: none"> • Age 18 years or older; • Patient with out-of-hospital cardiac arrest on medical team's arrival • Resuscitation attempted • Medical insurance
Non-inclusion criteria	<ul style="list-style-type: none"> • Massive suspected aspiration • Presence of do-not-resuscitate order • Pregnancy • Prisoners
Clinical phase	<i>III</i>
Study Centre(s)	20 study centres in 2 countries (France and Belgium)
Number of subjects :	2000 patients
Research period	<p>Inclusion period : 24 month</p> <p>Duration of participation for each patient : 28 day</p> <p>Total study duration : 24 month and 28 day</p>

Number of inclusions expected per centre and per month	100 patient/centre 5 patient/month/centre
Statistical analysis:	<p>Intent-to-treat and Per Protocol analysis on non-inferiority of bag-mask ventilation over tracheal intubation.</p> <p>Primary criterion: The primary ITT analysis on the primary endpoint will be carried out by calculating the 95% two-sided confidence interval (CI) (as recommended by EMEA guidelines) of the difference $\pi_{\text{bag}} - \pi_{\text{tracheal}}$. If the lower limit of this CI is higher than -0.01 then the conclusion of non inferiority will be accepted. If Necessary exact rather than asymptotic CI will be used.</p> <p>Secondary Efficacy Criteria: The secondary ITT analysis will be carried out by the chi-square test on proportions for all secondary criteria expressed as rates. The corresponding 95% confidence interval on their odds ratio and differences will also be presented.</p> <p>For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.</p> <p>Interim analyses An interim analysis will be carried out after 50% and 75% of inclusion. The only scope of these interim analyses will be to test futility and/or allow sample size recalculation (using ADDPLAN software)</p> <p>Sample size issues The sample size calculation is based on non-inferiority hypotheses using the confidence interval approach. The sample size is based on Hasegawa's study (JAMA 2013) that reported a survival rate with favorable neurological function in the bag-valve-mask group of 3% and Gueugniaud's study (NEJM 2008) of 2% survival rate with tracheal intubation. We defined a non-inferiority margin of 1%. We would need 956 patients per group for a study power of 0.8 and a type I error rate of 0.025. A total of 2,000 patients will be recruited (based on 5000 simulations using the Newcomb-Wilson score method, Statistics in Medicine 1988, 17:873-890)</p>
Funding source	Programme Hospitalier de Recherche Clinique (PHRC)
Data Safety Monitoring Board anticipated	Yes

2. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1. HYPOTHESIS FOR THE RESEARCH

Our hypothesis is that basic airway management (i.e. bag-valve-mask ventilation) is safe and may avoid the deleterious effects of tracheal intubation including interruption of chest compressions.

2.2. SCIENTIFIC BACKGROUND

Better survival of out-of-hospital cardiac arrest (OHCA) has been associated with the improvement in early access to emergency medical care, early cardiopulmonary resuscitation (CPR), rapid defibrillation, and integrated post-cardiac arrest care.^{1,2} Early advanced life support is often considered of benefit since that provides intravenous drug therapy and advanced airway management but few authors have challenged this concept.^{3,4}

Airway management in the resuscitation of cardiopulmonary arrest seeks to maintain or create an open pathway to the lungs to ensure adequate oxygenation and ventilation. Because the strategy of bag-valve-mask ventilation does not maintain an open pathway for gas exchange easily and does not protect the lungs from aspiration of gastric contents, tracheal intubation (TI) has become the “gold standard” of care in the resuscitation of OHCA. TI has been used in OHCA since the 1970s. However, recent retrospective and prospective studies have questioned the wisdom of the wide use of TI in OHCA.^{2,4-8} In the only large-scale prospective, randomized trial in 830 pediatric patients, authors found that addition of out-of-hospital TI to airway management practice did not improve survival or neurological outcome compared to bag-valve-mask ventilation alone.⁷ However, this study was limited to children and included a heterogeneous range of medical conditions beyond OHCA. A recent retrospective population based study including 649,359 patients found that TI was associated with decreased odds of neurologically favorable survival from OHCA.⁹ In this study, Hasegawa et al observed that 30-day neurologically favorable survival was higher among those who received bag-valve-mask ventilation alone (2.9% among 367,837 patients) compared with those who received tracheal intubation (1.0% among 41,972 patients).⁹ In another study, authors found that 33% (40/120) patients were alive in the group intubated after return of spontaneous circulation (ROSC) compared with 12% (69/573) in the group of patients intubated before ROSC ($p < 0.0001$).¹⁰

2.3. TRACHEAL INTUBATION

The reasons to suggest that tracheal intubation may not be the best technique for pre-hospital airway management in cardiac arrest are multi-factorial:

2.3.1. Intubation failure and implications in cardiac arrest

Failure to insert a tracheal tube during cardiac arrest has a number of implications. Most importantly, tracheal intubation during cardiac arrest can interfere with cardiopulmonary resuscitation continuity of chest compression, which can adversely influence cardiac arrest survival.^{11,12} Multiple attempts to instrument the airway imply a period of limited ventilation whilst each attempt takes place. During OHCA, a very real concern is that intubation causes a marked pause in chest compressions.¹¹ As any intubation can lead to lengthy pauses in chest compressions it is likely that a failed intubation attempt will have a major impact on the effectiveness of resuscitation. Recent resuscitation guidelines have emphasized further the importance of effective chest compressions and minimizing any interruption in these.¹³

2.3.2. Other intubation's complications

Tracheal intubation is also associated with a number of major complications. The most important is unrecognized oesophageal intubation, rendering the patient effectively apneic until the situation is identified and rectified.¹⁴ Other complications of TI such as iatrogenic hypoxia, aspiration and bronchial intubation are also known to occur.

So, some practitioners suggested that the airway may be swiftly and successfully managed with a supraglottic airway (SGA) device, reducing both complications and interruptions in chest compressions. Since the use of SGA devices in cardiac arrest, abandoning tracheal intubation was compelling. This has been supported by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Airway Working Group in the UK, who in 2008 published 'A Critical Reassessment of Ambulance Service Airway Management in Pre-Hospital Care', which recommended that *'The majority of those managing patients' airways in the pre-hospital setting should be trained to insert a supraglottic airway device instead of a tracheal tube'*.¹⁵ However, the use of SGA devices showed worst results than with TI.^{8,16} In Wang's study that included 10,455 adult OHCA, 8,487 of these received TI and 1,968 a SGA.⁸ The survival to hospital discharge was 4.7% for TI and 3.9% for SGA. This study was a secondary analysis of data from the multi-centre 'Resuscitation Outcomes Consortium (ROC) PRIMED trial, looking at adult non-traumatic OHCA receiving successful SGA insertion of the King Laryngeal Tube™, Combitube®, and Laryngeal Mask Airway, or successful TI. In addition, a recent animal study suggests potential neurologic harm from use of these SGA devices.¹⁶

Given the recent literature, some suggests to cease advanced airway maneuvers in OHCA. However, the choice of airway management is a potential surrogate marker of other care events or the skill of the rescuer. TI can provide very effective ventilation if performed correctly. It is a highly technical skill and skill fade will occur when there is a lack of regular exposure to the procedure. While intubation is often performed by physician staffed

emergency team, intubation opportunities can be sparse in some emergency medical services (EMS) systems with paramedics. Deakin et al. report that paramedics in the UK perform tracheal intubation between 1 and 4 times annually.¹⁷

Therefore, it is unclear whether advanced airway management such as TI performed by physician-staffed prehospital emergency medical services improves outcomes following OHCA compared with conventional bag-valve-mask ventilation. To date, there is no prospective, randomized study to directly assess the outcome of adult patients with cardiac arrest comparing the basic ventilation (bag-valve-mask ventilation) with TI.

This project is the first large, randomized multicenter clinical trial implicating European physician-staffed prehospital emergency medical services (EMS) that aims to compare bag-valve-mask ventilation to tracheal intubation in OHCA patients. Our hypothesis is that basic airway management (i.e. bag-valve-mask ventilation) is safe and may avoid the deleterious effects of tracheal intubation including interruption of chest compressions. This trial will allow verifying if this hypothesis is correct with adequately trained EMS personnel who often perform tracheal intubation.

The results of this project could modify international guidelines concerning cardiac arrest management: TI could be abandoned for the benefit of the optimization of chest compression.

2.3.3. Expected patient or public health benefit

Sudden cardiac arrest accounts for 600,000 annual deaths in industrialized countries and more than 80% of sudden cardiac arrests occur outside hospital settings.¹⁸ Despite improved resuscitative efforts provided by prehospital emergency medical services (EMS) for millions of annual victims of out-of-hospital sudden death, OHCA survival remains very low.¹⁹⁻²²

Recent resuscitation guidelines on cardiac arrest have emphasized further the importance of effective chest compressions and minimizing any interruption in these. As any intubation can lead to lengthy pauses in chest compressions, it is likely that intubation attempts have a major impact on the effectiveness of resuscitation and initial airway management during OHCA with bag-valve-mask ventilation may be preferred. The understanding of which airway management approach is optimal in out-of-hospital cardiac arrest resuscitation is necessary, and those caring for patients need to know if tracheal intubation harm or help. Given the limitations of observational data, our prospective controlled study of airway management is well suited to answer these questions. We are convinced that this randomized clinical trial is urgently required in this area. Absent this investment, the emergency medical services community risks turning a blind eye and embracing ineffective or harmful airway interventions. Patients with cardiac arrest and the out-of-hospital rescuers who care for them deserve to know what is best.

The results of our clinical trial could improve the survival rate of OHCA patients due to the optimization of airway management. In addition, this study will allow clinical practices assessment of physician-staffed EMS.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The main objective of this study is to compare the impact of two airway management techniques on the survival at 28-day with favorable neurological function of OHCA patients. The survival rate at 28-day with favorable neurological function will be compared in the TI group versus the bag-valve-mask group.

3.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To compare the survival rate at hospital admission and at 28-day and the neurologic outcomes in the TI group versus the bag-valve-mask group.
- To estimate the immediate adverse events and serious adverse events related to the TI.
- To evaluate the difficulty of intubation.
- To evaluate the difficulty of ventilation with the bag-valve-mask.
- To estimate the time to completion of TI.
- To estimate and compare the duration of the interruption of chest compression in the TI group versus the bag-valve-mask group.

4. PLAN FOR THE RESEARCH

On medical team's arrival at the scene and after verification of participant's eligibility, patients will be enrolled in the study and randomly assigned to either initial bag-valve-mask ventilation or TI. After the hospital admission, all patients will be intubated whatever the initial airway management.

➤ GROUP A (experimental)

Airway management including initial bag-valve-mask ventilation by the medical team during OHCA. When standard bag-valve-mask ventilation is possible, the patient will be intubated in case of a return of spontaneous circulation. When standard bag-valve-mask ventilation is impossible or in case of massive regurgitation of gastric content (after randomisation), intubation of patient is the preferred alternative

➤ GROUP B (reference)

Tracheal intubation during OHCA by the medical team: The standard intubation procedure is to use a non-stylettet tube and no sedation. When standard laryngoscopy-assisted intubation is not possible, an alternate procedure will be used based on the French consensus conference guidelines on difficult airway management.

The group A and the group B will be compared using primary and secondary criteria described below

4.1. PRIMARY AND SECONDARY ASSESSMENT CRITERIA

4.1.1. Primary Endpoint

Survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less (see 17.2).

