Supplementary Online Content

Guihard B, Chollet-Xémard C, Lakhnati P. Effect of rocuronium vs succinylcholine on endotracheal intubation success rate among patients undergoing out-of-hospital rapid sequence intubation: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.18254

Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study.

CURASMUR

Promoter code:

BIOMEDICAL RESEARCH PROTOCOL

Version 1.0 of 23/01/2012
which has received the favourable opinion of the CPP (Institutional Review Board), the date, and the authorization of the Afssaps

EudraCT Number:

This biomedical research project was funded by *funding source*

Sponsor:
Regional Hospital Center of Reunion Island
Félix Guyon Hospital Center
97405 Saint Denis Cedex

Coordinating researcher:
Dr Xavier Combes
Regional Hospital Center of Reunion Island – Site of CHFG
SAMU 974,
97405 St Denis of Reunion Island

Methodological support:
CHR of Reunion Island – Site of CHFG
97 405 Saint Denis Cedex

SAMU of Paris, Necker Hospital - Enfants Malades
149 rue de Sèvres
75015 PARIS

Safety and Surveillance Unit for Clinical Research:
Pharmacovigilance Center
CHU Pellegrin Hospital
Place Amélie Raba-Léon
33076 Bordeaux Cedex

This protocol was designed and edited from version 2.0 of 01/09/2011 of the DIRC Sud-Ouest Outre-Mer protocol type

41 # PROTOCOL VERSION HISTORY

42

VERSION	DATE	REASON FOR UPDATE
1.0	23/01/2012	Submission to the National Clinical Research Hospital Programme 2012

PROTOCOL SIGNATURE PAGE

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study.

CURASMUR

Sponsor code :

Sponsor

Regional Hospital Center of Reunion Island
Félix Guyon Hospital Center
Route de Bellepierre
97 405 Saint Denis cedex

at on this day, the:

General Manager of Reunion Island CHR
Michel CALMON
And by delegation, Deputy Director for Research

Joaquin MARTINEZ

Coordinating researcher

Dr. Xavier COMBES

SAMU 974
CHR of Reunion Island – Site of CH Félix Guyon
Route de Bellepierre
97405 St Denis Cedex
Tel : 02 62 90 20 72
Mail: x.combes.samu974@chr-reunion.fr

Dr. Xavier Combes

MAIN CORRESPONDENTS

Coordinating Researcher
Dr Xavier COMBES
SAMU 974
Regional Hospital Center of
Reunion Island – Site of CHFG
Route de Bellepierre
97405 St Denis Cedex
Tel : 02 62 90 20 72
Mail : x.combes.samu974@chr-reunion.fr

Project leader – Internal Promotion
Fidéline FILLEUL
Regional Hospital Center of Reunion Island –
Site of CHFG
Route de Bellepierre
97 405 Saint Denis cedex
Tel : 02 62 90 68 84 - Fax : 02 62 90 69 21
Mail : fideline.filleul@chr-reunion.fr

Methodological Support Unit

Dr. Laetitia HUIART
Cyril FERDYNUS
Regional Hospital Center of Reunion Island
Site of CHFG
Route de Bellepierre
97 405 Saint Denis cedex
Tel : 02 62 90 68 81 / 82
Mail : usm@chr-reunion.fr

Patricia JABRE

SAMU de Paris, Hôpital Necker - Enfants
Malades
149 rue de Sèvres
75015 PARIS
Tel : 01 44 49 24 72
Mail: patricia.jabre@nck.aphp.fr

Sponsor
Sponsor
Regional Hospital Center of Reunion Island – Site
of CHFG
97 405 Saint Denis cedex

Head of Research in the capacity of sponsor
Joaquin MARTINEZ
Deputy Director for Research
Tel: 02 62 71 98 52 – Fax : 02 62 71 98 34
Mail : joaquin.martinez@chr-reunion.fr

Clinical Research Director
Vanessa BASQUE
CHR of Reunion Island – Site of GHSR
Bd François Mitterrand – BP 350
97448 Saint Pierre Cedex
Tel : 02 62 35 95 25 - Fax : 02 62 35 97 21
Mail : vanessa.basque@chr-reunion.fr

Safety and surveillance unit for clinical research:
Pharmacovigilance Center
CHU Pellegrin Hospital
Place Amélie Raba-Léon,
33076 Bordeaux Cedex
Tel: 05 57 57 46 64 - Fax: 05 56 79 49 26
anne.gimbert@pharmaco.u-bordeaux2.fr
francoise.haramburu@u-bordeaux2.fr
ghada.miremont@u-bordeaux2.fr

SUMMARY

LIST OF ABBREVIATIONS

RSI	Rapid Sequence Induction
IDS	Intubation Difficulty Scale
SMUR	Emergency Mobile Resuscitation Unit
SAMU	Emergency Services

279 **1. SUMMARY OF THE RESEARCH**

PROMOTER	CHR of Reunion Island – Site of CHFG
COORDINATING RESEARCHER	Dr. Xavier COMBES, SAMU 974, CHR of Reunion Island – site of CH Félix Guyon, Route de Bellepierre, 97405 St Denis Cedex
TITLE	Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. CURASMUR
JUSTIFICATION / CONTEXT	An emergency tracheal intubation is facilitated by the use of sedation. The reference technique links the use of a hypnotic treatment with a depolarising curare of which the onset of action is approximately 60 seconds: succinylcholine. One of the risks associated with an emergency intubation is the occurrence of a difficult intubation, which, when accompanied by ventilation difficulties with the face mask, can lead to the occurrence of hypoxemia. This hypoxemia, if it is profound and prolonged, can lead to cardiac arrest. The spontaneous decurarization that allows for the recovery of effective spontaneous ventilation by the patient is a safety measure. Its delay of occurrence is variable with an average of 8 minutes after injection of a standard dosage of 1mg/kg of succinylcholine, but there is a large inter-individual variability. Rocuronium, which is a non-depolarising curare, is an alternative to succinylcholine, as with a dosage of 1,2mg/kg it allows for equivalent intubation conditions in the same delay of 60 seconds. The challenge presented by the use of rocuronium is that the delay of a spontaneous decurarization after said dosage is prolonged, to as much as one hour. A binding agent for reversal of neuromuscular blockade has recently been made available : sugammadex. An injection of a heavy dosage (16mg/kg) of sugammadex allows for an extremely speedy counteracting of curarization, even very prematurely after the injection of rocuronium. This delay of decurarization is thus 4 minutes long, which is less than the spontaneous delay of decurarization of succinylcholine. The use of rocuronium, which is associated with the potential use of sugammadex in the event of difficult intubation, could thus provide additional safety after emergency sedation, provided that it provides similar intubation conditions to that of succinylcholine. Succinylcholine and rocuronium have never been compared in terms of efficacy and safety of use in terms of intubation in pre-hospitalisation emergency conditions. The tested hypothesis is that intubation in pre-hospitalisation emergency

	situations is equally facilitated with the use of rocuronium or succinylcholine.
OBJECTIVES	The primary objective is to show that the conditions of emergency intubation are not inferior when rocuronium is used, compared to succinylcholine in the context of a rapid sequence induction type sedation.
RESEARCH PLAN	Multi-centric, non-inferior, randomized, controlled, blind study
INCLUSION CRITERIA	All older patients in need of sedation for a tracheal intubation in pre-hospitalisation situations
NON-INCLUSION CRITERIA	Patients with cardiac arrest, younger patients, pregnant women, patients presenting with a contraindication to the following three medications: rocuronium, succinylcholine, sugammadex, patients that are not members of a medical aid scheme (beneficiary or main member)
TREATMENTS OF THE RESEARCH	In the two groups, the induction of the sedation is done after preoxygenation. A hypnotic treatment (etomidate (Hypnomidate®) 0,3 mg.kg-1 or ketamine (Ketamine®) 2 mg.kg-1 injected in the IV line, followed immediately by either the injection of succinylcholine Celocurine®) 1 mg.kg-1, or the injection of 1,2 mg/kg of rocuronium (Esmeron®). The intubation is done 60 seconds after the injection of the curare. If the patient is randomized in the Rocuronium group, the physician in charge has the possibility of reversing the action of the rocuronium by using sugammadex at a dosage of 16 mg/kg
JUDGEMENT CRITERIA	**Primary judgement criterion:** Success rate of intubation after the first laryngoscopy **Secondary judgement criteria:** Evaluation of the quality of the direct laryngoscopy, the intubation conditions through the use of the Copenhagen score, measure of global difficulty of the intubation process as evaluated by the intubation difficulty score, evaluation of the need for the use of devices for difficult intubation (long endotracheal tube, Fastrach laryngeal intubation mask and cricothyrotomy), the rate of immediate complications of intubation in terms of the type of curares used.
STUDY SIZE	1300 patients are needed. Assuming that the rate of intubation on the first attempt is 75%, 602 (bilateral test) patients per group are needed to show that the rate of intubation on the first attempt is not lower in the test group, compared to the controlled group with a risk of first kind of 0.05, a risk of second kind of 0.2 and an epsilon (maximum acceptable difference of rate of intubation after the first laryngoscopy between the two groups) of 7%. The presence of a safety margin of 10%, of additional inclusions

	linked to the risk of deviations, in relation to protocol associated with the "on the spot" inclusion and randomization of the emergency, induces the need for 650 patients having to be included in each group.
EXPECTED NUMBER OF CENTRES	16 centres
DURATION OF THE RESEARCH	Duration of the period of inclusion: 3 years Duration of participation for each patient: Duration of pre-hospitalisation care (less than 3 hours) Total duration of the research: 3 years
STATISTICAL DATA ANALYSIS	The clinical equivalence (i.e. non-inferiority) between the percentages of successful intubation will be tested with the aid of the Dunnett and Gent method. The equivalence test will be a unilateral one resting on the hypothesis of a non-inferiority margin δ of 7%. The analysis will be conducted in per protocol, as recommended for non-inferiority tests, and will be completed with an intent-t-treat analysis.
EXPECTED IMPLICATIONS	Intubation is also facilitated in emergency situations where either rocuronium or succinylcholine is used to perform the curarization of patients.