In case of neurological disability before randomization, the survival associated the same degree of disability will be considered a favorable neurological function

4.1.2. Secondary Endpoints

The secondary endpoints of this study are:

- Survival at hospital admission
- Survival at 28-day
- Survival at hospital discharge
- Neurologic outcomes assessed by modified Rankin scale score at 28-day (see 17.1)
- Rate of return of spontaneous circulation (ROSC)
- Intubation difficulty assessed by Intubation difficulty Scale score (IDS) (see 17.3)
- Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, **aspiration pneumonia**, dental trauma, extubation
- Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, **aspiration pneumonia**
- Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group)
- Ventilation difficulty with bag-valve-mask measured with a visual-analog-scale (VAS) (see 17.4)
- Han's mask ventilation classification
- Difficult mask ventilation signs
- Time to completion of TI procedure measured from the instant that the laryngoscope blade touches the patient to the moment that the tracheal tube cuff is inflated
- Duration of the interruption of chest compression during TI procedure
- Duration of the interruption of chest compression during advanced CPR (from medical team's arrival to decision to stop CPR)
- Duration of advanced CPR (from medical team's arrival to decision to stop CPR)

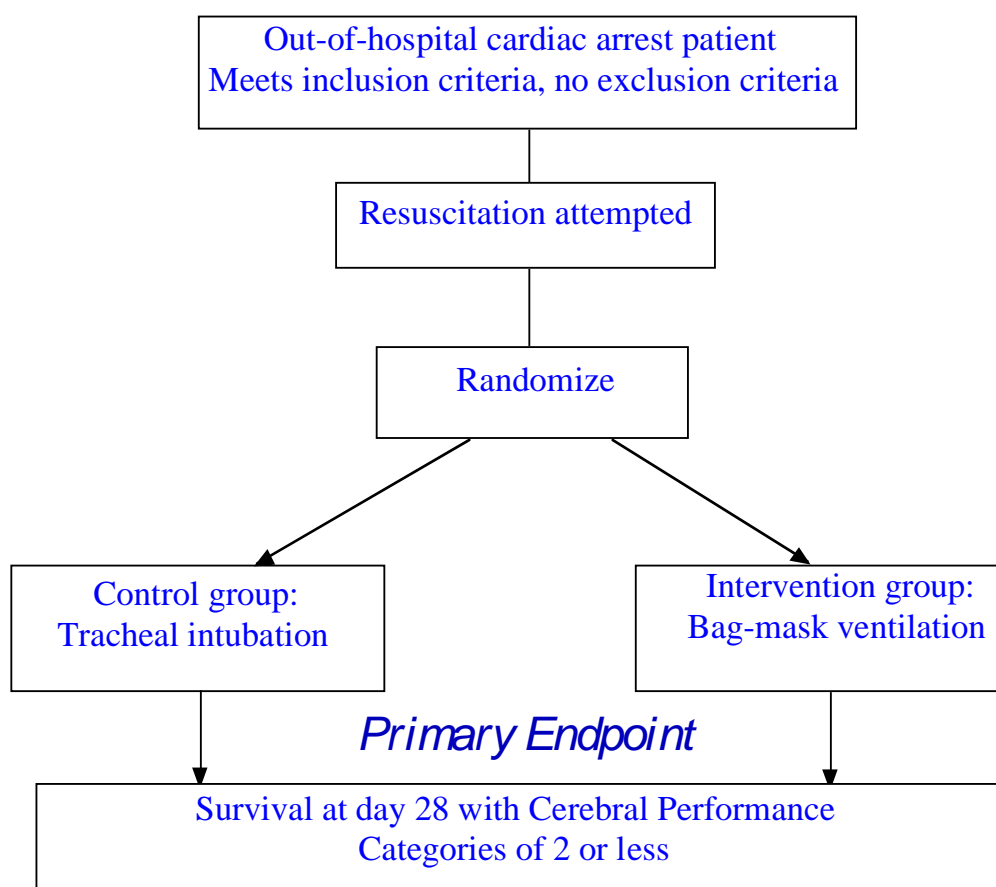
4.2. DESCRIPTION OF RESEARCH METHODOLOGY

4.2.1. Experimental plan

This study is a prospective, open randomized, non-inferiority, controlled, international,

multicentre, parallel-group trial evaluating the efficacy of airway management in cardiac arrest patients by comparison of bag-mask ventilation with tracheal intubation.

The trial design is as follows:



4.2.2. Number of centres participating

It is a multicentre study, with 20 participating centres: 15 in France and 5 in Belgium

4.2.3. Identification of the subjects

The subjects will be identified in the following way:

The number of the center (3 digital positions) – The order of selection of the person in the center (4 digital positions) - initial name - initial first name

This subject identification is unique and will be kept for all the duration of the research.

4.2.4. Randomisation

The randomisation will be stratified by centre and, within the centres, performed in blocks to ensure balanced distribution of the treatment groups at any time.

5. PROCEDURE FOR THE RESEARCH

The study is divided in three distinct periods:

- Enrolment and out-of-hospital period;
- In-hospital period.
- Follow-up period at day 28 (+7days).

5.1. ENROLLEMENT AND OUT OF HOSPITAL PERIOD

This period starts when a given patient is randomised and finish at the time of hospital admission.

This research will take place in a context of inclusion under the emergency provisions of the law (Article L1122 -1-2 of the CSP).

Inclusion and non-inclusion criteria are first verified by physicians of the mobile intensive care units. Patients fulfilling the eligibility criteria may be randomized according to emergency clause.

In the case of cardiac arrest, it is impossible to collect a prior consent from patient or from family/relative before the inclusion. Because of the extreme emergency situation, the physicians have to act quickly and perform cardiopulmonary resuscitation. Airway management is one of the multiple urgent actions that physicians have to control to save the patient. That's why if relatives are present at the arrival of the mobile intensive care unit, it is impossible to inform them and to ask for their consent before patient management.

All patients must be enrolled according to emergency clause; in case patient out-of-hospital resuscitation succeeds a delayed consent must be collected as soon as patient condition improves.

Subjects whose consent is sought	Who informs the subject and collects their consent	When is the subject informed	When is the subject's consent collected
Patient	Investigator who participates to the study (SAMU investigator or Corresponding investigator in ICU)	As soon as he recovers and his condition improves.	Up to day 28 (+7 days), corresponding to the patient follow-up.
Legal representative (guardian designated by the law)	Investigator who participates to the study (SAMU investigator or Corresponding investigator in ICU)	in case resuscitation succeeds : after patient inclusion	Up to day 28 (+7 days), corresponding to the patient follow-up

During the out-of-hospital phase, patients will be resuscitated according to international recommendations.¹³

On arrival, physicians of the mobile intensive care units initiate airway management according to the randomized group (i.e. intubation or bag-mask-ventilation). Patients are transported to the hospital only if they are successfully resuscitated at the scene, which approximately corresponds to 20% to 23% of total enrolled patients^{20,23}. In this case, patients

enrolled in the bag-mask-ventilation group are intubated and mechanically ventilated before transportation to the hospital.

In case the patient resuscitation succeeds, as soon as he recovers and his condition improves a delayed consent will be asked for further participation to the study.

As we are in the case of an extreme emergency situation, it is possible that patients under guardianship are included.

Because of an alteration of corporal or mental capacities, these patients have a legal representative (guardian) designated by the guardianship judge. The condition of a patient under guardianship makes him incapable to express his consent. According to the law (art. L1122-2 and L1121-8 of the Public Health code), it belongs to the legal representative (guardian designated by the law) to give his consent for a further participation to the research and the collection and the exploitation of the data.

Data collected during this period will be:

- Medical history (previous cardiovascular, neurologic, metabolic or haematologic disease)
- Characteristic of patient (demographic data, baseline information)
- Factors associated with difficult mask ventilation and/or difficult intubation
- Aetiology of cardiac arrest
- Time of collapse
- Duration of basic resuscitation
- Duration of advanced resuscitation
- Number of shock delivered
- Drug administration (name, quantity)
- Return of spontaneous circulation
- Intubation difficulty Scale score (IDS) (see 17.3)
- Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve (see 17.4)
- Han's mask ventilation classification (see 17.6)
- Difficult mask ventilation signs
- Survival to hospital admission
- Serious adverse events
- Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, **aspiration pneumonia**
- Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, **aspiration pneumonia**, dental trauma extubation
- Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group)

5.2. IN-HOSPITAL PERIOD

This period starts after randomization at the time of hospital admission and finish Up to patient discharge from hospital.

No procedures or treatments are added for the research during the hospitalization. The patient is followed-up at the intensive care unit and hospital ward according to the routine care (according to standard procedures).

If the patient condition improves during his hospitalization, the investigator has to inform him about his enrolment into the study. If the patient agrees to continue to participate to the study, the investigator has to collect a delayed consent.

If the patient is under guardianship, the investigator has to inform his legal representative (guardian designated by the law) about his enrolment into the study.

According to the law (art. L1122-2 and L1121-8 of the Public Health code), it belongs to the legal representative (guardian designated by the law) to give his consent for a further participation to the research and the collection and the exploitation of the data.

Data collected during this period will be:

- Death from any cause
- Primary cause of death

5.3. FOLLOW-UP PERIOD AT DAY 28 (+7 DAYS)

The patient's vital status will be established 28 day after randomisation.

The 28 day follow-up will be performed in the window 28 + 7 days, but give the status at 28 days will be done by clinic appointment or by contact (phone or mail) with the patient, a family member, the legal representative, the family physician or in the hospital if the patient is still hospitalized.

This follow-up is ideally completed on day 28, but may be postponed up to 7 days. If done later, than at the actual day the **vital status should be given for day 28**. It may NOT be given for an earlier date unless the patient died before day 28 (even so it will be recorded that the patient is dead at day 28).

During his participation to the study (up to follow-up at day 28 (+ 7 days)), if the patient condition improves, the investigator have to inform him about his enrolment into the study. If the patient agrees to continue to participate to the study, the investigator has to collect a delayed consent.

Also, if the patient is under guardianship, the investigator has to inform his legal representative (guardian designated by the law) about his enrolment into the study.

According to the law (art. L1122-2 and L1121-8 of the Public Health code), it belongs to the legal representative (guardian designated by the law) to give his consent for a further participation to the research and the collection and the exploitation of the data.

Only 3% to 5% of total patients admitted to the hospital will be able to sign a delayed consent.²⁰⁻²³

Data collected during this period will be:

- Death from any cause
- Primary cause of death
- Cerebral Performance Categories (CPC) Scale at day 28 (see 17.2)
- Modified Rankin scale score at day 28 (see 17.1)

5.4. EXPECTED LENGTH OF PARTICIPATION AND DESCRIPTION OF THE CHRONOLOGY AND DURATION OF THE RESEARCH

Inclusion period:	24 Months
Follow-up period:	Day 28 (+7 days)
Total research period:	24 month and 28 day

5.5. TABLE OR DIAGRAM SUMMARISING THE CHRONOLOGY OF THE RESEARCH

	Enrolment and out of hospital period	In-hospital	28-day follow-up
Medical history (previous cardiovascular, neurologic, metabolic or haematologic disease)	X		
Demographic data	X		
Baseline information	X		
Inclusion - exclusion criteria	X		
Inclusion according to emergency clause	X		
Informed consent	X	X	X
Randomisation	X		
Study airway management administration	X		
Intubation Difficulty Scale (IDS)	X		
Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve	X		
Cerebral Performance Categories scale (CPC)			X
Modified Rankin Scale (mRS)			X
Serious Adverse Events (SAEs)	X		
Mortality	X	X	X

5.6. DISTINCTION BETWEEN CARE AND RESEARCH

Procedures and treatments carried out as part of the research	Procedures and treatments associated with care	Procedures and treatments added because of the research
Medical history	X	
Demographic data	X	
Baseline information	X	
Inclusion - exclusion criteria		X
Inclusion according to emergency clause		X
Informed consent		X
Randomisation		X
Study airway management administration	X	
Intubation Difficulty Scale (IDS)		X
Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve		X
Cerebral Performance Categories scale (CPC)		X
Modified Rankin Scale (mRS)		X
Serious Adverse Events (SAEs)		X
Mortality		X

5.7. TERMINATION RULES**5.7.1. Criteria and methods for the premature termination of participation to the research**

- Any subject can withdraw from participating in the research at any time and for any reason.
- The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

If a subject leaves the research prematurely, data relating to the subject can be used unless an objection was recorded.