280
281

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1. CURRENT STATE OF KNOWLEDGE

2.1.1. PATHOLOGY

The control of the airways is regularly needed in pre-hospitalisation emergency medical treatment when patients presenting with a vital distress are being treated. Among the various techniques and invasive control systems of airways that are available, tracheal intubation is by far the most frequently used technique, particularly in cases of pre-hospitalisation medical care systems (1, 2).

In a country such as France, which is equipped with a pre-hospitalisation medical care system, the epidemiology of tracheal intubation is well known. It is estimated that approximately 8% of primary interventions of the Mobile Emergency Resuscitation Unit (SMUR) will lead to the tracheal intubation of patients being treated. In France, 30% to 45% of intubations performed in pre-hospitalisation medical cases are done on patients in cardio-respiratory arrest. The second group of patients is made up of those having spontaneous cardiac activity after intubation. Among these patients, neurological failure, whether it is linked to a pathology of the central nervous system (Cerebral Vascular Accident, epileptic fit) or whether it be secondary to the ingestion of toxins (voluntary intoxication of psychotropic drugs) is the primary indication of intubation (1-3). The number of intubations performed annually in France by the different SMUR units can be easily estimated. If one considers the fact that in approximately 8% of primary interventions, a tracheal intubation is performed, between 40 000 to 50 000 intubations are performed in France in a non-hospital setting. Setting aside patients intubated for cardiac arrest, sedation is an indispensable element when a tracheal intubation is performed. In fact, once the intubation is performed without any pharmacological sedation, even in patients in a profound coma, difficulty of control of the airways is significant and the failure rate of intubation is higher (4). Various studies have illustrated that the sedation technique in reference to facilitate emergency intubation is rapid sequence intubation (5-7). This technique associates the use of hypnotic treatment and a curare which has an onset delay, and a short duration of action, succinylcholine. The rapid sequence intubation sequence is carried out in the following methods: the patient is pre-oxygenated for 3 minutes, breathing in pure oxygen, thereafter the hypnotic treatment is administered, followed by succinylcholine (1mh/kg). The two hypnotic treatments recommended for emergency situations are hypnomidate (0,3 to 0,4 mg/kg) and ketamine (2 to 3 mg/kg) due to their extremely good hemodynamic tolerance. The difficulty of intubation is similar between the 2 hypnotic treatments (8). Once intubation has been done, a continued sedation is often necessary in order for the patient to adjust to the ventilator.

2.1.2. STANDARDS OF CARE AND THE STUDY

Succinylcholine is the curare of reference for emergency intubation as it possesses two essential characteristics: its onset delay is very short, making intubation possible in less than 60 seconds after injection. In emergency situations, the time it takes to create conditions for optimal intubation is a major element of safety. In fact, one should avoid ventilation with a mask for those patients who are all at risk of pulmonary inhalation and the use of rapid onset delay medications shortens the high-risk period that exists between the injection of the hypnotic treatment and the curare, the moment when the intubation tube is correctly inserted into the trachea, and its balloon inflated. The duration of action of succinylcholine is relatively short, about 8 minutes, which allows for the recovery of a rather rapid spontaneous ventilation, should intubation prove to be impossible. However, there is an important unpredictable inter-individual variability and for certain patients, recovery of spontaneous ventilation after the injection of succinylcholine only occurs after 20 minutes (9). In emergency situations, where intubation is impossible and mask ventilation is ineffective, arterial desaturation swiftly becomes the most common occurrence in less than 5 minutes, even if a correct pre-oxygenation was performed before the start of the intubation process (10).
Furthermore, if succinylcholine is for the moment the curare that allows for the fastest intubation in emergency situations, it still presents a few hard and fast side effects and its use is associated with a certain number of undesired effects. The primary side effects of the use of succinylcholine are: hyperkalaemia and situations carrying the risk of hyperkalaemia, myopathies, denervation symptoms (paraplegia, tetraplegia, hemiplegia), eyeball wounds and allergic reactions. The main adverse effects found after the administering of succinylcholine are the following: bradycardia, ventricular arrhythmia, augmentation of kalaemia.

Rocuronium is a curare that has been used for several years. When a standard dosage (0,6 mg/kg) is used, this non-depolarising curare makes it possible to obtain curarization, making intubation possible with a delay of 90 seconds. When the dosage of rocuronium is increased to 1,2 mg/kg, optimal intubation conditions are achieved in the same time period as when succinylcholine is used, in other words, in less than 60 seconds (11-13). There is no hard and fast side effect with the use of rocuronium, other than allergic reactions. The only problem that the administering of a higher dosage (1,2 mg/kg) of rocuronium presents, is the length of inducted curarization, which can be around 60 minutes (14). This prolonged curarization presents a potential risk in cases where intubation is impossible, as the patient is unable to resume fast spontaneous ventilation.

Sugammadex is a binding agent for reversal of neuromuscular blockades in particular with rocuronium, which has been studied for many years and placed on the market in 2009. The mode of operation of sugammadex makes it very advantageous compared to other curares. It allows for the reversal of neuromuscular blockades caused by rocuronium without inhibiting acetylcholinesterase, thus avoiding the undesired effects of neostigmine (bradycardia, extrasystoles, bronchoconstriction) and the need to co-administer vagolytic drugs such as atropine. Furthermore, it has been established that sugammadex, when a dosage of 16 mg/kg is

administered, allows for the curarization induced by the rocuronium to be lifted in a very short delay of 4 minutes (15). This delay of decurarization is significantly lower than the spontaneous decurarization after the use of succinylcholine. There are no hard and fast side effects with the use of sugammadex, other than allergic reactions.

The administering of rocuronium at a dosage of 1,2 mg/kg could thus be an alternative to the use of succinylcholine, as it has the possibility of counteracting curarization in cases where intubation is impossible. The use of rocuronium was proposed at the last conference of experts on emergency sedation as an alternative to the use of succinylcholine, provided that its effects could be reversed with the use of sugammadex (16). The experts recommended that validation studies of this practice be carried out.

The use of rocuronium could be proposed in place of the use of succinylcholine to perform intubation in emergency situations, as the side effects and secondary effects of rocuronium seem to be much less frequent than those found with succinylcholine. Nevertheless, it has not been shown that rocuronium could allow for intubation in conditions as easily as what succinylcholine allows in pre-hospitalisation emergency medical treatment.

2.2. HYPOTHESES OF RESEARCH

If it is shown that rocuronium allows for intubation in emergency situations with conditions not inferior to those produced by succinylcholine, it could be proposed to use rocuronium as drug of preference, based on its profile of tolerance.

2.3. EXPECTED IMPLICATIONS

This research project should allow for the presenting of evidence of the non-inferiority of rocuronium compared to succinylcholine in rapid sequence intubation of patients with vital distress. If intubation is equally easy with the use of rocuronium as with succinylcholine, rocuronium could become the top recommended drug to use in rapid sequence intubation as it has less adverse secondary effects than succinylcholine. Based on this fact, the results of this study will have a considerable impact on clinical practices in emergency resuscitation cases.

2.4. EXPERIENCE OF PARTICIPATING TEAMS ON THIS SUBJECT

The medicalization of non-hospital emergencies in France has, after various years, allowed for quality scientific studies to be done that other countries, in particular North-American countries, cannot develop. The uniformity of sedations used in pre-hospitalization medical treatment, based on national recommendations, makes it possible to guarantee a coherence in the French multi-centric studies carried out by SMUR. The total of SAMU-SMUR research centres of this study have experience in the conducting of clinical studies in difficult conditions of pre-hospitalisation medical treatment.

2.5. FEASIBILITY OF THE STUDY

The feasibility of the study relies on the competence of the pilot committee and the previously mentioned research centres, but also on the capacity of each centre to include a sufficient

number of RSI with the hopes of achieving the indispensable number of 1300 RSI over 3 years. The practical survey conducted by each centre regarding the number of RSI by their SMUR in 2001 (Cf. table below) allows one to envisage the inclusion of approximately 450 RSI in one year, estimating a percentage of inclusion of about 40%.

Research centres	RSI in 2010
SAMU 75 (Necker)	100
SAMU 93 (Bobigny)	100
SAMU 92 (Garches)	100
SMUR Beaujon	70
SMUR Lariboisière	50
SMUR Pitié-Salpêtrière	50
SMUR Hotel-Dieu	40
SMUR Melun	100
SMUR Gonesse	50
SAMU 974 (Saint Denis de la Réunion)	80
SAMU 30 (Nîmes)	150
SAMU 59 (Lille)	150
SAMU 21 (Dijon)	100
SAMU 74 (Annecy)	100
SMUR ST Pierre de la Réunion	100
SAMU 31 (Toulouse)	200
TOTAL	**1540**

3. OBJECTIVES OF THE RESEARCH

3.1. PRIMARY OBJECTIVE

The primary objective is to show that the conditions for emergency intubations are not inferior when rocuronium is used, compared to succinylcholine in the context of a rapid sequence induction type sedation.

3.2. SECONDARY OBJECTIVES

The secondary objectives for the evaluation of the efficacy of rocuronium are :

- To evaluate the quality of direct laryngoscopy, by using the Cormack and Lehane classification (Annex 1)
- To measure the global difficulty of the intubation process as evaluated by the intubation difficulty score (IDS, Annex 2) (17)
- To characterise the intubation conditions by using the Copenhagen score (Annex 3) (18)
- To evaluate the need for the use of difficult intubation devices (long endotracheal tube, Fastrach laryngeal intubation mask and cricothyrotomy)

A secondary objective evaluates the tolerance of these 2 treatments. It involves the comparison of the rate of complications observed with the use of rocuronium or succinylcholine.

4. RESEARCH DESIGN

4.1. RESEARCH PLAN

This is a randomized pilot of non-inferiority comparing 2 single-blind treatments (patient). The administering of succinylcholine leads to the occurrence of fasciculation (small twitch movements localised mainly on the face and upper part of the thorax), just before curarization. This effect which has been observed in more than 90% of patients makes it impossible to conduct a double-blind study in emergencies, as the operator is in fact witness of the occurrence of fasciculations when succinylcholine is used. In the context of emergencies, particularly pre-hospitalisation ones, it is not conceivable that the person performing the intubation not be present, at the patient's side, at the time of administering of succinylcholine. Rocuronium does not cause fasciculation.

4.2. METHODS FOR RANDOMIZATION

The method to be used will be block randomization, and stratified by centre. Numbered, opaque and sealed envelopes will be used in each ambulance for the allotment of types of curares.

Randomization is done after the inclusion and exclusion criteria are verified. Each centre will be allotted a randomization table. The physician is informed of the treatment group (succinylcholine or rocuronium group) after opening the envelope.

5. CRITERIA FOR ELIGIBILITY

5.1. INCLUSION CRITERIA

All adult patients presenting with spontaneous cardiac activity and in need of an endotracheal intubation, and treated by the SMUR and SAMU participants will be included in the study. These patients will be treated by senior operators qualified in anaesthesia-resuscitation or emergency medical care.

5.2. NON-INCLUSION CRITERIA

The criteria for non-inclusion are:

- Patients in cardiac arrest
- Young patients
- Pregnant women
- Presence of a contraindication to succinylcholine:
    1. Personal or family history of known malignant hyperthermia
    2. Known allergy to succinylcholine
    3. Congenital muscular damage
    4. Myasthenia
    5. Specific hyperkalaemia

6. Open eye surgery
7. Known congenital deficit in plasma pseudocholinesterases

- Presence of a contraindication to rocuronium: known allergy to rocuronium
- Presence of a contraindication to sugammadex: known allergy to sugammadex
- Patients that are not members of a medical aid scheme (beneficiary or main member)

5.3. RECRUITMENT PROCESS

Patients will be consecutively recruited among 16 SMUR participants.

6. TREATMENTS OF THE RESEARCH

6.1. TREATMENT OF THE STUDY

Rocuronium: Muscle relaxant medication in the class of curares. Non-depolarizing curare in the amino steroids family. Vials of 5 to 10 ml (50mg/5ml or 100mg/10ml). The dosage for intubation outside the context of emergency is 0,6 mg/kg. In order to perform an intubation in less than 60 seconds in the case of a patient considered to be at risk of pulmonary inhalation, the recommended dosage is 1,2 mg/kg. The drug is administered via direct intravenous route.

Sugammadex : Decurarizing medication allowing for the counteracting of the effects of rocuronium and vecuronium. Sugammadex encases the curare molecule, thus rendering it inactive. It does not inhibit acetylcholinesterase, thus avoiding the undesired effects of neostigmine (bradycardia, extrasystoles, bronchoconstriction) as well as the need to co-administer vagolytic drugs such as atropine. To counteract a dosage of 1,2 mg/kg of rocuronium, 3 minutes after its injection, one must administer a dosage of 16 mg/kg of sugammadex. Sugammadex is administered intravenously.

6.2. COMPARISON TREATMENT

Succinylcholine: muscle relaxant medication in the class of curares. Depolarizing curare that functions by focusing on the receptors to acetylcholine. Vial of 2 ml (50 mg/ml). The dosage is 1 mg/kg in real weight. The drug is administered intravenously.

6.3. DESCRIPTION OF THE METHODS OF USE OF MEDICATION

With regard to succinylcholine and rocuronium, they are administered in the context of a rapid sequence intubation procedure. In both groups, induction of sedation is done after preoxygenation. A hypnotic drug (etomidate (Hypnomidate®) 0,3 mg.kg-1 of estimated weight or ketamine (Ketamine®) 2 mg.kg-1 of estimated weight is injection in IV, followed immediately either by the injection of succinylcholine (Célocurine®) 1 mg.kg-1 of estimated weight in IV, or by the injection of 1,2 mg/kg of rocuronium (Esmeron®). The Sellick manoeuvre (cricoid pressure in

order to limit the risk of pulmonary inhalation) is systematically used according to standard recommendations. The intubation is done 60 seconds after the injection of the curare.

If the patient is randomized in the Rocuronium group, the physician in charge has the possibility of reversing the action of rocuronium by using sugammadex, at a dosage of 16 mg/kg. Reversal of the neuromuscular blockades is done in patients who cannot be intubated through direct laryngoscopy and cannot be neither intubated nor ventilated using alternative techniques for difficult intubation as recommended by the national expert conference on intubation, which are the long endotracheal tube or the laryngeal intubation mask (21). This situation, based on the medical literature that has already been published, has the likelihood of occurrence that is lower than 1% (1, 2, 8, 19, 20, 22).

6.4. DESCRIPTION OF ALL MEDICATION USED FOR THE PURPOSES OF RESEARCH OTHER THAN THE MEDICATION THAT FORMS THE SUBJECT OF THE RESEARCH

A maintenance sedation is done with the association of midazolam (initial dosage of 0,1 mg.kh-1.h-1) and of fentanyl (2 to 5 µg.kg-1.h-1) or of sufentanil (0,2 to 0,5 µg.kg-1.h-1). In the event of inadequate sedation, the use of a supplementary sedation is left to the discretion of the clinician and will be arranged.

The nature and dosage of products used will be noted in the observation notebook. In the same manner, the usage of filling solutions will be logged in the observation notebook if necessary. In the event of an adverse incident or effect, the tubes required will be specific to the type of accident and logged in the observation notebook.

6.5. PRODUCT PIPELINE

Bearing in mind the fact that the test will be done pre-hospitalisation, and in emergency situations, the medication will be available in each ambulance and provided by pharmacies for internal use for each participating centre.

7. ASSOCIATED TREATMENTS/PROCEDURES

7.1. AUTHORIZED ASSOCIATED TREATMENTS/PROCEDURES

Apart from the randomization affecting the choice of curare that will be used, all other associated treatments will be done according to the usual recommendations and practices. Notably, in the event of hemodynamic occurrences of the hypotension type, the treatment of this secondary effect will call for a vascular filling using crystalloids and ephedrine. A prolonged hypotension will be treated with the continued administration of catecholamines. The sedation treatment following the intubation will be done according to the recommendations and will associate a benzodiazepine (midazolam) and morphine type (fentanyl or sufentanil) but other hypnotics were allowed. The dosages of these agents will be adapted by the physician in charge, based on the clinical condition of the patient and to the objectives of the sedation which vary, based on the pathology and the indication of mechanical ventilation. If the patient is randomized in the Rocuronium group, the physician in charge has the possibility of reversing the actions of rocuronium by using sugammadex at a dosage of 16 mg/kg. The action of reversing is brought

about for patients who cannot be intubated through direct laryngoscopy and who cannot be neither intubated nor ventilated using alternative techniques for difficult intubation, as recommended by the national expert conference on intubation, which are the long endotracheal tube or the laryngeal intubation mask.

7.2. PROHIBITED ASSOCIATED TREATMENTS/PROCEDURES

Apart from the randomization on the choice of curare used for the induction of sedation, there is no change to the usual practices. There is thus no treatment or associated procedures that are prohibited for this research.

8. JUDGMENT CRITERIA

8.1. PRIMARY JUDGMENT CRITERION

Proportion of successful intubation after the first laryngoscopy

8.2. SECONDARY JUDGMENT CRITERIA

Distribution of Cormack and Lehane classification grades (Annex 1) in the 2 treatment groups. The intubation difficulty score (IDS, Annex 2) (17) in the 2 treatment groups. Copenhagen Score (Annex 3) (18) in the 2 treatment groups. Proportion of the use of devices for difficult intubation (long endotracheal tube, Fastrach laryngeal intubation mask and cricothyrotomy) in the 2 treatment groups.

Tolerance

To evaluate the rate of immediate complications (first 15 minutes) of intubation based on the type of curare used: arterial hypotension, troubles with cardiac rhythm, cardiac arrest, pulmonary inhalation, occurrence of arterial hypoxemia episodes, allergic reaction.

9. PROGRESS OF THE RESEARCH

9.1. TIMELINE FOR RESEARCH

- Start of inclusions: 4th trimester of 2012
- Duration of period of inclusion: 3 years
- Duration of participation for each patient: duration of their pre-hospitalisation admission (less than 3 hours)
- Total duration of the research: 4 years

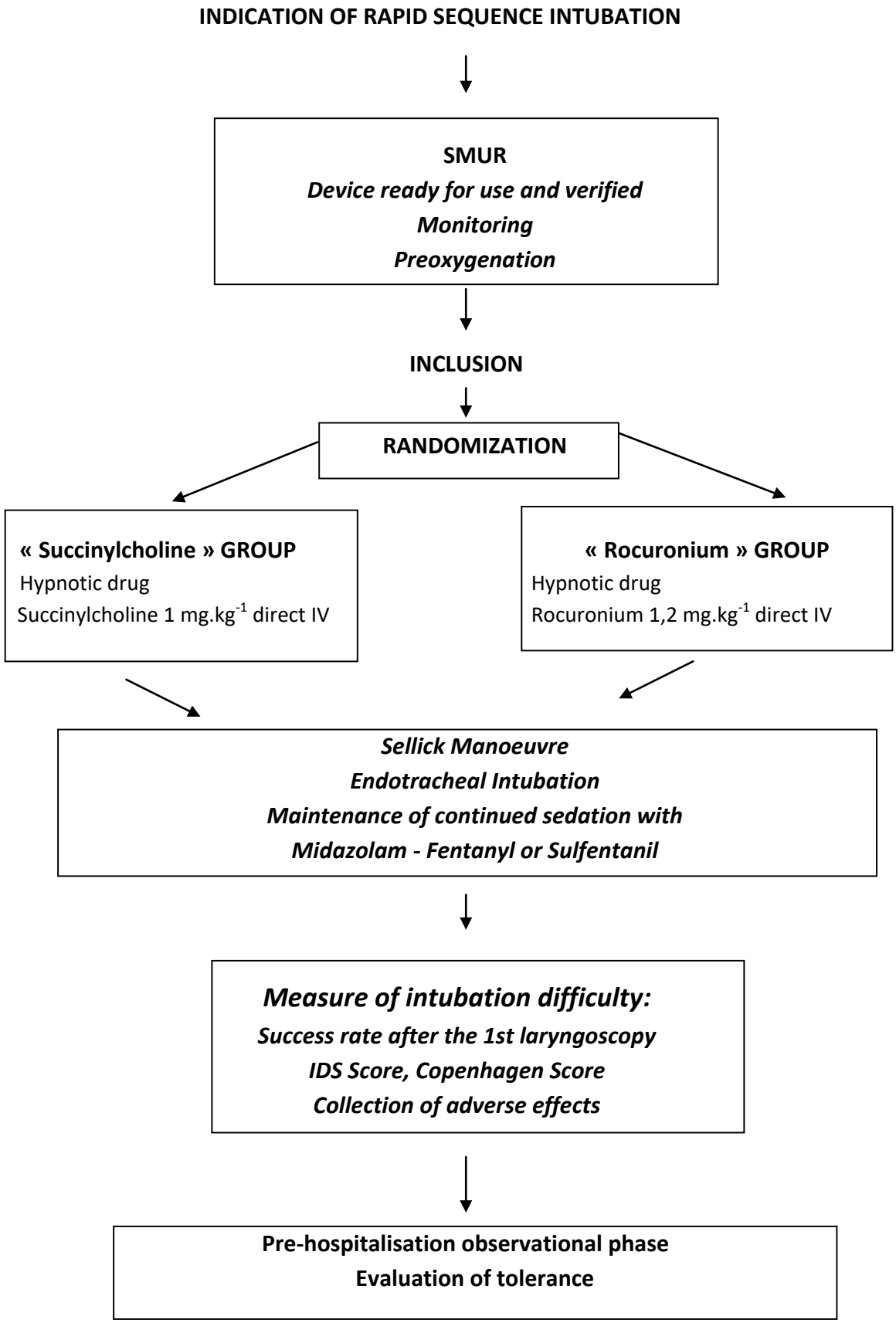
9.2. SUMMARIZED TABLE OF PATIENT MONITORING