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. In practice, the subject is excluded from the research.

The case report form must list the various reasons for ending participation in the research:

- Ineffective
- Adverse reaction
- Other medical problem
- Subject's personal reasons
- Explicit withdrawal of consent

5.7.2. Follow-up of the subjects after the premature termination of participation to the research

Ending a subject's participation does not affect the normal management of the subject's illness in any way.

If there are serious adverse events, the investigator must notify the sponsor and monitor the subject.

5.7.3. Terminating part or all of the research

Premature termination of the trial may happen under the following conditions:

- Occurrence of unexpected serious adverse reactions (SUSARs) or increase of known adverse events that render the risk/benefit ratio unacceptable;
- In the case of interim analysis demonstrating the need to stop the study due to futility (see 11.3.4)
- Ethical justification;
- Recruitment rate is too low such that it is unrealistic to consider completion of the trial within period of time acceptable by the Sponsor (DRCD)
- At the request of the Marketing Authorisation Holders (MAH)
- Decision of the authorities. If the research is terminated prematurely, the decision and justification will be given by the sponsor, AP-HP, to the Competent Authority (ANSM) and to the CPP within 15 days.

6. ELIGIBILITY CRITERIA

6.1. INCLUSION CRITERIA

Patients must fulfil the following inclusion criteria:

- Age 18 years or older;
- Patient with out-of-hospital cardiac arrest on medical team's arrival
- Resuscitation attempted
- Medical insurance

6.2. NON-INCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from randomization into the study:

- Massive suspected aspiration
- Presence of do-not-resuscitate order
- Pregnancy
- Prisoners

6.3. RECRUITMENT METHODS

We expect to enroll 2000 adult patient with out-of-hospital cardiac arrest on medical team's arrival and with a resuscitation attempted.

	Number of subjects
Total number of subjects chosen	2000
Number of centres	20
Inclusion period (months)	24 months
Number of subjects/centre	100
Number of subjects/centre/month	5

7. ASSESSMENT OF EFFICACY

Efficacy will be evaluated by using clinically relevant outcome variable as endpoints.

7.1. DESCRIPTION OF PARAMETERS FOR ASSESSING EFFICACY

7.1.1. Medical history and physical examination

Medical history data will be assessed in out-of-hospital and hospital setting, which will include information on previous cardiovascular, neurologic, metabolic or hematologic disease and physical examination of the patient.

7.1.2. Intubation Difficulty Scale (IDS)

The intubation Difficulty Scale (IDS) is a quantitative measure which allows the assessment of the complexity of intubation. It is based on seven parameters known to be associated with difficult intubation : number of supplementary attempts, number of supplementary operators, number and type (in chronologic order) of alternative techniques used, laryngoscopic grade, subjective lifting force, the use of external laryngeal manipulation, and mobility or position of the vocal cords^{21,24}

7.1.3. Visual-analog-scale (VAS)

The bag-valve mask ventilation difficulty is directly evaluated by the investigator using a Visual Analog Scale (VAS). It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured.

7.1.4. Modified Rankin Scale (mRS)

At 28 day, the mRS will be determined to evaluate the degree of disability or dependence in their daily activities.

7.1.5. CPC scale

At 28 day, the Cerebral Performance Categories scale will be determined to assess neurologic outcome following cardiac arrest.

7.1.6. Resuscitation procedure other than airway management

Resuscitation procedures will be performed in accordance with international guidelines¹³. In case of ROSC, patients included in the bag-mask ventilation group will be intubated with or without sedation.

7.2. ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE PARAMETERS FOR ASSESSING EFFICACY

Information about the medical history, physical examination and resuscitation procedure other than airway management are requested for the routine care (not added for the research). However, the IDS, VAS, mRS and the primary endpoint CPC scale are used in the context of this trial, for the assessment of the neurologic function at day 28. No circuit is established specially for the research.

8. SPECIFIC RESEARCH COMMITTEES

Two independent committees, the Steering Committee and the Executive Committee, supervise and support the conduct of the study.

8.1. STEERING COMMITTEE

The Steering Committee is composed of the Study Chairman, Co-chairman, the Coordinating Investigators, and the Principal Investigators acting as representatives /coordinators for each one of the participating countries.

The Steering Committee will meet periodically to assess the progress, provide scientific input, and address policy issues and operational aspects of the protocol.

At the end of the trial, the Steering Committee will meet in a closed session to discuss the trial results.

8.2. EXECUTIVE COMMITTEE

The Executive Committee is composed of the Study Chairman, the Co –chairman, Coordinating Investigators, sponsor and clinical research unit representative.

The executive committee gives scientific input on the protocol and possible amendments as well as on the “state of the art” and any on-going development during the study, which could have consequences for the performance of the study. The Executive Committee is responsible for proposing actions which need to be discussed and approved by the Steering Committee.

When the results of the study become available, the Executive Committee will provide a publication policy and provide advice on the interpretation of the results and the eventual impact on current therapy.

8.3. ADHERENCE TO PROTOCOL

The rules set out in the protocol should be well known by all persons involved in the study. This is of particular importance for the site personnel and can be achieved by sufficient training of the staff and a well-defined procedure for delegation and authorisation of different tasks to various staff members. This training and authorisation process at any site is the responsibility of the investigator.

9. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

9.1. PROCEDURES IN PLACE FOR RECORDING AND REPORTING ADVERSE EVENTS

9.1.1. Definitions

According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012):

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**

Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- **Unexpected adverse reaction**

An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product

According to the notice to sponsors of clinical trials for medications (ANSM):

- **New safety issue**

Any new information regarding safety:

- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

9.1.2. The investigator's roles (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see section N° 9.1.2.1). These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see section 9.1.3).

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible. The investigator assesses the severity of the adverse events. All serious and non-serious adverse events must be reported in the CRF.

9.1.2.1. Serious adverse events that do not require the investigator to immediately notify the sponsor

Normal and natural evolution of the pathology:

Despite improved resuscitative efforts provided by prehospital emergency medical services (EMS), survival to out of hospital cardiac arrest remains very low.

That's why in this study we consider that death is a serious adverse event to record only in the "adverse event" section of the case report form (e-CRF).

Complications related to airway management:

Airway management in the tracheal intubation group includes tracheal intubation by the medical team during OHCA.

Airway management in the bag-valve-mask group includes initial bag-valve-mask ventilation by the medical team during OHCA. The patient will be intubated in case of a return of spontaneous circulation (ROSC).

Known complications related to intubation or bag-mask ventilation that will be recorded only in the "adverse event" section of the e-CRF are:

◆ **Tracheal intubation group**

Aspiration during tube insertion

Mainstem intubation

Esophageal intubation

Dental trauma

Aspiration pneumonia

◆ **Bag-valve-mask group**

Aspiration during bag-mask ventilation

Aspiration pneumonia

Bag-valve-mask ventilation failure

Vomiting during intubation after ROSC

Desaturation during intubation after ROSC

Hypotension during intubation after ROSC

Aspiration during tube insertion after ROSC

Bronchospasm and/or laryngospasm during intubation after ROSC)

Mainstem intubation after ROSC

Esophageal intubation after ROSC

Dental trauma during intubation after ROSC

Special circumstances

Following hospitalizations don't require immediately notification to sponsor; they have to be recorded only in the "adverse event" section of the case report form.

- Hospitalization for a pre-existing pathology
 - Hospitalization for a medical or surgical treatment planned before the participation to this study
 - Admission for social or administrative reasons
 - Admission to the Emergency Department(<12 hours)

9.1.2.2. Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 9.1.2.1 as not requiring notification:

- 1- Death
- 2- Life threatening situation
- 3- Requiring hospitalisation or prolonging hospitalisation
- 4- Persistent or significant disability or incapacity
- 5- Congenital abnormality or birth defect
- 6- Or any other adverse event considered "medically significant"

The serious adverse event related to the research and which is expected is: failure to insert the device for intubation.

9.1.3. Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE (see Appendix 17.6). The report must be signed by the investigator.

Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor **via fax** only to the Vigilance Division, fax No. **+33 (0)1 46 99 02 17** and to the **Clinical Research Unit fax N° +33 (0)1.40.05.49.74**.

For studies using e-CRF:

- the investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form found in Appendix 17.6. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must comply with all requests from the sponsor for additional information. For all questions relating to the notification of an adverse event, the Vigilance Division can be contacted via email: pharmacovigilance@adds.com

9.1.4. Period for notifying the sponsor

The investigator must report all SAE that occur in research subjects:

- At the end of the prehospital medical management

9.1.5. The sponsor's roles

The sponsor, represented by its Vigilance Division, continuously assesses the safety of each experimental medication throughout the research.

➤ Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the research procedures are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.
- The initial declaration must be made no later than 15 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.
- The follow-up declaration must be made no later than 8 days after the 7- or 15-day deadline (depending on the seriousness).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

➤ **Analysis and declaration of other safety data**

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the research, or which could altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

➤ **Annual safety report**

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report which includes, in particular:

- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

9.1.6. Data safety monitoring board

A Data and Safety Monitoring Board (DSMB) will be convened for this biomedical research. The DSMB will be established by the sponsor. Its mission is to serve as a committee for monitoring safety data. The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The members of the DSMB will be named after the research starts. During the first meeting of the DSMB, a chairman will be appointed and the members will determine their operating methods and the meeting schedule.

All missions as well as the precise operating methods of the DSMB will be described in the DSMB's charter for the research.

1- General information about the DSMB

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
 - o safety data: serious adverse reactions

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one clinician specialising in the pathology being studied and possibly a methodologist/biostatistician.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research.

2- Definition of the DSMB's mission:

- Validation of tolerance monitoring methods:
 - o nature of the evaluated parameters
 - o frequency of the evaluations, consultation schedule

- Validation of termination criteria:
 - o criteria for terminating a subject's participation for tolerance reasons
 - o criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))

- Modification of the protocol and recommendations:

In light of the analysis of tolerance data for the research, the DSMB can, when applicable: propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, etc.). Likewise the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

3- Definition of the DSMB's operating methods:

- meeting types (open session, then closed sessions) and schedule
 - desired methods and format of SAE notification from the sponsor to the DSMB
- The DSMB appoints its chairman at the first meeting.

The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and the CPP.

10.DATA MANAGEMENT

10.1.DATA COLLECTION METHODS

10.1.1. Enrolment and out-of hospital period data

During the enrolment and out of hospital period all requested data are collected from the SAMU data sheet and also from the CRF

Data collected during the intervention of the mobile intensive care unit are:

- Medical history (previous cardiovascular, neurologic, metabolic or haematologic disease)
- Characteristic of patient (demographic data, baseline information)
- Factors associated with difficult mask ventilation and/or difficult intubation
- Aetiology of cardiac arrest
- Time of collapse

- Duration of basic resuscitation
- Duration of advanced resuscitation
- Number of shock delivered
- Drug administration (name, quantity)
- Return of spontaneous circulation
- Intubation difficulty Scale score (IDS) (see 17.3)
- Visual-analog-scale (VAS) for Ventilation difficulty with bag-valve (see 17.4)
- Han's mask ventilation classification
- Difficult mask ventilation signs
- Survival to hospital admission
- Serious adverse events
- Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, **aspiration pneumonia**
- Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, **aspiration pneumonia**, dental trauma extubation
- Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group)

10.1.2. In-hospital period

Data collected during in-hospital period, at ICU and then at other hospital departments, are:

- Death from any cause
- Primary cause of death

These data can be collected from patient medical record.

All collected data are entered in an eCRF.