	Selection and inclusion J0 Visit
Verification of inclusion criteria – non-inclusion, Information	X
Information - Consent	*

Randomization	X
Treatment	X
Clinical examination	X

570

571 * Collection of consent of relatives if they are present as well as that of the patient once
572 this is possible, once the patient is awake and able to give consent.
573



9.3. INFORMATION AND COLLECTION OF CONSENT

Bearing in mind the inclusion of patients in emergency situations, it would not be possible to put into place the standard process of prior oral and written information, time for reflection after the formalised consent of the person availing themselves for research. The consent of this

person will not be sought and only the consent of family members will be requested if they are present, and as default, the advice of the support person.

The patient will be informed and his/her consent will be requested for the tracking of the research, after extubation at the hospital and recovery from the neurological state allowing this collection. For patients who were included and are deceased prior to hospitalisation, consent will be sought from their relatives if the latter are present.

9.4. RANDOMIZATION METHODOLOGY

The method to be used will be a block randomization, and stratified by centre. Numbered, opaque and sealed envelopes will be used in each ambulance for the allotment of types of curares.

Randomization is done after verification of the inclusion and exclusion criteria. Each centre will have their own table of randomization allocated to them. The physician is informed of the treatment group (succinylcholine or rocuronium group) after opening the envelope.

9.5. INCLUSION

The clinical data and immediate complications will be collected at J0, during the prehospitalisation admittance phase.

An observation notebook is filled by the researcher of prehospitalisation intervention. The medical data collection sheet will compile:

- The randomization, the date, time, initials of the patient, the physician involved
- The condition of the patient prior to being admitted, and his/her medical history
- Clinical data: hemodynamic state, neurological state, respiratory state
- His/her estimated weight and height
- The intubation conditions
- The necessary parameters for the calculation of the IDS and the Copenhagen score (annexes 2 and 3)
- Treatments administered for intubation: type (hypnotic, morphine-type) and dosage used
- Complications occurring after intubation

There will be no specific examination or act conducted during the pre-hospitalisation or during the hospitalisation phase.

9.6. RULES FOR CESSATION OF RESEARCH

The reasons for and date of premature release date of the study need to be noted in the observation notebook of the patient in question (e.g. withdrawal of patient consent, adverse events of a serious nature, etc.).

10. MANAGEMENT OF ADVERSE EVENTS AND NEW FACTS

10.1. DEFINITIONS

Adverse event (Article R.11223-39 of the Public Health Code)
Any untoward medical occurrence in a person participating in a biomedical trial, whether this occurrence is linked or not to the research or the product on which research is being carried out.

Serious adverse event (Article R.1123-39 of the Public Health Code and the ICH E2B guide)
Any adverse event which:

- ✓ causes death,
- ✓ puts the life of the person participating in the research in danger
- ✓ requires hospitalisation or extension of hospitalisation
- ✓ causes a disability or serious or lasting handicap
- ✓ is reflected by an anomaly or congenital abnormality
- ✓ or any event considered medically serious

And which requires medication, no matter the dose administered.

The expression “to put a life in danger” is used to refer to an immediate vital threat, at the time of the adverse event, irrespective of the consequences that corrective or palliative therapy might have.

Certain circumstances requiring hospitalisation do not carry the criteria of seriousness in terms of “hospitalisation” such as:

- admission for social or administrative reasons,
- hospitalisation predefined by protocol,
- hospitalisation for medical treatment or planned surgery prior to the research,
- Day visit to the hospital.

Unexpected adverse effect (article R.1123-39 of the public health code)
Any adverse effect of the product of which the nature, severity or evolution does not match the information appearing in the opinion request files to the CPP and demand for authorisation from the competent authority.

New factor (decree of 24 May 2006)
New safety data, able to lead to a re-evaluation of the report of the benefits and risks of the research, or which could be sufficient to envisage modifications to the documents related to the research, of how the research is conducted as well as, in the case of failure, the use of the product.

10.2. DESCRIPTION OF EXPECTED SERIOUS ADVERSE EVENTS

The following serious adverse events are expected:

- Linked to the treatment of the study: Serious allergic reaction: bronchospasm, hypotension
- Linked to the evolution of the illness:
  - State of shock
  - Hypoxemia
  - Pulmonary inhalation
  - Cardiac arrest

10.3. PROCESS TO FOLLOW IN THE EVENT OF AN ADVERSE EVENT OR NEW FACTORS

The researcher evaluates each adverse event based on its gravity. He should inform the promoter, without delay from the day when he learns of it, of any serious adverse event or new factor, should these occur:

- from the date that the consent form was signed
- throughout the foreseen duration of monitoring of the patient for research
- up until 3 days after the foreseen end of monitoring of the participant for research, once it is subject to be ascribed to research
- Without limitation of duration once it is subject to be ascribed to experimental treatment.

TYPE OF EVENT	NOTIFICATION METHODS	DELAY OF NOTIFICATION OF PROMOTER
UE that is not adverse	In the observation notebook	No immediate notification
Expected SAE	Initial EIG declaration form + written report if necessary	**Immediate notification of promoter**
Unexpected SAE	Initial EIG declaration form + written report if necessary	**Immediate notification of promoter**
New factor	Declaration form + written report if necessary	**Immediate notification of promoter**

DRCI of Reunion Island CHR
Tel.: 02 62 35 95 25
Fax: 02 62 35 97 21
mail: vanessa.basque@chr-reunion.fr

All these events need to be monitored up until the **complete resolution**. An information supplement (complementary declaration note) regarding the evolution of the event, if it is not mentioned in the first report, will be sent to the sponsor by the researcher.

10.4. DECLARATION AND REGISTRATION OF UNEXPECTED SAE AND NEW FACTORS

The sponsor/safety unit declares, according to the existing delays, the unexpected SAE and new factors occurring in the course of the research:

- to Afssaps,
- to the relevant Institutional Review Board (CPP). The board assures, if necessary, that the subjects participating in the research have been informed of adverse effects and that they confirm their consent.

The sponsor/safety unit registers all unexpected SAE in the EudraVigilance database.

10.5. ANNUAL SAFETY REPORT

On the anniversary date of the authorisation of the research, the sponsor edits a safety report comprising of:

- the list of susceptible serious adverse effects that are linked to experimental medication of the research, including the expected and unexpected adverse effects,
- A concise and critical analysis of the safety of participants availing themselves for research.

This report is sent to the Afssaps and the IRB in the 60 days following the anniversary date of the authorisation of the research.

11. STATISTICAL ASPECTS

11.1. CALCULATION OF THE STUDY SIZE

In pre-hospitalisation medical treatment, once intubation is performed using a rapid sequence induction technique, the rate of successful intubation after the first laryngoscopy varies from 70 to 80% in the different studies published (1, 6, 19, 20).

Assuming that the rate of intubation at the first attempt is 75%, we have estimated the sample size to be 602 patients, per group, to show that the rate of intubation upon first attempt is not lower in the test group as compared to the controlled group. This subject number has been determined by making the hypothesis of an acceptable maximum difference of intubation rate after the first laryngoscopy between the two groups of 7% (normally fixed margin for this criteria) (20) to the unilateral risk α of 0.025 (23) and to a risk of second type of 0.2. A safety margin of about 10% of additional inclusions linked to the risk of deviations relative to the protocol with respect to the inclusion “on the field” and the randomization in emergency induces the need to include 650 patients in each group.

11.2. DESCRIPTIVE ANALYSIS

All the quantitative parameters will be summarized in a descriptive manner in each therapeutic modality group, and for each time that they are collected. The descriptive statistical analysis will, for each quantitative parameter at every time, be composed of: means, standard deviation, minimum, maximum, median and quartiles, number of missing values. The qualitative parameters will be illustrated by the frequency of distribution and bilateral confidence ranges to 95% associated ones.

11.3. STATISTICAL TESTS

Univariate analysis

The Student t-test or Mann-Whitney test will be used to compare the quantitative variables according to the conditions of applications. The comparisons of proportions will be done with the use of the Chi2 test or the Fisher exact test, according to the conditions of applications.

11.4. PRIMARY CRITERION OF EFFICACY: FREQUENCY OF SUCCESSFUL INTUBATION

In the case of a clinical test of non-inferiority, where Δl is the threshold value of the margin of clinical non-inferiority, the null and alternative hypotheses can be formulated as illustrated below (24):

For the proportions (i.e. primary criterion of proportion of successful intubation)

H0 : $\Pi 1 - \Pi 2 < -\Delta l$

Against an alternative hypothesis

Ha : $\Pi 1 - \Pi 2 \geq -\Delta l$

With $\Pi 1$, the proportion of successful intubation after the first laryngoscopy in the rocuronium group

And $\Pi 2$, the proportion of successful intubation after the first laryngoscopy in the succinylcholine group.