10.1.3. Follow-up period at day 28 (+7 days)

Data collected during patient follow-up are:

- Death from any cause
- Primary cause of death
- Cerebral Performance Categories (CPC) Scale at day 28 (see 17.2)
- Modified Rankin scale score at day 28 (see 17.1)

The 28 day follow-up will be performed in the window 28 + 7 days, but give the status at 28 days will be done by clinic appointment or by contact (phone or mail) with the patient, a family member or the family physician or at the hospital if the patient is still hospitalized.

10.2. IDENTIFICATION OF DATA COLLECTED DIRECTLY IN THE CRFS AND THAT WILL BE CONSIDERED AS SOURCE DATA

CPC scale data, mRS, IDS and VAS are collected directly from the CRF at day 28 (+7 days).

10.3. RIGHT TO ACCESS TO SOURCE DATA AND DOCUMENTS

10.3.1. Access to data

In accordance with GCPs:

- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor.
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.3.2. Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

10.3.3. Data and Subject confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).

During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialized parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown.

The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

10.4. DATA PROCESSING AND STORAGE OF DOCUMENTS AND DATA

10.4.1. Recording of study data

All subject data generated during the study will be recorded in the Case Report Form (CRF) provided by the Sponsor. CRF will be specifically designed to meet the data recording requirements of the Clinical Study Protocol. Only the investigator and co-workers authorized

by him (as listed on the specific form provided by the Sponsor) will be allowed to fill in the CRF or to make corrections.

CRF will be filled in with a black ballpoint pen. Entries will be easily legible and complete. Each CRF will be signed and dated by the investigator after completion. For all laboratory data, the units or any transformation of units will be clearly defined (if not otherwise agreed).

Corrections of wrong entries will be done by crossing out the entry in such a way that it will remain legible. Correction fluids will not be allowed. The correction will then be initialed and dated by the investigator or his/her authorized delegate.

At the end of the study, the investigator will be provided with copies of the CRFs.

10.4.2. Data processing (CNIL, the French Data Protection Authority) in France

The law provides for the declaration of the computerized files of personal data collected for research must be done before the actual start of research. A methodology for specific reference to processing of personal data made in biomedical research as defined by law 2004-806 of August 9, 2004 as falling within the scope of Articles L.1121-1 of the Code of Public Health was established by the CNIL in January 2006.

This methodology allows a simplified declaration procedure when the nature of the data collected in research is consistent with the list provided by the CNIL in its reference document.

When the protocol has a data quality control by a CRA represents the promoter and enters into the scope of the simplified procedure CNIL, the DRCD as promoter asked the head of the computer file commit writing on respect for the reference methodology MR06001 simplified.

10.4.3. Retention of essentials study documents - Archiving

In compliance with the ICH/GCP guidelines, the investigator will maintain all CRFs and all source documents that support the data collected from each subject, until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator as to when these documents no longer need to be retained.

The investigator will take measures to prevent accidental or premature destruction of these documents.

Investigator file

The investigator is responsible for maintaining all the records, which enable the conduct of the study at the site to be fully understood, in compliance with the ICH GCP filing standard. The study documentation including all the relevant correspondence should be kept by the investigator for at least 15 years after the completion or discontinuation of the study, if no

further instructions are given by the sponsor.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named patient source records and anonymous CRF data for the sponsor. The investigator must arrange for the retention of this subject identification log and signed informed consent for at least 15 years after the completion or discontinuation of the study.

The investigator file must contain:

- All protocol versions and appendices
- ANSM agreements and ethic committee opinion
- Correspondence mails
- List of inclusions
- The final research report

No study site document may be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the sponsor must be notified.

↳ Trial Master File

The Sponsor will archive the trial master files in accordance with ICH GCP and applicable regulatory requirements.

10.5. OWNERSHIP OF THE DATA

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

11. STATISTICAL ASPECTS

11.1. STATISTICAL DESIGN / MODEL

A multicentric prospective, randomized, controlled, open two-arm non inferiority study to compare two technics for airway management.

11.2. NULL AND ALTERNATIVE HYPOTHESES

The primary aim of the trial is to demonstrate non inferiority of the bagmask vs tracheal intubation with regard to primary endpoint as the survival rate with favorable neurological function, The null and alternative hypotheses are as follows:

$H_0: \pi_{\text{bag}} - \pi_{\text{tracheal}} \leq -0.01$ succes rate of the bag-valve – mask is inferior to tracheal intubation

Versus.

$H_1: \pi_{\text{bag}} - \pi_{\text{tracheal}} \geq -0.01$ succes rate of the bag-valve – mask is not inferior to tracheal intubation

In case of demonstration of non-inferiority a test of difference will be carried out.

11.3.PLANNED ANALYSES

11.3.1. Populations to be analysed

Since it is a non-inferiority trial the main analysis will be based on both the intent-to-treat population (ITT) of all patients randomised (irrespective of which study treatment is given or if any study treatment is adequately received) and in per protocol analysis (PP) of all patients randomized & treated without major protocol violations/deviations.

11.3.2. Patient accountability

Disposition of patients, patient status and patients excluded from PP populations will be summarised by treatment group. Descriptive statistics for primary reason for patient's withdrawal will be also presented by treatment group as well as a list of these patients sorted by treatment group.

DROP-OUTS

Reasons for drop-outs in each treatment group will be displayed. A detailed list of drop-out patients will also be provided.

11.3.3. Baseline characteristics

Baseline characteristics will be tabulated and comparability / differences between the treatment groups will be examined by means of descriptive statistics. As recommended by CONSORT no tests will be carried on baseline variables.

11.3.4. Interim analysis

An interim analysis will be carried out after 50% and 75% of inclusion. The only scope of these interim analyses will be to test futility and/or allow sample size recalculation (using ADDPLAN software)

The sponsor delivers interim analyses reports to the Competent Authority (ANSM) and the CPP.

11.4.EFFICACY ANALYSIS

11.4.1. Main Efficacy Criterion

The primary ITT analysis on the primary endpoint will be carried out by calculating the 95% two-sided confidence interval (CI) (as recommended by EMEA guidelines) of the difference $\pi_{\text{bag}} - \pi_{\text{tracheal}}$. If the lower limit of this CI is higher than -0.01 then the conclusion of non inferiority will be accepted. If necessary exact rather than asymptotic CI will be used.

11.4.2. Secondary Efficacy Criteria

The secondary ITT analysis will be carried out by the chi-square test on proportions for all secondary criteria expressed as rates. The corresponding 95% confidence interval on their odds ratio and differences will also be presented.

For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non-Gaussian statistical distribution.

11.5.SAFETY ANALYSIS

(Serious) adverse events will be tabulated per treatment group. All (dichotomized) endpoints will be analyzed by chi-square test on proportions and the 95% confidence interval on the odds-ratio will be presented.

11.6.EXPLORATORY ANALYSES

Potentially important prognostic factors for the main and/or secondary efficacy parameters will be identified by means of multivariate logistic regression.

11.7.HANDLING OF MISSING DATA

In the intent-to-treat analysis missing data for the primary endpoint will be imputed according to the worst case principle (no success). In case of large differences between PP and ITT populations, an analysis of sensitivity using different methods for missing data replacement, including multiple imputation technique, will be carried out.

11.8.RANDOMISATION

The randomisation will be stratified by centre and, within the centres, performed in blocks to ensure balanced distribution of the treatment groups at any time.

11.9.SAMPLE SIZE ISSUES

The sample size calculation is based on non-inferiority hypotheses using the confidence interval approach. The sample size is based on Hasegawa's study (JAMA 2013) that reported a survival rate with favorable neurological function in the bag-valve-mask group of 3% and Gueugniaud's study (NEJM 2008) of 2% survival rate with tracheal intubation. We defined a non-inferiority margin of 1%. We would need 956 patients per group for a study power of 0.8 and a type I error rate of 0.025. A total of 2,000 patients will be recruited (based on 5000 simulations using the Newcomb-Wilson score method, Statistics in Medicine 1988, 17:873-890)

11.10.STATISTICAL SOFTWARE AND RESPONSABILITY

All analyses will be made using SAS Software version 9.2 under the responsibility of Pr Eric Vicaut.

12.QUALITY CONTROL AND ASSURANCE

The biomedical research projects supported by the AP- HP are classified according to the estimated risk for persons participating in research through the classification of biomedical research to promote AP- HP A to D.

The conduct of research in the study centers and support issues will be made in accordance with the Declaration of Helsinki and Good Practices in force .

12.1.GENERAL ORGANIZATION

The promoter must ensure the safety and respect of the people who agreed to participate in research. It must establish a quality assurance system to monitor the progress of the best research in the study centers.

To this end, the mandate Clinical Research Associates (CRA) whose primary mission is to conduct regular monitoring visits to the research sites after making openings visits

The objectives of the follow-up research, as defined in the Good Clinical Practices (GCP § 5.18.1) are to verify that:

- The right to safety and protection of persons who consent to research are met,
- The data reported are accurate, complete and consistent with the source documents,
- Research is conducted in accordance with established protocol, GCP and the applicable laws and regulations in force.

12.1.1. STRATEGY FOR OPENING CENTERS

An opening visit of each center will be performed by the ARC in charge of the study before the start of inclusions, for implementation of the protocol and getting to know the various stakeholders in the biomedical research .

12.1.2. Level of centre monitoring

The choice of an appropriate level of monitoring was weighted according to the complexity, impact and research budget. To this end, the promoter in accordance with the coordinating investigator determined the logistics and impact score that yielded the monitoring level to implement this research.

12.2.QUALITY CONTROL

A Clinical Research Associate (CRA) mandate by the promoter will ensure the successful completion of the research, data collection generated by writing their documentation, recording and reporting in accordance with the Standard Operating Procedures implemented to DRCD within and in accordance with Good Clinical Practice and the laws and regulations in force.

The investigator and his team members agree to make available during visits of quality control carried out at regular intervals by the Clinical Research. During these visits, the following items will be reviewed:

- Written consent;
- Compliance with the research protocol and procedures that are defined;
- Quality of data collected in the case report form: accuracy, missing data, data consistency with the documents 'source' (medical records, appointment books, original lab results, etc.).
- Management of the treatments used
- Verification and transmission promoter SAEs occurred in accordance with SAE grid.
- Verification of product management research through visits to the hospital pharmacy.
- For the closing Visit of each center: Clinical research associate (CRA) will regulatory study documents maintained in the center. Prepare envelopes consents for archiving.

12.3.CASE REPORT FORM

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.

This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.

When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. 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 investigator must archive a copy of the authenticated document that was delivered to the sponsor.

12.4.MANAGEMENT OF NON-COMPLIANCES

Any event occurring due to non-compliance with the protocol, standard operating procedures, good clinical practices or laws and regulations by an investigator or any other person involved in the conduct of the research should be stated. Non-compliance with the promoter. At first, these statements will be reviewed and processed by the medical coordinator DRCD to take corrective or preventative actions. Then in a second time, sent to the Quality Risk Management department of DRCD for verification and analysis. These audits may be a request for information, visits or audit compliance with the investigator in charge of the concerned place of research.

12.5.AUDIT/INSPECTION

Investigators agree to accept the quality assurance audits conducted by the promoter as well as inspections by the competent authorities. All data, all documents and reports may be subject to audits and regulatory inspections can be opposed without medical confidentiality.

An audit may be conducted at any time by persons authorized by the promoter of responsible and independent research. It aims to ensure the quality of research, the validity of its results and compliance with the law and regulations in force.

Those who direct and supervise research agree to comply with the requirements of the promoter and to the competent authority regarding an audit or inspection of the research.

The audit can be applied at all stages of research, protocol development to publication of results and classification of data used or generated in the course of research.

12.6.PRIMARY INVESTIGATOR'S COMMITMENT TO ASSUME RESPONSIBILITY

Before starting the research, each investigator will give the sponsor's representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.

The investigators and their employees will sign a delegation of duties form specifying each person's role.

13.ETHICAL AND LEGAL CONSIDERATIONS

13.1.PROCEDURES FOR INFORMING AND OBTAINING CONSENT OF THE PERSONS UNDERGOING RESEARCH

Following Article L1122 -1-1 of the Code of Public Health, no biomedical research can be performed on a person without their free and informed consent. It must be collected after he was issued the information provided for in Article L . 1122-1 of the same Code.

➤ Information of the person who is willing to a research

Following Article L. 1122-1 of the Public Health Code, the person who prepared the research received prior oral and written information on biomedical research, allowing him to give free and informed consent. He is aware of full and fair way, understandable terms, objectives, risks and constraints of research, monitoring measures and security measures, treatment of personal data necessary for the purpose of research, the right to refuse to participate in the research or the possibility to withdraw consent at any time, etc... All this information must be included in a written document.

➤ Specificity of this study for obtaining consent of the person who is part of the research

This research will take place in a context of inclusion under the emergency provisions of the law (Article L1122 -1-2 of the CSP). Undeniably, given the inclusion and non-inclusion criteria (cardiac arrest patients), the consent of patients or relatives if present cannot be collected at baseline. **Thus the extreme emergency situation not allowing collecting the prior consent of the person or relative, the protocol provides that their consent is not necessary.** In case the resuscitation succeeds a delayed consent will be asked to the patient for further participation to the study. **The participant shall be informed about the study during his hospitalization as soon as his condition allows it.** Then, if the patient agrees he signs the delayed consent form to pursue his participation to the research and a "no objection to the use of its data" form for the possible continuation of this research will be completed.

According to the law (art. L1122-2 and L1121-8 of the Public Health code), if the patient has a legal representative (guardian designated by the law), it belongs to his guardian to give his consent for a further participation to the research and the collection and the exploitation of the data.

➤ **Notification in the medical record**

In addition, the investigator shall specify in the medical record of the person 's participation in this research , the methods of obtaining consent of the person who cannot give consent in writing (as provided by Articles L. 1122 -1-1 to L. 1122-2 of the CSP) and the terms of issue of information in order to collect. It retains the original copy of the form to obtain signed and dated consent of the individual. A copy of the Information Statement and Consent Form will be placed at the end of the study in a tamper sealed envelope containing all the consent forms. It will be archived by the promoter.

➤ **Subject Information Card**

The subject will be provided with a study information card bearing the following information:

- That he/she is participating in a clinical study.
- The name and phone number of the investigator.

13.2.SUPPORT ON RESEARCH

The management of patients included in this study was modeled on the assumption usually recommended. However, the results of acts of routine care will be used for research. Thus, a TEC will be recruited for the collection of these data in different ICUs. It will also be responsible for conducting follow tours on telephone (see section 6.3.2).

13.3.COMPENSATION FOR SUBJECTS

No patient compensation is provided in the protocol.

13.4.SUBJECT PROHIBITED FROM PARTICIPATING IN ANOTHER RESEARCH

During the period of the patient's participation, the subject may not participate in other biomedical research protocols relating to medications until after his follow-up at day 28 (+7 days)

However, patients can simultaneously participate to other non interventional trials.

13.5.ROLE OF THE SPONSOR

The Assistance Publique Hôpitaux de Paris (AP- HP) is the promoter of the research and by delegation the Department of Clinical Research and Development (DRCD) ensures missions, in accordance with Article L.1121 - 1 of the public health code. The Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any time for medical or administrative reasons, in this case, a notification will be provided to the investigator.

13.6. INDEPENDENT ETHICS COMMITTEE(S) AND REGULATORY AUTHORITIES REQUIREMENTS

The study protocol, the “Participant information and consent form” document, and the list of investigators document will be submitted for review to the appropriate Independent Ethics Committee(s) by the Coordinator or the Sponsor in accordance with local regulations.

The study will not start before written approval by corresponding Ethics Committee(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the technical protocol by each contractual party involved has been obtained.

In accordance with local regulations, the investigator and/or the Sponsor will inform the Director of the Hospital involved in the study.

13.7. REQUEST FOR ANSM AUTHORIZATION

To start the study, AP-HP as a sponsor must submit an application license to the competent authority ANSM in France. The competent authority, as defined by Article L. 1123-12, speaks regarding of safety of persons who consent to biomedical research, including the safety and quality of products used in research in accordance, where appropriate, existing repositories, their condition use and safety of persons in respect of the acts and methods used and the arrangements for tracking people.

13.8. MODIFICATIONS TO THE RESEARCH

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the Ethics Committee(s) and authorisation from the competent authorities within the scope of their respective authorities.

The information sheet and the consent form can be revised if necessary; in particular if there is a substantial modification to the research or if adverse reactions occur.

13.9. FINAL REPORT OF RESEARCH

The final report of biomedical research referred to in Article R1123 - 60 of the CSP will be co-written by the coordinator and biostatistician for this research. This report will be submitted to each of the investigators for review. Once a consensus has been reached, the final version must be endorsed by the signature of each of the investigators and sent to the promoter as soon as possible after the effective end of the search. A report in the reference plane of the competent authority must be submitted to the competent authority and the CPP within one year after the end of the research, being understood as the last follow-up visit of the last included patient. This period is reported at 90 days in case of premature termination of the research.

14.FUNDING AND INSURANCE

14.1.RESEARCH BUDGET

The costs associated with this research are:

- Recruitment of staff:
 - Recruitment of physician time
 - Recruitment of a clinical study technician
- Quality control by an clinical research associate (CRA) by the promoter
- Taxes, insurance, Ethic committee (CPP)
- Data management: report forms, data-management, statistical analysis
- Miscellaneous expenses: meetings, missions coordinator, notebooks, miscellaneous items.

14.2.INSURANCE

Pursuant to Article L.1121-10 of the Code of Public Health, insurance contracts should ensure the liability of the promoter and that of all involved and cover the financial consequences of claims finding their generating cause in biomedical research.

The Promoter, subscribed for the entire duration of the research insurance covering its own liability and that of any doctor involved in the conduct of research. It also provides full compensation for damaging the search for the person who is ready and assigns, subject to proof to bear the damage is not due to his fault or that of any participant without consequences that may be the opposite of a third party or the voluntary withdrawal of the person who had originally agreed to pay for research.

The Assistance Publique-Hôpitaux de Paris (AP-HP) has taken an insurance with the company HDI-Gerling through BIOMEDIC-INSURE for the duration of the research, ensuring civil liability as well as any stakeholder (doctor or personnel involved in the conduct of research), in accordance with Article L.1121-10 of the CSP.

15.PUBLICATION RULES

The Sponsor (APHP) shall retain ownership of all case report forms, data analyses, and reports, which result from this study. All information obtained as a result of the study will be regarded as confidential, until appropriate analysis and review by the Sponsor and the Coordinator are completed.

The results of the study remain the exclusive property of the Sponsor, which will be able to freely exploit the results and forward them to other investigators and administrative authorities in various countries.

No communication or publication (irrespective of the medium used) concerning the study or its results may take place during the period of technical protocol implementation or after the end of the study without the prior, written, signed agreement of the Sponsor.

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17. ANNEXES:

17.1. MODIFIED RANKIN SCALE (MRS)

Score Description

0 No symptoms at all

1 No significant disability despite symptoms; able to carry out all usual duties and activities

2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 Moderate disability; requiring some help, but able to walk without assistance

4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 Dead

TOTAL (0–6): _____

17.2. CEREBRAL PERFORMANCE CATEGORIES SCALE (CPC SCALE)

Note: If patient is anesthetized, paralyzed, or intubated, use “as is” clinical condition to calculate scores.

CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.

CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.

CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.

CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

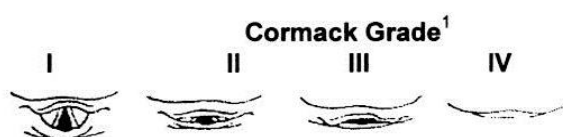
17.3. INTUBATION DIFFICULTY SCALE SCORE (IDS)

Parameter	Score
Number of Attempts >1	N ₁
Number of Operators >1	N ₂
Number of Alternative Techniques	N ₃
Cormack Grade - 1	N ₄
Lifting Force Required	
Normal	N ₅ =0
Increased	N ₅ =1
Laryngeal Pressure	
Not applied	N ₆ =0
Applied	N ₆ =1
Vocal Cord Mobility	
Abduction	N ₇ =0
Adduction	N ₇ =1
TOTAL: IDS = SUM OF SCORES	N₁-N₇

IDS Score	Degree of Difficulty
0	Easy
0 < IDS ≤ 5	Slight Difficulty
5 < IDS	Moderate to Major Difficulty
IDS = ∞	Impossible intubation

Rules for Calculating IDS Score:

N₁	Every additional attempt adds 1 pt.
N₂	Each additional operator adds 1 pt.
N₃	Each alternative technique adds 1 point: Repositioning of the patient, change of materials (blade, ET tube, addition of a stylette), change in approach (nasotracheal/orotracheal) or use of another technique (fibroscopy, intubation through a laryngeal mask).
N₄	Apply Cormack grade for 1st oral attempt. For successful blind intubation N ₄ = 0.
N₆	Sellick's maneuver adds no points.
Impossible intubation: IDS takes the value attained before abandonment of intubation attempts.	

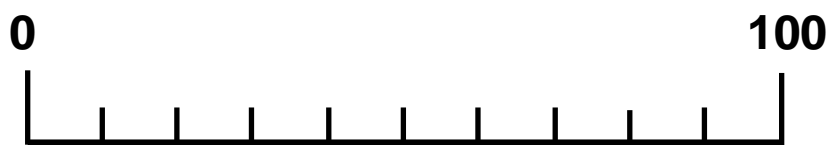


¹ Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984;39:1105-1111.

17.4. VISUAL-ANALOG-SCALE (VAS)

The difficulty of ventilation by bag valve mask is assessed by the following Visual Analog Scale (VAS):

Was the ventilation difficult by bag valve mask?



No, not at all

Yes, extremely difficult

17.5.HAN'S MASK VENTILATION CLASSIFICATION

Classification	Description/definition
Grade 0	Ventilation by mask not attempted
Grade 1	Ventilated by mask
Grade 2	Ventilated by mask with oral airway or other adjuvant
Grade 3	Difficult mask ventilation (inadequate, unstable, or requiring two practitioners)
Grade 4	Unable to mask ventilate

Reference: Han R, Tremper KK, Kheterpal S, O'Reilly M. Grading scale for mask ventilation. Anesthesiology 2004;101:267.