The clinical equivalence (i.e. non-inferiority) between the percentages of successful intubation will be tested using the Dunnett and Gent method (25). The equivalence test will be a unilateral test based on the hypothesis of a non-inferiority margin δ of 7%. The unilateral confidence range at 97.5% (23) of the difference of the percentages of successful intubation will be equally calculated using the Wald method. This method allows for a type I error control in the context of non-inferiority (26). The analysis will be done as per protocol, as recommended by the non-inferiority tests, and completed with an intent-to-treat analysis. The statistical analysis will be done with the use of SAS 9.2 software (SAS Institute Inc).

11.5. SECONDARY CRITERIA

The quantitative variables will be compared through the Student t-test for the Gaussian variables and through the Mann-Whitney test for non-Gaussian variables. The qualitative variables will be compared using the Chi-2 test. In the case of Chi-2 non-validity, a Fisher exact probability test will be used. The risk of first type has been fixed at 5%. All tests will be bilateral.

11.6. STUDY POPULATIONS

Population per protocol (PP) : patients having followed the protocol without any major violation. The criteria corresponding to major violations will be determined after a committee meeting on the monitoring of the test. Any classification of a violation having occurred in the course of the test will be done in blind treatment.

Population to be treated (ITT): This is an ensemble of randomized patients (intent-to-treat analysis).

The conclusion of non-inferiority requires the coherence of analyses done on the populations ITT and PP. In the event of a missing value on the primary criterion, the patient will be classified as having failed. The analyses of difference will be done on population ITT.

11.7. INTERIM ANALYSIS

There is no interim analysis foreseen.

11.8. DATA ANALYSIS AND GROUPWARE CONTROLLER

The full analysis will be done by the Methodological Support Unit of the CHR of Reunion Island. The full analysis will be done using SAS software (version 9.2; SAS Institute Inc, Cary, North Carolina).

12. RESEARCH MONITORING

12.1. PILOT COMMITTEE

The committee is made up by the study coordinator (Dr. Xavier Combes), the statistician, the methodologist, the project leader and the main researcher in charge of each participating centre:

- Pr. Frédéric ADNET
- Dr. Xavier COMBES
- Dr. François DOLVECK
- Dr. Patricia JABRE
- Dr. Agnès RICARD-HIBON
- Pr. Marc FREYSZ
- Dr. Karim TAZAROURTE
- Dr. Dominique SAVARY
- Dr. Patrick ECOLLAN
- Dr. Papa GUEYE
- Dr. Gérald KIERZEK
- Dr. Jean Louis SEBBAH
- Pr. Jean Emmanuel DE LA COUSSAYE
- Pr. Eric WIEL
- Dr. Arnaud BOURDE

12.2. INDEPENDENT MONITORING COMMITTEE

The Independent Monitoring Committee of serious adverse events will be responsible for assessing said events or any unexpected events occurring during the study.

This committee will be composed of 3 members, all appointed by the sponsor in agreement with the coordinating researcher. They will meet after the inclusion of 25, 50 and 75% of patients.

Their role will be that of assessing the safety problems linked to the study (in particular, the potential difference in the frequency of intubation difficulty in the two groups) and will either

recommend that the study be halted or continued. All serious adverse events will be reported to this committee, who will also be requested to make a ruling in the event of an occurrence of one or more unexpected events, but also in the event of an increased frequency of an adverse event.

13. SOURCE RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

13.1. ACCESS TO DATA

The sponsor is responsible for obtaining the agreement of all parties involved in the research, in order to guarantee direct access to all the sites where the research will be carried out, access to source data, to source documents and to the reports for the purposes of quality control and auditing by the sponsor.
The researchers will make the documents and individual data that are strictly necessary for the monitoring, quality control and audit of the biomedical research, available to all persons having access to these documents, in accordance to the current legislative and regulatory provisions (Articles L.1121-3 and R.5121-13 of the Public Health Code).

13.2. SOURCE DATA

Any document or original object that allows for the proof of the existence or accuracy of data or fact registered in the course of the research is defined as a source document.

13.3. DATA CONFIDENTIALITY

In accordance to the current legislative provisions (Articles L.1121-3 and R.5121-13 of the Public Health Code) all persons having access to source data will take all necessary precautions with the goal of ensuring the confidentiality of information relating to experimental medication, to research, to the persons participating in the research, particularly with regard to their identity and the results obtained. These persons, in the same way as the researchers themselves, are submitted to professional confidentiality.

During the biomedical research or at its publication, the data collected on participating individuals and sent to the sponsor by the researchers (or any other specialised participants) will be rendered anonymous. The data should in no way make the names or addresses of the participating individuals public.

The patients will be coded with the use of a unique number for the research indicating their order of inclusion, the centre and their initials.

The sponsor will ensure that each person participating in the research has given their written consent for access to individual data relating to them and which are strictly necessary for quality control of the research.

14. QUALITY ASSURANCE AND CONTROL

14.1. INSTRUCTIONS FOR DATA COLLECTION

All information required by protocol needs to be logged in the observation notebooks and an explanation needs to be provided for each missing data. The data need to be collected progressively as they are obtained, and transcribed in these notebooks in a neat and legible manner.

Any incorrect data captured in the observation notebooks will be clearly crossed out and the new data will be entered, next to the crossed-out information, accompanied by initials, the date and possibly an explanation by the researcher or authorised person who will have done the correction.

The data is captured in a hard copy observation notebook during pre-hospitalisation, then later captured in an electronic observation notebook.

14.2. RESEARCH MONITORING

The monitoring of the research will be guaranteed by the coordinating researcher, in conjunction with a clinical research technician who will be in charge of :

- capturing data in the electronic observation notebook
- verifying that the observation notebook is kept up to date (request for additional information, corrections, …),
- the logistics and monitoring of the research
- publishing reports regarding its progress level,
- Transmission of SAE to the sponsor.

He will carry out his work in accordance to the standardised operational procedures, in collaboration with the clinical research director appointed by the sponsor.

14.3. QUALITY CONTROL

A clinical research director mandated by the sponsor will regularly visit each research centre, once or a few times during the course of the research as per the rate of inclusions and for the purposes of research. During these visits, the following elements will be reviewed:

- clear consent,
- respect of the research protocol and the procedures defined by it,
- quality of data collected in the observation notebook : accuracy, missing data, coherence between data and source documents (medical dossiers, appointment books, original copies of laboratory results, etc., …),
- Management of future proceeds.

Each visit will be done for the purposes of monitoring with a report written up.

14.4. MANAGEMENT OF DATA

Data will be entered onto a paper form by the emergency physician immediately after the intubation. Then, an electronic entry will be done by a clinical research technician.

14.5. AUDIT AND INSPECTION

An audit can be carried out at any point by the persons authorised by the sponsor and independent persons from the heads of research. The goal is to ensure the quality of the research, the validity of its results and that there is compliance to the law and current regulations.

The researchers agree to comply to the demands of the sponsor and those of the relevant authority with regard to an audit or inspection of the research.

The audit could be applicable to all stages of the research, the development of protocol for the publication of results and to the classification of data used or produced in the framework of the research.

15. ETHICAL AND REGULATORY CONSIDERATIONS

The promoter and the researcher(s) are committed to ensuring that this research is carried out in accordance to Act n° 2004-806 of 9 August 2004, as well as in agreement with the Good Clinical Practices (I.C.H. version 4 of 1st May 1996 and the decision of 24 November 2006) and the Helsinki declaration (of which the full version can be found on the website http://www.wma.net).
The research is carried out in accordance with the current protocol.

This research has received the favourable opinion of the CPP (Institutional Review Board) of the South-West Overseas III region, and the authorization of the *Afssaps.*

The CHR (university health centre) of Reunion Island, sponsor of this research, has underwritten an insurance contract in civil liability alongside SHAM in accordance with the provisions of Article L1121-10 of the Public Health Code.

The data registered at the time of this research are subject to computer processing at the CHR of Reunion Island, with due regard to the Act n° 78-17 of 6 January 1978 related to Information Technology, Data Files and Civil Liberties, modified by Act 2004-801 of 6 August 2004.

This research falls within the framework of “Reference Methodology” (MR-001) pursuant to the provisions of Article 54 paragraph 5 of the Act of 6 January 1978, modified and related to Information Technology, Data Files and Civil Liberties. This change has been approved by the decision of 5 January 2006. The CHR of Reunion Island has signed a compliance undertaking to this “Reference Methodology”.

This research is logged in the EudraCT European data base under number *log number* in accordance with Art. L1121.15 of the public health code.

This research is logged on the website http://clinicaltrials.gov/

AMENDMENT TO PROTOCOL

Any substantial modification, that is, any modification of a nature that it would have a significant impact on the protection of persons, on the conditions of validity and the research results, on the quality and safety of experimented products, on the interpretation of scientific documents that support the progress of the research or on the modalities of conduct of said research, is subject to a written amendment that is sent to the sponsor; the sponsor should obtain, prior to its implementation, a favourable opinion of the IRB and the authorization of the Afssaps.

All non-substantial modifications, that is, those that do not have a significant impact on any aspect of the research, regardless of what it is, are communicated to the IRB (CPP) for information purposes.

All amendments are validated by the sponsor, and by all research participants affected by the modification, before submission to the IRB (CPP) and the Afssaps. This validation might require a meeting between the CS and/or the CIS.

All amendments to the protocol need to be communicated to all participating researchers. The researchers are committed to respecting the contents.

Any amendment that affects the admission of patients or the benefits, risks and limitations of the research are subject to a new briefing note and a new consent form of which the collection follows the same procedure as the aforesaid ones.

16. STORING OF DOCUMENTS AND DATA RELATED TO THE RESEARCH

The following documents related to this research are archived as defined in the Good Clinical Practices:

- By the researching physicians :
  - **for a period of 15 years following the conclusion of the research**
    - The protocol and potential amendments to the protocol
    - The observation notebooks (copies)
    - The source dossiers of patients that have signed consent
    - Any other documents and mail related to the research
  - **for a period of 30 years following the conclusion of the research**
    - The original copy of signed, clear consent forms of participants

  All these documents are the responsibility of the researcher during the regulatory archiving period

- By the sponsor:
  - **for a period of 15 years following the conclusion of the research**
    - The protocol and potential amendments to the protocol
    - The original copies of observation notebooks

- Any other documents and mail related to the research

- for a period of 30 years following the conclusion of the research

- A copy of the signed, clear consent forms of participants
- Documents relating to serious adverse events

All these documents are the responsibility of the sponsor during the regulatory archiving period.