17.6.FORM FOR REPORTING SERIOUS ADVERSE EVENTS

Direction de la Politique Médicale (DPM) Département de la Recherche Clinique et du Développement (DRCD)	 Form for reporting a Serious Adverse Event (SAE) occurring in a biomedical research for not health products	PART RESERVED FOR THE SPONSOR ___ - DRRC 20 ___ - ___
--	---	---

This form must be correctly filled out (2 pages), signed and sent immediately via fax to the Vigilance Division, fax No. +33 (0)1 46 99 02 17 and to the Clinical Research Unit fax N° +33 (0)140 05 49 74 as soon as the investigator becomes aware of the serious adverse event

Initial reporting Follow-up of a reported SAE Follow-up number |__|__|

1. Clinical trial identification	
CAAM	Date of this report : __ _ __ _ 2_ 0_ __ _ dd mm yyyy
Sponsor's trial number : P130932	Date of investigator first learning of the SAE : __ _ __ _ 2_ 0_ __ _ dd mm yyyy
Title: CAAM study "Initial airway management in patients with out-of-hospital cardiac arrest: tracheal intubation vs. bag-valve-mask ventilation":	Research risk : <input type="checkbox"/> A <input checked="" type="checkbox"/> B <input type="checkbox"/> C <input type="checkbox"/> D
	Study design : <input type="checkbox"/> Non comparative trial <input checked="" type="checkbox"/> Comparative trial : <input type="checkbox"/> Double-blind <input type="checkbox"/> Single-blind <input checked="" type="checkbox"/> Open-label <input checked="" type="checkbox"/> Randomized <input type="checkbox"/> Non- randomized

2. Investigator centre	
Name of the centre :	Investigator (Last name/First name) :
City – post code : Country	Tél : Fax :
Department :	

3. Identification number and medical history of the patient	
Identification number : __ _ - __ _ - __ _ - __ _ <small>center Nb. randomization No. lastname firstname initial</small>	Relevant surgical-medical/family history to facilitate the assessment of the case (attach a medical hospitalization report if required) :
Gender : <input type="checkbox"/> M <input type="checkbox"/> F	
Weight : __ _ kg	Date of birth : __ _ __ _ __ _ __ _ dd mm yyyy
Height : __ _ cm	Age : __ _ years
Date of inclusion according to emergency clause = Date of randomization : __ _ __ _ 2_ 0_ __ _ dd mm yyyy	
Signature of the delayed consent date : __ _ __ _ 2_ 0_ __ _ dd mm yyyy	Randomization group : <input type="checkbox"/> Bag-valve-mask ventilation <input type="checkbox"/> Tracheal ventilation

4. Procedures and care added by the research (ex. : biopsies, MRI, blood samples ... <i>Strikethrough the box 5. if the procedures and care have not been realized</i>) :	Realisation date (dd/mm/yyyy)	Chronology	
		Before SAE occurrence	After SAE occurrence
.....	__ _ __ _ 2_ 0_ __ _	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ _ __ _ 2_ 0_ __ _	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ _ __ _ 2_ 0_ __ _	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ _ __ _ 2_ 0_ __ _	<input type="checkbox"/>	<input type="checkbox"/>
.....	__ _ __ _ 2_ 0_ __ _	<input type="checkbox"/>	<input type="checkbox"/>

5. Concomitant medicinal product(s) at the time of the SAE, exclude those used to treat the adverse event (fill the table below and if necessary the concomitant drug(s) appendix ⇨ Appendix attached to this form : <input type="checkbox"/> Yes <input type="checkbox"/> No						
Brand name (preferably) or International Nonproprietary Name including the pharmaceutical form and the dose	Indication	Route (1)	Daily dose	Starting date (dd/mm/yyyy)	On going (2)	Stopping date (dd/mm/yyyy)
.....	__ _ __ _ __ _ __ _	<input type="checkbox"/>	__ _ __ _ 2_ 0_ __ _
.....	__ _ __ _ __ _ __ _	<input type="checkbox"/>	__ _ __ _ 2_ 0_ __ _
.....	__ _ __ _ __ _ __ _	<input type="checkbox"/>	__ _ __ _ 2_ 0_ __ _
.....	__ _ __ _ __ _ __ _	<input type="checkbox"/>	__ _ __ _ 2_ 0_ __ _
.....	__ _ __ _ __ _ __ _	<input type="checkbox"/>	__ _ __ _ 2_ 0_ __ _

CAAM

PART RESERVED FOR THE SPONSOR
- DRRC 20 -

Patient identification number : | | | | - | | | | | | - | | - | |
center Nb. randomization No. lastname firstname initial

(1) Route of administration : PO = oral route ; IM=intramuscular ; IV=intravenous ; SC=subcutaneous or other (specify) (2) On going at the time of the SAE

6. Serious Adverse Event [SAE]

<p>Diagnosis : <input type="checkbox"/> Final <input type="checkbox"/> Provisional</p>	<p>Body site(s) :</p>	<p>Symptom(s) :</p>
<p>Date of the first symptoms' occurrence : 2 0 </p> <p>Precise those symptoms :</p>		<p>Seriousness criteria :</p> <p><input type="checkbox"/> Involved or prolonged hospitalisation : from 2 0 to 2 0 <input type="checkbox"/> on going</p> <p><input type="checkbox"/> Death</p> <p><input type="checkbox"/> Life-threatening</p> <p><input type="checkbox"/> Involved persistence or significant disability or handicap</p> <p><input type="checkbox"/> Congenital anomaly</p> <p><input type="checkbox"/> Other medically significant criteria, specify :</p>
<p>Start date of onset of the SAE : 2 0 dd mm yyyy</p> <p>Time of onset : hh min <input type="checkbox"/> missing data</p>	<p>Delay of occurrence between the last procedure/care added by the research and the date of onset of the SAE : / dd hh min</p>	
<p>Has the event conducted to an interruption of the procedure/care added by the research? <input type="checkbox"/> No <input type="checkbox"/> Yes Date : 2 0 </p> <p>The interruption of the procedure/care added by the research has been : <input type="radio"/> Temporary <input type="radio"/> Permanent</p> <p>If required, date of the return to the procedure/care added by the research : 2 0 </p> <p>Recurrence of the SAE after this return : <input type="radio"/> No <input type="radio"/> Yes - Date : 2 0 </p> <p>Has the event conducted to unblinding ? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> NA Date : 2 0 </p>		
<p>SAE's outcome</p> <p><input type="checkbox"/> Death : <input type="radio"/> unrelated to the SAE <input type="radio"/> related to the SAE Date : 2 0 dd mm yyyy</p> <p><input type="checkbox"/> Resolved : <input type="radio"/> without sequelae <input type="radio"/> with sequelae, specify sequelae : 2 0 dd mm yyyy hh min</p>		<p><input type="checkbox"/> On going : <input type="radio"/> Stable condition <input type="radio"/> Worsening <input type="radio"/> Improvement</p> <p>Symptomatic measures were taken : <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, specify :</p>
<p>Severity criterion : <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe</p>		

7. Other aetiology(ies) considered :

No Yes If yes, specify :

8. Additional investigation(s) done :

No Yes If yes, specify :

9. According to the investigator, the SAE is (several possible cases) :

Related to the clinical trial :

Yes : to the procedure/care of the clinical trial ; specify :
 Specify : Certain relation Probable relation Possible relation Unlikely relation
 Specify : Certain relation Probable relation Possible relation Unlikely relation

No : to the disease progression :
 to the pregnancy
 to one (or several) concomitant medicinal product(s) administered, specify :
 to an intercurrent disease, specify :
 other, specify :

Reporter	Investigator	Department stamp :
Name and role :	Name :	
Signature :	Signature :	



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POLE : ACCUEIL - URGENCES - IMAGERIE

SAMU DE LA SEINE SAINT DENIS

BATIMENT SAMU - SMUR
SECTEUR ORANGE PORTE 11

Professeur Frédéric ADNET

Chef de Pôle Accueil - Urgences - Imagerie
Chef de Service des Urgences - SMUR
Directeur Médical du SAMU 93

Ligne directe : 01 48 96 44 08
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Télécopie : 01 48 96 44 93
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Bobigny, le 23 Septembre 2015

DRCD
Hôpital Saint Louis
Porte 23, carré historique
1 avenue Claude Vellefaux
75475 Paris Cedex 10

Objet : Modifications substantielles apportées au document du protocole : MS1

Réf. Promoteur : P140501
N° EUDRACT 2 : 014-003707-30
Réf. CPP : JLD/AP_Protocolo 28_2014

Titre: "Initial airway management in patients with out-of-hospital cardiac arrest: tracheal intubation vs. bag-valve-mask ventilation" CAAM study

Madame,

Je vous adresse cette lettre pour solliciter l'avis du CPP et de l'ANSM suite aux modifications substantielles apportées au protocole CAAM.

Ces modifications concernent les points suivants :

1/ Critère d'évaluation principal :

Une précision a été rajoutée concernant l'état neurologique initial des patients (avant randomisation). En effet, ce paramètre doit être pris en compte lors de l'évaluation neurologique à 28 jours après l'arrêt cardiaque. Ceci, afin d'éviter un biais lors de l'interprétation des résultats.

2/ Modification de la liste des centres :

- Ajout de centres : 6 centres Français seront rajoutés afin d'augmenter le rythme des inclusions.
- Désistement d'un centre : Le centre Belge N°19 ne souhaite plus participer à l'étude.
- Changement d'investigateur principal : Dr Bertrand LIONEL ne travaillera plus au SAMU-SMUR de l'hôpital Montauban (centre N°11). Le nouvel investigateur principal sera Dr Sophie FAUROUX

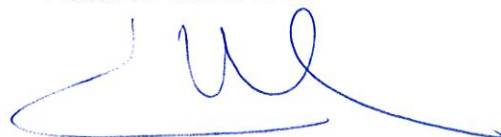
3/ Corrections de coquilles : Ces coquilles sont principalement dues à des erreurs lors de la consolidation des protocoles suite aux remarques des instances réglementaires.

Vous trouverez ci-joints : le protocole V1.4 du 22/09/2015, le tableau mentionnant toutes les modifications apportées et leur justification, la liste des centres dissociée du protocole, ainsi que les CVs des investigateurs.

Je vous prie de croire, Madame, à mes sentiments les meilleurs

ASSISTANCE PUBLIQUE
HÔPITAUX DE PARIS
HOPITAL AVICENNE
SAMU 93
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Chef de Service des Urgences - SMUR
Directeur Médical du SAMU 93

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POLE : ACCUEIL - URGENCES - IMAGERIE

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Bobigny, le 27 Janvier 2016

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Objet : Modifications substantielles apportées au document du protocole : MS2

Réf. Promoteur : P140501
N° EUDRACT 2 : 014-003707-30
Réf. CPP : JLD/AP_Protocol 28_2014

Titre: "Initial airway management in patients with out-of-hospital cardiac arrest: tracheal intubation vs. bag-valve-mask ventilation" CAAM study

Madame,

Je vous adresse cette lettre pour solliciter l'avis du CPP et de l'ANSM suite aux modifications substantielles apportées au protocole CAAM.

Ces modifications concernent l'ajout de complications connus dans le cadre de la ventilation au masque et de l'intubation trachéale. Ces complications sont rajoutées dans la liste des évènements attendus dans chaque groupe de randomisation.

1/ Evènement indésirable attendu rajouté dans le groupe intubation trachéale : Pneumopathie d'inhalation

2/ Evènements indésirables attendus rajoutés dans le groupe Ventilation au masque : Echec de ventilation au masque, Pneumopathie d'inhalation

Vous trouverez ci-joints : le protocole V2 du 22/01/2016, le tableau mentionnant ainsi que toutes les modifications apportées et leur justification.

Je vous prie de croire, Madame, à mes sentiments les meilleurs

Professeur Frédéric ADNET

«INITIAL AIRWAY MANAGEMENT IN PATIENTS WITH OUT-OF-HOSPITAL CARDIAC ARREST: TRACHEAL INTUBATION VS. BAG-VALVE-MASK VENTILATION» *ETUDE CAAM*
P130932
NUMÉRO EUDRACT 2014-A01109-38

Protocole version 1.3 du 20/11/2014	Protocole modifié version 1.4 du 22/09/2015	Justification de la modification substantielle
<p>SUMMARY:</p> <p>Secondary endpoints (page 8-9)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma • Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure 	<p>Secondary endpoints (page 8-9)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma extubation • Technique's failure defined as mortality at 28-day or regurgitation during the procedure or failure of the procedure (failure to ventilate in the bag-valve-mask ventilation or failure to intubate in the intubation group) 	<p>Coquille: erreur lors de la consolidation du protocole à partir des versions V1.1 et V1.2 Information présente dans le protocole V1.2, section 4.1.2 (secondary endpoints) correction pour uniformiser le protocole</p> <p>Coquille : correction pour uniformiser le protocole Information présente dans la section 4.1.2 et 5.1 du protocole V1.3</p>
<p>4. PLAN FOR THE RESEARCH</p> <p>Groupe A (experimental) (Page 14) When standard bag-valve-mask ventilation is impossible or in case of massive aspiration (after randomisation)</p>	<p>4. PLAN FOR THE RESEARCH</p> <p>Groupe A (experimental) (Page 14) When standard bag-valve-mask ventilation is impossible or in case of massive aspiration massive regurgitation of gastric content (after randomisation)</p>	<p>Coquille: erreur lors de la consolidation du protocole à partir des versions V1.1 et V1.2 Information présente dans le protocole V1.2 correction pour uniformiser le protocole</p>
<p>4.1.1 PRIMARY ENDPOINT (PAGE 14)</p> <p>Survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less.</p>	<p>4.1.1 PRIMARY ENDPOINT (PAGE 15)</p> <p>Survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less. In case of neurological disability before randomization, the survival associated the same degree of disability will be considered a favorable neurological function</p>	<p>Précision rajoutée dans le critère d'évaluation principal afin d'éviter les biais liés à l'état initial du patient (avant l'arrêt cardiaque). Pour une meilleure évaluation des fonctions neurologiques à 28 jours post arrêt cardiaque, l'état initial du patient doit être pris en compte (avant l'arrêt cardiaque).</p>

Protocole version 1.3 du 20/11/2014	Protocole modifié version 2.0 du 18/06/2015	Justification de la modification substantielle
4.1.2 SECONDARY ENDPOINTS (PAGE 15)	<p>4.1.2 SECONDARY ENDPOINTS (PAGE 15)</p> <p>Correction par ajout de :</p> <ul style="list-style-type: none"> • Han's mask ventilation classification • Difficult mask ventilation signs 	<p>Coquille : correction pour uniformiser le protocole Information présente dans le résumé et dans la section 5.1 du protocole V1.3</p> <p>correction pour uniformiser le protocole</p>
5.1 ENROLLEMENT AND OUT OF HOSPITAL PERIOD (PAGE 18)	<p>5.1 ENROLLEMENT AND OUT OF HOSPITAL PERIOD (PAGE 18)</p> <p>Correction par ajout de :</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma extubation 	<p>Coquille: erreur lors de la consolidation du protocole à partir des versions V1.1 et V1.2 Information présente dans le protocole V1.2, section 4.1.2 (Secondary endpoints)</p> <p>correction pour uniformiser le protocole</p>
10.1.1 Enrolment and out-of hospital period data (Pages 30-31)	<p>10.1.1 Enrolment and out-of hospital period data (Pages 30-31)</p> <p>Correction par ajout de :</p> <ul style="list-style-type: none"> • Factors associated with difficult mask ventilation and/or difficult intubation • Han's mask ventilation classification • Difficult mask ventilation signs <p>Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma extubation</p>	<p>Coquille : correction pour uniformiser le protocole</p>

Annexe : Participating centers	Annexe modifié	Justification de la modification substantielle
<p>PARTICIPATING CENTERS (PAGES 45-47) : Nombre total de centres participants: 20</p> <p>La liste des centres participants est associé au protocole V1.3 (Pages 45-47)</p>	<p>PARTICIPATING CENTERS : Nombre total de centres participants: 25</p> <p>La liste des centres participants sera en annexes, dissociée du protocole</p> <p><u>CENTRE NE PARTICIPANT PAS :</u></p> <p>Center 19 Principal Investigator (PI) Michel VERGNION Service des Urgences et du SMUR, CHR de la Citadelle - site Citadelle Boulevard du 12ème de Ligne 1 B 4000 Liège michel.vergnion@chrcitadelle.be</p> <p><u>AJOUT DE 6 CENTRES</u></p> <p>Centre 21 Principal Investigator (PI) Dominique SAVARY Urgences SAMU 74 Centre Hospitalier Annecy Genevois (CHANGE) 1 Avenue de l'Hôpital, BP 90074 – Metz-Tessy 74374 PRINGY Cedex dsavary@ch-annecygenevois.fr</p> <p>Centre 22 Principal Investigator (PI) François BRAUN Urgences SAMU CHR Metz-Thionville, hôpital de Mercy 1, allée du Château CS 45001 57085 Metz cedex 03 Fr.braun@chr-metz-thionville.fr</p> <p>Centre 23 Principal Investigator (PI) Brigitte HENNEQUIN SMUR de Saint-Denis hôpital Delafontaine</p>	<p>Dans le cas de futures modifications de centres, cela évitera de changer de version de protocole.</p> <p>Désistement du centre pour le protocole</p> <p>Ajout de centres 21, 22, 23, 24, 25 et 26 dans le but d'augmenter le rythme des inclusions</p>

	<p>2 rue du Dr Delafontaine 93205 Saint Denis Seine-Saint-Denis</p> <p>Centre 24 Principal Investigator (PI) Pr Pierre-Yves GUEUGNIAUD Hôpital Edouard Hériot - Organigramme du SAMU 69 pierre-yves.gueugniaud@chu-lyon.fr</p> <p>Centre 25 Principal Investigator (PI) Yannick AUFFRET SMUR Quimper 14 Avenue Yves Thépot 29107 Quimper Cedex</p> <p>Centre 26 Principal Investigator (PI) Jean-Pierre TOURTIER SMUR BSPP (Brigade de sapeurs-pompiers de Paris)</p>	
<p>CHANGEMENT D'INVESTIGATEUR PRINCIPAL</p> <p>Center 11 Principal Investigator (PI) Bertrand LIONEL Urgences -Samu, Hôpital Montauban 100 R Leon Cladel BP 765 82013 Montauban bertrandfredie@aol.com</p>	<p>CHANGEMENT D'INVESTIGATEUR PRINCIPAL</p> <p>Center 11 Principal Investigator (PI) Dr Sophie FAUROUX Urgences -Samu, Hôpital Montauban 100 R Leon Cladel BP 765 82013 Montauban sophie_fauroux@hotmail.com</p>	<p>Changement d'investigateur principal. Dr Bertrand LIONEL ne travaillera plus au SAMU-SMUR de l'hôpital Montauban (changement de lieu de travail)</p>

«INITIAL AIRWAY MANAGEMENT IN PATIENTS WITH OUT-OF-HOSPITAL CARDIAC ARREST: TRACHEAL INTUBATION VS. BAG-VALVE-MASK VENTILATION» *ETUDE CAAM*
P130932
NUMÉRO EUDRACT 2014-A01109-38

Protocole version 1.4 du 22/09/2015	Protocole modifié version 2 du 22/01/2016	Justification de la modification substantielle
<p>SUMMARY:</p> <p>Secondary endpoints (page 8-9)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content 	<p>Secondary endpoints (page 8-9)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, aspiration pneumonia, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, aspiration pneumonia 	<p>Complication connue pouvant résulter de la régurgitation lors de l'intubation trachéale et de la ventilation au masque en préhospitalier Complication rajoutée car oubliée dans les versions précédentes</p>
<p>4.1.2 SECONDARY ENDPOINTS (PAGE 15)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content 	<p>4.1.2 SECONDARY ENDPOINTS (PAGE 15)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, aspiration pneumonia, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, aspiration pneumonia 	<p>Complication connue pouvant résulter de la régurgitation lors de l'intubation trachéale et de la ventilation au masque en préhospitalier Complication rajoutée car oubliée dans les versions précédentes</p>

Protocole version 1.4 du 22/09/2015	Protocole modifié version 2 du 22/01/2016	Justification de la modification substantielle
<p>5.1 ENROLLEMENT AND OUT OF HOSPITAL PERIOD (PAGE 18)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content 	<p>5.1 ENROLLEMENT AND OUT OF HOSPITAL PERIOD (PAGE 18)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, aspiration pneumonia, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, aspiration pneumonia 	<p>Complication connue pouvant résulter de la régurgitation lors de l'intubation trachéale et de la ventilation au masque en préhospitalier Complication rajoutée car oubliée dans les versions précédentes</p>
<p><u>Complications related to airway management (PAGE 26)</u></p> <ul style="list-style-type: none"> ◆ Tracheal intubation group <ul style="list-style-type: none"> Aspiration during tube insertion Mainstem intubation Esophageal intubation Dental trauma ◆ Bag-valve-mask group <ul style="list-style-type: none"> Aspiration during bag-mask ventilation Vomiting during intubation after ROSC Desaturation during intubation after ROSC Hypotension during intubation after ROSC Aspiration during tube insertion after ROSC Bronchospasm and/or laryngospasm during intubation after ROSC) Mainstem intubation after ROSC Esophageal intubation after ROSC Dental trauma during intubation after ROSC 	<p><u>Complications related to airway management (PAGE 26)</u></p> <ul style="list-style-type: none"> ◆ Tracheal intubation group <ul style="list-style-type: none"> Aspiration during tube insertion Mainstem intubation Esophageal intubation Dental trauma Aspiration pneumonia ◆ Bag-valve-mask group <ul style="list-style-type: none"> Aspiration during bag-mask ventilation Aspiration pneumonia Bag-valve-mask ventilation failure Vomiting during intubation after ROSC Desaturation during intubation after ROSC Hypotension during intubation after ROSC Aspiration during tube insertion after ROSC Bronchospasm and/or laryngospasm during intubation after ROSC) Mainstem intubation after ROSC Esophageal intubation after ROSC Dental trauma during intubation after ROSC 	<p><u>Aspiration Pneumonia</u> : Complication connue pouvant résulter de la régurgitation lors de l'intubation trachéale et de la ventilation au masque en préhospitalier Complication rajoutée car oubliée dans les versions précédentes</p> <p><u>Bag-valve mask ventilation failure</u> : déjà décrit dans les critères d'évaluation secondaires (secondary endpoints). Cependant cette complication n'apparaissait pas dans les événements indésirables attendus des versions précédentes. Nous souhaitons rectifier cet oubli</p>

Protocole version 1.4 du 22/09/2015	Protocole modifié version 2 du 22/01/2016	Justification de la modification substantielle
<p>10.1.1 Enrolment and out-of hospital period data (Pages 31)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content 	<p>10.1.1 Enrolment and out-of hospital period data (Pages 31)</p> <ul style="list-style-type: none"> • Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, aspiration pneumonia, dental trauma, extubation • Complications related to bag-valve-mask ventilation during advanced CPR: regurgitation of gastric content, aspiration pneumonia 	<p>Complication connue pouvant résulter de la régurgitation lors de l'intubation trachéale et de la ventilation au masque en préhospitalier Complication rajoutée car oubliée dans les versions précédentes</p>

APPENDIX OF CAAM PROTOCOL**Statistical Analysis Plan (SAP)****Approval of SAP– Version 1****Local Signatures*:****Prepared by:**Dr P.Jabre

Signature

Date**Project
Clinician:**Pr F. Adnet



Signature

20 FEB 2015

Date**Local Head of
Biometrics:**Pr Vicaut

Signature

Date

*Signature above indicates approval of this plan, for the analysis and reporting of this study.