No relocation nor destruction can be done without the sponsor's agreement. In terms of the regulatory archiving period, the sponsor needs to be consulted for destruction. All data, documents and reports could be subject to an audit or inspection.

17. RULES REGARDING PUBLICATION

17.1. SCIENTIFIC PAPERS

The analysis of data provided by the research centres is done by the Methodological Support Unit of the CHR of Reunion Island. This analysis gives rise to a written report which is to be submitted to the sponsor, who will forward it to the Institutional Review Board (CPP) and the relevant authority.

All written or oral communication of the research results need to have the prior consent of the coordinating researcher and, failing which, that of the committee established for the research.

The publication of primary results indicate the name of the sponsor, of all researchers having included or monitored patients in the research, of methodologists, of the project leader, of the biostatistician and data manager that participated in the research, the members of the committee which has been established for the research and source of funds. The International Rules for writing and publishing (*The Uniform Requirements for Manuscripts* du ICMJE, April 2010) will be taken into consideration.

17.2. COMMUNICATION OF RESULTS TO PATIENTS

In accordance with Act n°2002-303 of 4 March 2002, patients are informed, on their request, of the overall research results.

17.3. TRANSFER OF DATA

The collection and management of data are ensured by the Methodological Support Unit of the CHR of Reunion Island. The conditions for transfer of all or part of the database of the research are determined by the sponsor of the research and are subject to a written contract.

BIBLIOGRAPHY

1. Combes X, Jabre P, Jbeili C, et al. Prehospital standardization of medical airway management: incidence and risk factors of difficult airway. Acad Emerg Med 2006;13(8):828-34.
2. Adnet F, Jouriles NJ, Le Toumelin P, et al. Survey of out-of-hospital emergency intubations in the French prehospital medical system: a multicenter study. Ann Emerg Med 1998;32(4):454-60.
3. Ricard-Hibon A, Chollet C, Belpomme V, Duchateau FX, Marty J. Epidemiology of adverse effects of prehospital sedation analgesia. Am J Emerg Med 2003;21(6):461-6.
4. Adnet F, Borron SW, Finot MA, Lapandry C, Baud FJ. Intubation difficulty in poisoned patients: association with initial Glasgow Coma Scale score. Acad Emerg Med 1998;5(2):123-7.
5. Adnet F, Minadeo JP, Finot MA, et al. A survey of sedation protocols used for emergency endotracheal intubation in poisoned patients in the French prehospital medical system. Eur J Emerg Med 1998;5(4):415-9.
6. Ricard-Hibon A, Chollet C, Leroy C, Marty J. Succinylcholine improves the time of performance of a tracheal intubation in prehospital critical care medicine. Eur J Anaesthesiol 2002;19(5):361-7.
7. Rose WD, Anderson LD, Edmond SA. Analysis of intubations. Before and after establishment of a rapid sequence intubation protocol for air medical use. Air Med J 1994;13(11-12):475-8.
8. Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet 2009;374(9686):293-300.
9. Heier T, Feiner JR, Lin J, Brown R, Caldwell JE. Hemoglobin desaturation after succinylcholine-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. Anesthesiology 2001;94(5):754-9.
10. Benumof JL, Dagg R, Benumof R. Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology 1997;87(4):979-82.
11. Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev 2008(2):CD002788.
12. Mazurek AJ, Rae B, Hann S, Kim JI, Castro B, Cote CJ. Rocuronium versus succinylcholine: are they equally effective during rapid-sequence induction of anesthesia? Anesth Analg 1998;87(6):1259-62.
13. Larsen PB, Hansen EG, Jacobsen LS, et al. Intubation conditions after rocuronium or succinylcholine for rapid sequence induction with alfentanil and propofol in the emergency patient. Eur J Anaesthesiol 2005;22(10):748-53.
14. McCourt KC, Salmela L, Mirakhur RK, et al. Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia. Anaesthesia 1998;53(9):867-71.

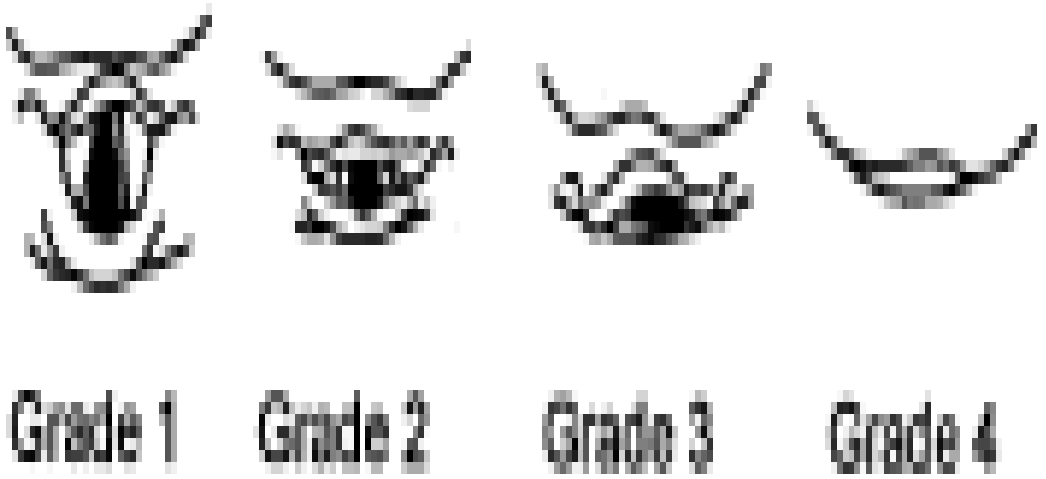
15. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. Anesthesiology 2009;110(5):1020-5.
16. Vivien B, Adnet F, Bounes V, et al. Sédation et analgésie en structure d'urgence (Réactualisation de la conférence d'experts de la Sfar de 1999). Ann Fr Anesth Reanim 2010.
17. Adnet F, Borron SW, Racine SX, et al. The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. Anesthesiology 1997;87(6):1290-7.
18. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007;51(7):789-808.
19. Cantineau JP, Tazarourte K, Merckx P, et al. [Tracheal intubation in prehospital resuscitation: importance of rapid-sequence induction anesthesia]. Ann Fr Anesth Reanim 1997;16(7):878-84.
20. Jabre P, Galinski M, Ricard-Hibon A, et al. Out-of-Hospital Tracheal Intubation With Single-Use Versus Reusable Metal Laryngoscope Blades: A Multicenter Randomized Controlled Trial. Ann Emerg Med.
21. Langeron O, Bourgain JL, Laccoureye O, Legras A, Orliaguet G. [Difficult airway algorithms and management: question 5. Societe Francaise d'Anesthesie et de Reanimation]. Ann Fr Anesth Reanim 2008;27(1):41-5.
22. Combes X, Jabre P, Margenet A, et al. Unanticipated Difficult Airway Management in the Prehospital Emergency Setting: Prospective Validation of an Algorithm. Anesthesiology 2011;In Press.
23. EMEA/CHMP. Guideline on the ch[1]oice of the non-inferiority margin. July 2005
24. Chow and Liu .Design and Analysis of bioavailability and bioequivalence studies. M.Dekker Eds New-York 1992
25. Dunnet CW, Gent M. Significance testing to establish equivalence between treatments with special reference to data in the form of 2 × 2 tables. Biometrics 1977;33:593–602.
26. Roebruck P, Kuhn A (1995) Comparison of tests and sample size formulae for proving therapeutic equivalence based on the difference of binomial probabilities. Stat Med 14: 1583–1594.

1112 **ANNEXES**

1113 **ANNEX 1 : LIST OF RESEARCH CENTRES**

Main researcher of the centre (name, title)	Service/Role	Address of hospital centre	Telephone number	Fax
Dr Benoit Vivien	SAMU 75	CHU Necker - Enfants Malades, 149 rue de Sèvres, 75015 PARIS	01 44 49 24 72	01 44 49 23 25
Pr Marc Freysz	SAMU 21	CHU de Dijon, 3 rue du Faubourg Raines, 21034 DIJON Cedex	03 80 29 37 70	03 80 29 31 23
Pr Jean-Emmanuel De La Coussaye	SAMU 30	CHU Nîmes, Place du Professeur Robert Debré, 30029 NIMES Cedex	04 66 68 30 50	04 66 68 38 51
Pr Eric Wiel	SAMU 59	CHRU de Lille 5 avenue Oscar Lambret, 59037 LILLE cedex	03 20 44 46 38	03 20 44 49 15
Dr Karim Tazarourte	SAMU 77	CH Marc Jacquet, Rue Fréteau de Pény, 77011 MELUN Cedex	01 64 71 61 27	01 64 71 62 62
Dr Agnès Ricard-Hibon	SMUR Beaujon	CHU Beaujon, 100 boulevard du Général Leclerc, 92110 CLICHY LA GARENNE	01 40 87 59 13	01 40 87 58 59
Pr Frédéric Adnet	SAMU 93	CHU Avicenne, 125 rue de Stalingrad, 93009 BOBIGNY Cedex	01 48 96 44 08	01 48 96 44 93
Dr Papa Gueye	SMUR Lariboisière	CHU Lariboisière , 2, rue Ambroise-Paré, 75475 PARIS Cedex	01 49 95 63 91	01 49 95 85 45
Dr Jean Louis Sebbah	SMUR Gonesse	CH Gonesse, 25, rue Pierre de Theilley, GONESSE	01 34 53 21 21	01-34-53-21-90
Dr Gérald.Kierzek	SMUR Hôtel Dieu (75)	CHU de l'Hôtel-Dieu, 1 Place du Parvis de Notre Dame, 75004 PARIS	01 42 34 88 19	01 42 34 85 53
Dr François Dolveck	SAMU 92	CHU Raymond Poincaré, 104 boulevard Raymond Poincaré, 92380 GARCHES	01 47 10 70 01	01 47 10 70 07
Dr Patrick Ecollan	SMUR Pitiè-Salpêtrière (75)	CHU Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75013 PARIS	01 42 16 22 51	01 42 16 22 69
Dr Dominique Savary	SAMU 74	CH Annecy, 1 avenue de l'hôpital, 74370 PRINGY	04 50 63 63 63	04 50 45 59 30
Dr Bertrand Guihard	SAMU 974	CHR Félix Guyon, 97405 SAINT DENIS Cédex, ILE DE LA RÉUNION	02 62 90 60 76	02 62 90 57 01
Dr Pierre Jean Marianne	SMUR St Pierre de la Réunion	CHR de la Réunion – Site du GHSR, Bd François Mitterrand, BP 350 97448 Saint Pierre Cedex	……..	……
Dr Vincent Bounes	SAMU 31	CHU Purpan, TSA 40031, Toulouse	05 67 69 14 21	05 67 69 16 54

ANNEX 2 : CLASSIFICATION OF LARYNGEAL VIEW AFTER DIRECT LARYNGOSCOPY ACCORDING TO CORMACK AND LEHANE.