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Version 1

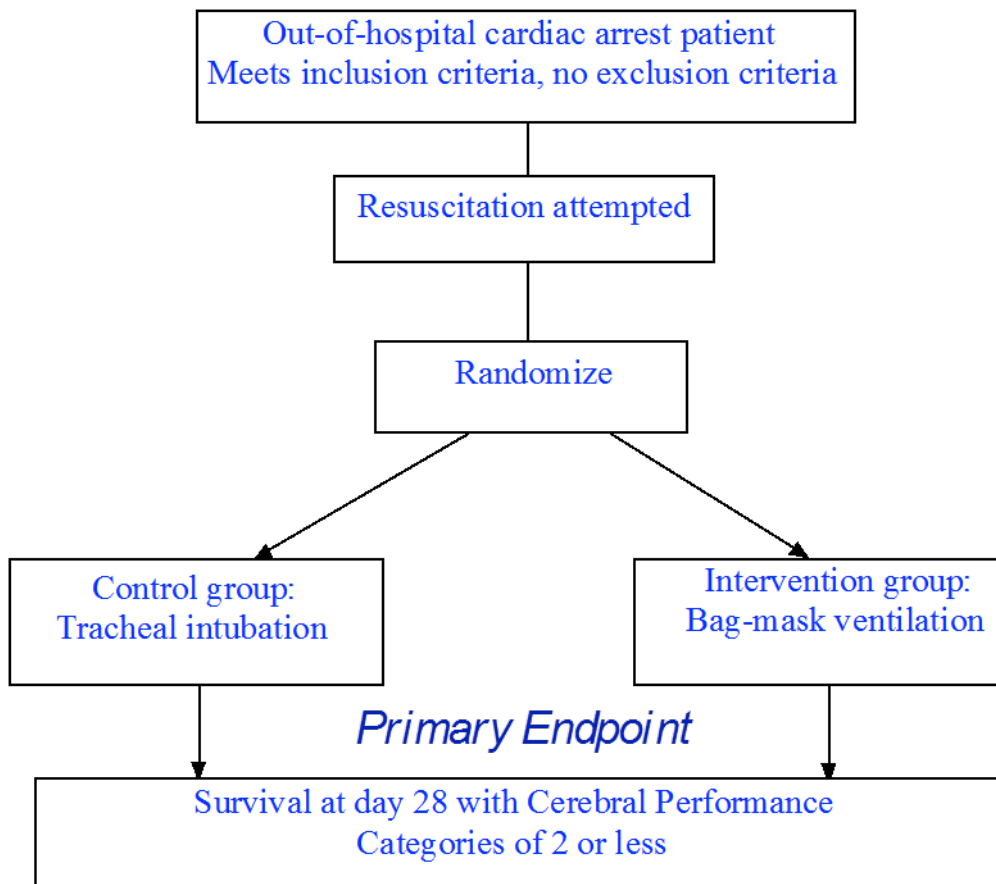
2 INTRODUCTION

The aim of this clinical trial is to compare the impact of two airway management techniques on the survival at 28-day with favorable neurological function of OHCA patients.

The survival rate at 28-day with favorable neurological function will be compared in the Tracheal Intubation (TI) group versus the bag-valve-mask (BVM) group.

2.1 STUDY DESIGN

This study was a multicenter, prospective, non-inferiority open randomized controlled trial in patients with out-of-hospital cardiac arrest carried out in physician-staffed EMS, comparing airway management by bag-valve-mask ventilation with tracheal intubation. (see schematic design)



2.2 STUDY OBJECTIVES

Primary objective: The objective of this clinical trial is to compare the survival rate at 28-day with favorable neurological function in the TI group versus the BVM group.

Secondary objectives

The secondary objectives of this clinical trial are:

- To compare the survival rate at hospital admission and at 28-day and the neurologic outcomes in the TI group versus the BVM group.
- To estimate the immediate adverse events and serious adverse events related to the TI and BVM.
- To evaluate the difficulty of intubation and the difficulty of ventilation with the BVM.

3 INTERIM ANALYSES, FINAL ANALYSES

Interim analysis were planned but were cancelled due to the rapid enrollment in the study. Consequently only final analysis was done and no adjustment for multiplicity was done.

4 HYPOTHESES AND DECISION RULES

Sample size:

The sample size calculation is based on non-inferiority hypotheses using the confidence interval approach. The sample size is based on Hasegawa's study (JAMA 2013) that reported a survival rate with favorable neurological function in the BVM group of 3% and Gueugniaud's study (NEJM 2008) of 2% survival rate with TI. We defined a non-inferiority margin of 1%. We would need 956 patients per group for a study power of 0.8 and a type I error rate of 0.025. A total of 2,000 patients will be recruited (based on 5000 simulations using the Newcomb-Wilson score method , Statistics in Medicine 1988, 17:873-890)

4.1 STATISTICAL HYPOTHESES

The primary aim of the trial is to demonstrate non inferiority of the BVM vs TI with regard to primary endpoint as the survival rate with favorable neurological function.

The null and alternative hypotheses are as follows:

$H_0: \pi_{BVM} - \pi_{TI} \leq -0.01$ success rate of the BVM is inferior to TI

Versus.

$H_1: \pi_{BVM} - \pi_{TI} \geq -0.01$ success rate of the BVM is not inferior to TI

In case of demonstration of non-inferiority, a test of difference will be carried out.

4.2 STATISTICAL DECISION RULES

All tests will be two-sided with an alpha value at 0.05.

5 ANALYSIS SETS

Since it is a non-inferiority trial the main analysis will be based on both the intent-to-treat population (ITT) of all patients randomised (irrespective of which study treatment is given or if any study treatment is adequately received) and in per protocol analysis (PP) of all patients randomized and treated without major protocol violations/deviations.

5.1 INTENTION-TO-TREAT ANALYSIS SET

The main analysis of the main criterion will be based on the ITT population of all randomised patients in cardiac arrest aged ≥ 18 years in cardiac arrest. Patients will be analysed according to their randomisation group irrespective of which study ventilation technique is given or if any study ventilation technique is received.

5.2 PER PROTOCOL ANALYSIS SET

The main criterion will also be analysed based on the PP population of all patients randomized & treated without major protocol violations/deviations.

5.3 'AS TREATED' ANALYSIS SET

The analysis of the main criterion will be based on randomised patients in cardiac arrest aged ≥ 18 years in cardiac arrest according to the ventilation technique really received by the patient, population (AT) .

6 ENDPOINTS

6.1 EFFICACY ENDPOINT(S)

Parameter for assessing the primary criterion

The parameter for assessing the primary criterion will be the survival at 28-day with favorable neurological function defined as Glasgow-Pittsburgh Cerebral Performance Categories (CPC) of 2 or less.

Parameters for assessing the secondary criteria

- Survival at hospital admission
- Survival at 28-day
- Rate of return of spontaneous circulation (ROSC)
- In addition intubation difficulty assessed by Intubation difficulty Scale score will be analysed for the intubated patients

6.2 SAFETY ENDPOINTS

This refers to any untoward medical occurrence in a biomedical research subject which does not necessarily have a causal relationship with the research or research product. This research deals with the follow-up of subjects who have received a ventilation procedure.

The adverse event that will be taken into account are:

- Complications related to tracheal intubation during advanced Cardiopulmonary Resuscitation (CPR): failure, esophageal intubation, mainstem intubation, vomiting, pulmonary aspiration, dental trauma, extubation
- Ventilation difficulty with bag-valve-mask measured with a visual-analog-scale (VAS)
- Complications related to bag-valve-mask ventilation during advanced CPR: failure, regurgitation of gastric content, gastric inflation
- Han's mask ventilation classification

7 HANDLING OF MISSING VALUES

In the intent-to-treat analysis missing data for the primary endpoint will be imputed according to the worst case principle (no success). In case of large differences between PP and ITT populations, an analysis of sensitivity using different methods for missing data replacement, including multiple imputation technique, will be carried out.

No imputations will be made for secondary criteria.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

8.1.1 Analysis of Continuous Data

Continuous variables will be summarized using number of observations, mean, standard deviation, minimum, maximum, 25%, 50%, 75% quantiles and the two sided 95% confidence intervals.. Means, medians, minimum, maximum and standard deviations will be presented to one further decimal place.

8.1.2 Analysis of Categorical Data

There will be counting of the absolute and relative frequencies (percentages) for categorical variables. Percentages for categorical variables will be based on all non-missing values (=100%). Percentages will be rounded to one decimal place and there may be occasions where the total of the percentages does not equal 100% exactly.

8.2 STATISTICAL ANALYSES

Intent-to-treat and Per Protocol analysis on non-inferiority of BMV over TI.

8.2.1 Primary Analysis

The analysis on the primary endpoint will be carried out by calculating the 95% two-sided confidence interval (CI) (as recommended by EMEA guidelines) of the difference $\Pi_{\text{bag}} - \Pi_{\text{tracheal}}$. If the lower limit of this CI is higher than -0.01 then the conclusion of non inferiority will be accepted. If necessary exact rather than asymptotic CI will be used. This analysis will be made for ITT, PP and AT populations.

8.2.2

8.2.3 Secondary Analyses

The secondary analysis will be carried out by the chi-square test on proportions for all secondary criteria expressed as rates. The corresponding 95% confidence interval on their odds ratio and differences will also be presented.

For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.

Secondary analyses will also be carried out on PP and AT populations .

Statistical tests will be 2-tailed with a type 1 error of 0.05 and $P < 0.05$ will be considered significant. Statistical tests were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina).

8.2.4 Safety Analyses

The safety analysis will be carried out on the ITT and AT analysis.

Serious and non serious adverse events will be tabulated per group

All (dichotomized) endpoints will be analyzed by chi-square test or Fisher's exact test on proportions and the 95% confidence interval on the odds-ratio will be presented.

For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.

APPENDIX OF CAAM PROTOCOL

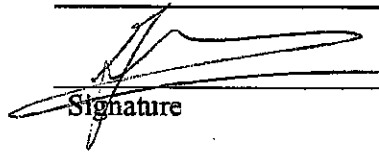
Statistical Analysis Plan (SAP)

Approval of SAP- Version 1

Local Signatures*:

Prepared by:

Dr P. Jabre


Signature

20 Feb 2015

Date

**Project
Clinician:**

Pr F. Adnet

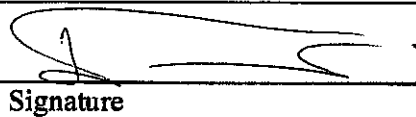

Signature

20 FEB 2015

Date

**Local Head of
Biometrics:**

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23 FEB 2015

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

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Versus.

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In case of demonstration of non-inferiority, a test of difference will be carried out.

4.2 STATISTICAL DECISION RULES

All tests will be two-sided with an alpha value at 0.05.

5 ANALYSIS SETS

Since it is a non-inferiority trial the main analysis will be based on both the intent-to-treat population (ITT) of all patients randomised (irrespective of which study treatment is given or if any study treatment is adequately received) and in per protocol analysis (PP) of all patients randomized and treated without major protocol violations/deviations.

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There will be counting of the absolute and relative frequencies (percentages) for categorical variables. Percentages for categorical variables will be based on all non-missing values (=100%). Percentages will be rounded to one decimal place and there may be occasions where the total of the percentages does not equal 100% exactly.

8.2 STATISTICAL ANALYSES

Intent-to-treat and Per Protocol analysis on non-inferiority of BMV over TL

8.2.1 Primary Analysis

The analysis on the primary endpoint will be carried out by calculating the 95% two-sided confidence interval (CI) (as recommended by EMEA guidelines) of the difference $\Pi_{\text{bag}} - \Pi_{\text{tracheal}}$. If the lower limit of this CI is higher than -0.01 then the conclusion of non inferiority will be accepted. If necessary exact rather than asymptotic CI will be used. This analysis will be made for ITT, PP and AT populations.

8.2.2

8.2.3 Secondary Analyses

The secondary analysis will be carried out by the chi-square test on proportions for all secondary criteria expressed as rates. The corresponding 95% confidence interval on their odds ratio and differences will also be presented.

For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.

Secondary analyses will also be carried out on PP and AT populations .

Statistical tests will be 2-tailed with a type 1 error of 0.05 and $P < 0.05$ will be considered significant. Statistical tests were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina).

8.2.4 Safety Analyses

The safety analysis will be carried out on the ITT and AT analysis.

Serious and non serious adverse events will be tabulated per group

All (dichotomized) endpoints will be analyzed by chi-square test or Fisher's exact test on proportions and the 95% confidence interval on the odds-ratio will be presented.

For quantitative secondary criteria t-test or Mann-Whitney will be used according to their Gaussian or non Gaussian statistical distribution.