Grade 1 : The whole glottic slit is visible

Grade 2 : Only the front part of the glottis is visible

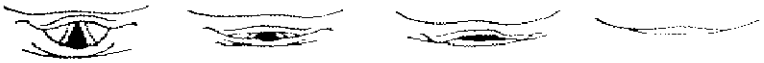
Grade 3 : Only the epiglottis is visible

Grade 4 : The epiglottis is not visible

ANNEX 3 : INTUBATION DIFFICULTY SCORE (IDS)

Number of additional tests (No point is added for the first attempt, count **ALL** additional attempts)	
Number of additional operators An operator is someone who tries to perform the intubation (no point is added for the first operator, indicate the number of additional operators)	
Cormack Grade minus one Grade I equals 0 points, grade II equals 1 point, etc. The Cormack grade should be evaluated at the first attempt. If the **first** blind technique is **successful**, allot 0 points, otherwise indicate the grade of the next laryngoscopy.	

0 **1** **2** **3**



Fully visible glottis	Lower portion visible	Visible Epiglottis	Invisible Epiglottis

Tractive Force on the laryngoscope Normal (standard cad) = 0 point; increased (unusual cad) = 1 point	
External pressure on the larynx Not applied: 0 point, applied: 1 point. No points added for the Sellick manoeuvre	
Mobility of vocal chords Abduction = 0 point; adduction (obstructing the passage of the probe) = 1 point	
Number of techniques used E.g. the addition of a tube is a new technique; (see list below) ; no points allotted for the first technique.	

. **If intubation is impossible : write down the value of the IDF before ceasing the procedure** and **mark with a cross here:**

Total points: I.D.S. =

ANNEX 4 : COPENHAGEN SCORE

Evaluated Variables	Clinically acceptable		Clinically not acceptable
	Excellent	Good	Poor
Laryngoscopy	Easy	Moderate difficulty	Difficult
Position of the vocal chords	Abduction	Interim Position	Closed
Reaction to insertion of the tracheal tube	None	Moderate	Vigorous

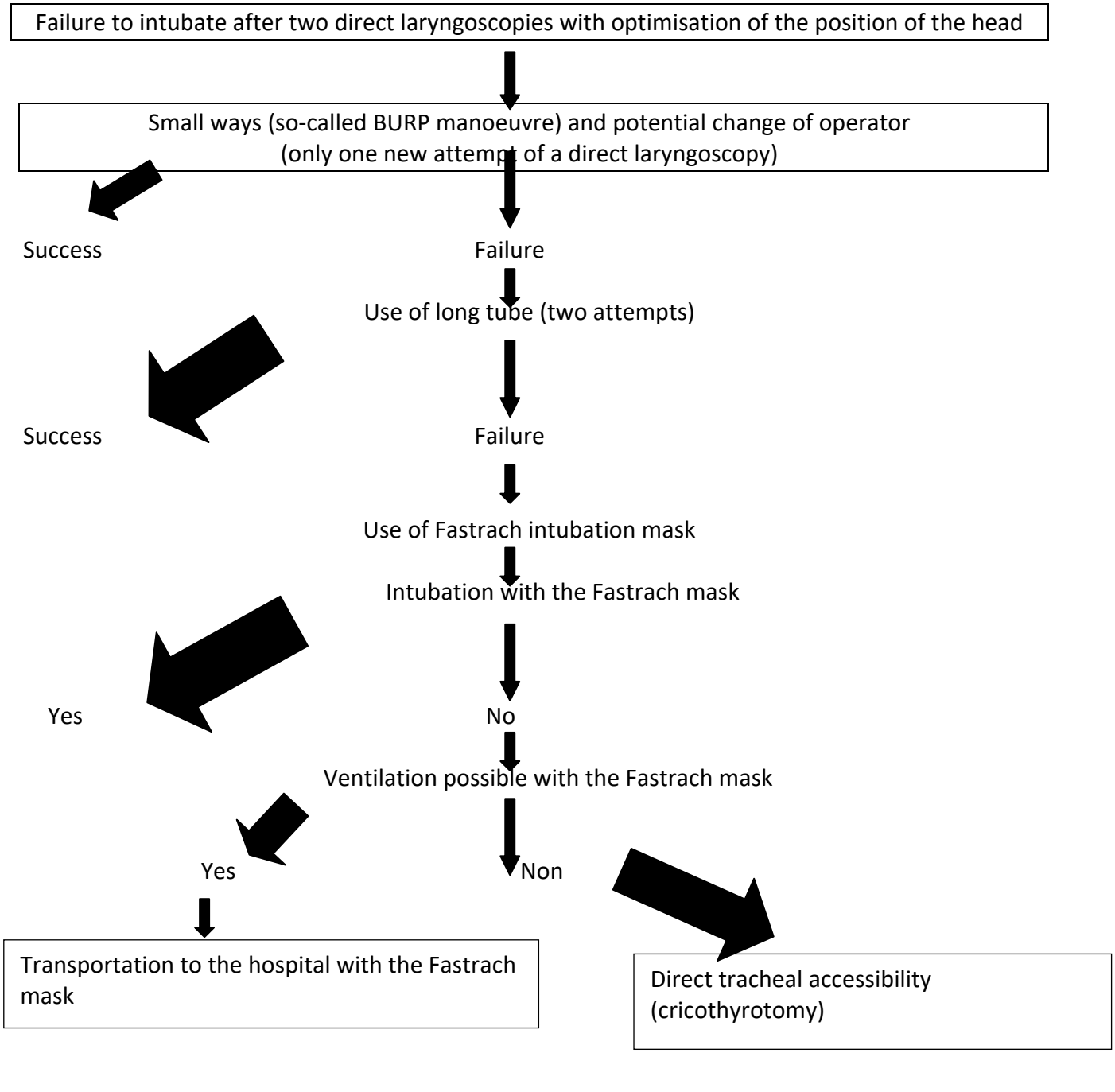
Intubation Conditions :

Excellent : if all variables are rated as excellent

Good: if all variables are rated good or excellent

Poor: if any one variable is rated as poor

ANNEX 5. ALGORITHM IN THE EVENT OF AN UNANTICIPATED DIFFICULT INTUBATION (AS PER 21 AND 22)



ANNEX 6.1 BRIEFING NOTE TO PATIENTS

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study: CURASMUR

Promoter: CHR of Reunion Island

BRIEFING NOTE

Dear Ma'am, Miss, Sir,

Doctor …….. (surname, first name), practising at the …….. hospital, would like to offer you the opportunity to participate in a medical research project in relation to the illness that you are presenting with. It is important that you read this note carefully before making your decision; do not hesitate to request further explanation from the doctor.
Should you decide to participate in this research, you will be asked to give written consent.

1) What is the purpose of this research?

This research deals with the comparison between two medications of which the effect is to relax the muscles in order to facilitate a tracheal intubation. The goal is to show that these two medications are sufficiently effective to facilitate a tracheal intubation, in other words, inserting a tube into the trachea which will allow for artificial ventilation of the lungs.
In order to respond to the question posed in the research, it is foreseen that 1300 patients in need of a tracheal intubation after being admitted by a SMUR (Emergency Resuscitation Unit), will be included. 16 Emergency Resuscitation Units (SMUR) will participate in this research throughout the whole of France.

2) What does the research consist of?

In the proposed research, we will assess the ease of intubation (in order words, insertion of an intubation tube to your trachea) according to what is used for the relaxation of your muscles at the time of this action, two different medications classified as curares : succinylcholine or rocuronium. You will receive an injection intravenously of either succinylcholine or rocuronium. A random draw will be done to determine which of the two medications will be used. In the case of emergency intubation, the recommendation is to use a curare to facilitate intubation and which lowers the risk of complications that could occur during this procedure. The curare that is currently recommended and which has been used for many years in these circumstances is succinylcholine. The main advantage of succinylcholine is its fast reaction, less than 1 minute, which also makes it possible for the intubation to be done very quickly. Furthermore, its onset is short, around 10 minutes, which allows the patient to resume spontaneous breathing quickly should the insertion of the intubation tube be difficult. Succinylcholine presents some side effects, but rarely, (allergy, decrease in heart rate) and there are situations where its use is

expressly contraindicated: when the kalaemia (rate of potassium in blood) is elevated, in cases of neuromuscular disease or if there is former paraplegia, tetraplegia or hemiplegia (in order words, present after at least a few days). Rocuronium is a curare that has been used on the operating table for many years to facilitate intubation of the trachea. The main complication reported with the use of rocuronium is the extremely rare onset of allergies. Rocuronium is not contraindicated in the cases of hyperkalaemia or neuromuscular diseases. By using rocuronium at a dosage of 1,2 mg/kg, which allows for speedy intubation, its onset delay is identical to that of succinylcholine, thus it could be a substitute for emergency intubation. The problem with the use of high doses of rocuronium is the fact that its onset (that is, the duration for which the muscles are relaxed) are long, in the range of one hour. Recently a counteracting product to rocuronium has been made available: sugammadex. This medication allows for the reversal, if necessary (that is, to completely remove curarization) of rocuronium in less than 2 minutes. Sugammadex does not present any reported serious side effects. The fact that it could counteract rocuronium speedily, makes it possible for it to be used without risk of prolonged curarization in emergency situations. Rocuronium could thus allow for an equally easy intubation as compared to succinylcholine with less side effects. The goal of this study is to compare the effectiveness of rocuronium and succinylcholine when these are used to facilitate intubation in emergency situations.

3) What is the timeline of the research?

The research will take place over 3 years and your participation will be for a few hours, limited to the time that you are treated by SMUR before your arrival at the hospital. After signing consent, after the first visit, we will not request any sample or specific text for this research from you.

4) What are the benefits and limitations linked to your participation?

There appears to be fewer side effects associated with the use of rocuronium, compared to the use of succinylcholine. Receiving rocuronium could thus diminish the risk of adverse events presenting, such as cardiac rhythm difficulties (bradycardia) or presenting with significant hyperkalaemia. By participating in this research, you will benefit from close and specific medical monitoring, for which no additional fees will be charged to you.

5) What are the foreseen risks of the research?

This study has the goal of illustrating that intubation is equally easy with the use of either succinylcholine or rocuronium. Irrespective of the medication that is used, there is the risk of serious allergic reaction but its prevalence is low (less than 1/10000). The potential risk with the use of rocuronium, apart from allergic reactions, is the prolonged curarization, but this risk is eliminated when it is possible to counteract rocuronium with a heavy dose of sugammadex. No serious complications have been reported with the use of sugammadex.

6) What are the potential medical alternatives?

In the event of non-participation in the research, the physician who will be treating you will apply the national recommendations concerning emergency intubation. The intubation will be done,

except in the event of contraindication, using succinylcholine which is the current recommended curare in this indication.

7) What are the medical care procedures at the end of your participation?

Your medical care procedures will remain unchanged with regard to a standard care procedure.

8) If you participate, what will happen with the data collected for the research?

In the framework of the biomedical research in which the CHR of Reunion Island is inviting you to participate, processing of your personal data will be done in order to analyse the research results with regard to its objective as presented to you.

For this purpose, the medical data concerning you will be sent to the sponsor of the research or the persons or companies operating on their behalf, in France or abroad. These data will be identified by code number and your initials. These data could also, where the conditions assure their confidentiality, be sent to the French health authorities [or foreign authorities, or other entities of the CHR of Reunion Island].

For any ceasing of participation without withdrawal of consent, the data previously collected prior to this ceasing will be used, unless you wish for it not be used.

9) How is this research overseen?

The CHR of Reunion Island has underwritten an insurance (membership number) assuring their civil responsibility and that of each participant alongside SHAM.

The CHR of Reunion Island has taken all provisions as foreseen by the law related to the protection of persons participating in biomedical research, Huriet law (n° 88-1138) of 20 December 1988, modified by the Public Health Law (n° 2004-806) of 9 August 2004.

The CHR of Reunion Island has obtained the favourable opinion of the Institutional Review Board of the South-West and Overseas Region III for this research on *[indicate the date of the meeting in the format dd/mm/yyyy*] and authorisation from the French Agency for the Safety of Health Products (Afssaps).

10) What are your rights?

Your participation in this research project is entirely free and voluntary. Your decision will not incur any prejudice on the quality of care and treatments to which you are entitled.

You can ask for explanations on the progress of the research at any time during the research, from the physician monitoring you.

You may withdraw from the research any time without explanation, without consequence on the monitoring of your treatment, nor the quality of care that will be provided to you and without

any consequence on the relationship with your physician. Once this withdrawal is issued, you could still be monitored by the same medical team.

In accordance with the provisions of the CNIL (law related to information technology, data files and civil liberties) you have the right of access and rectification. You equally have the right to oppose to the transmission of data covered by professional secrecy that could be used in the framework of this research and processed. These rights are practiced alongside the physician in charge of the research who is the sole person aware of your identity. You could also directly access, or have access via an intermediary of a physician of your choice to the totality of your medical data under the provisions of Article L 1111-7 of the Public Health Code.

Your medical file will remain confidential and could only be consulted under the responsibility of the physician in charge of your treatment as well as by the health authorities, and persons duly authorised by the CHR of Reunion Island for the research, and subject to professional secrecy.

At the end of the research and after analysis of the data related to this research, you may be informed of the overall results by the intermediary of the physician monitoring you in the framework of this research.

Should you agree to participate in the research after having read all information and after having discussed all the aspects with your physician, you will have to sign and date the clear consent form which can be found at the end of this document.

ANNEX 6.2 BRIEFING NOTE FOR AN ADULT INDIVIDUAL PARTICIPATING IN BIOMEDICAL RESEARCH (TRACKING IN RESEARCH AFTER EMERGENCY SITUATION)

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study: CURASMUR

Sponsor: CHR of Reunion Island

Dear Sir/Ma'am,

Due to the seriousness of your condition and the medical emergency, we were unable to request your prior consent and you have been included on the / / in a biomedical research project titled "Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study".

In accordance with the law (Art. L.1122-1-2 of the Public Health Code), it is the support person designed by you or your parent, if this person was present at the time of your care, from whom agreement to your participation in this research was requested. Otherwise the law authorises us to include persons without their consent in medical emergency situations.

Now that you are able to understand and express your volition, we are requesting your agreement to track your participation in this biomedical research project.

You were treated by a SMUR team (Mobile Emergency Resuscitation unit) because you were presenting with vital distress signs. During your treatment it was necessary to perform a tracheal intubation in order to ensure artificial ventilation by means of an intubation tube. In order to insert this intubation tube, sedation is needed. You were thus administered, intravenously, with a hypnotic drug of which the purpose is to render you unconscious at the time of intubation. Another medication is needed to be able to perform this intubation in the best conditions, which is a curare that relaxes all the muscles for a few minutes and in particular those of the upper airways that control the vocal chords. The use of a curare makes intubation easier and minimises the risks that could be associated with it. The curare that is generally used is succinylcholine which allows for an emergency intubation to be done in less than 1 minute and of which the length of onset is short (approximately 8 minutes) which allows the patient to resume effective spontaneous breathing quickly should intubation prove to be impossible.. This medication has some side effects that are rare but which could be severe : allergy, hyperkalaemia (fierce increase of concentration of potassium in blood) which could lead to cardiac rhythm difficulties, slowing heart rate. Another curare, rocuronium has been used for a number of years on the operating table. At a dose that is slightly higher than that used in the operating room, it makes it possible to perform an intubation just as quickly as with succinylcholine. Up until now rocuronium has not been used often for emergency intubation as its duration of action (time during which the muscles are relaxed) is long (approximately one hour) and in the event where it is impossible to insert the intubation tube, spontaneous breathing does not resume quickly.

A counteracting drug to rocuronium has been available for some months. This medication is called sugammadex. It makes it possible to counteract the effects of rocuronium in a few minutes. Sugammadex is a medication which presents very few side effects, the most of which are not serious (sensation of metallic taste in the mouth, very rare allergic reactions). Sugammadex counteracts the effect of rocuronium in less than 2 minutes, when administered at a dose of 16 mg/kg. The fact that it can counteract rocuronium quickly in the case of difficult intubation makes its use possible in emergency and it could replace succinylcholine, particularly when the latter is contraindicated. These two medications have already been compared in the operating room in patients needing to be anaesthetised outside of an emergency situation. Rocuronium, when used at a dose of 1,2 mg/kg has, in these circumstances, made intubation possible in the same conditions as those obtained with succinylcholine.

At present, rocuronium and succinylcholine have not been compared in emergency situations outside the hospital. Before the use of rocuronium can be recommended for performing emergency intubations, it needs to be determined whether this medication is equally effective as succinylcholine which remains the curare of reference for now, for emergency intubations.

It is the reason why you have been included in this study, where patients treated for a vital distress and in need of a tracheal intubation, receive, after a random draw either succinylcholine or rocuronium to facilitate the insertion of the intubation tube to the trachea. Once this study has been completed, it will be possible to determine whether rocuronium could be used instead of succinylcholine in emergency medical treatment, and with the same effectiveness.

This study has an expected duration of 3 years, which will allow for the inclusion of approximately 1300 patients.

The length of your monitoring in this study will not exceed a few hours, correspondent to the period during which you have been treated by the SMUR team.

The study will consist of evaluating the conditions in which intubation is performed and measuring whether the difficulty of intubation was different where succinylcholine or rocuronium were used. All potential side effects linked to the use of the products in question will be analysed. No exam (radiology, taking blood) or additional consultation with regard to a standard care is foreseen for this study.

The protocol does not in any way modify the nature of your treatment which will be done according to the current recommendations.

ANNEX 6.3 CONSENT FORM FOR PARTICIPATION IN BIOMEDICAL RESEARCH (TRACKING POST-EMERGENCIES)

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study: CURASMUR

Sponsor : CHR of Reunion Island

I, the undersigned

Mrs., Miss, Mr. *(cross out the titles that do not apply)* (*surname, first name*)……

freely and voluntarily accept to continue participating in the biomedical research project titled **« Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study »** of which the CHR of Reunion Island is the sponsor, and which has been proposed to me by Doctor (*surname, first name, telephone number*

)……, the physician in this research project.

Given that :

- The physician who informed me and answered all my questions, made it clear to me that my participation is voluntary and that I have the right to withdraw from this research at any point,
- Before participating in this research project, I received a medical exam of which the results were communicated to me,
- I could be in contact with the physician during or at the publication of the research of information concerning my health, which he possesses,
- I have understood from the briefing note given to me that in order to participate in this research, I need to be a member or beneficiary of a medical aid scheme. I confirm that this is the case.
- I am fully aware that I can withdraw my consent to participate in this research at any point, irrespective of my reasons and without any responsibility to do so, but I hereby agree to inform the physician in that event.,
- Should I wish, I will be informed by the physician of the overall results of this research once it has been completed,
- My consent does not in any form release the physician and the promoter of the totality of their responsibilities and I reserve my rights as accorded me by the law.
- My participation in this research project implies that I would not be able to participate in any other biomedical research project for a period of 60 days.

Signed at …….

Date : …… Signature

Signature of the physician who certifies having fully explained the goal, terms and conditions as well as potential risks of the research project to the person signing this document.

Date : …… Signature

This document is to be made available in 3 original copies, of which the first should be kept for 30 years by the researcher, a second copy sent to the person giving their consent and the third sent to the sponsor.

ANNEX 6.4 : COLLECTION OF EMERGENCY CONSENT

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study: CURASMUR

Sponsor : CHR of Reunion Island

I, the undersigned, Dr. …….. *(surname and first name)*, researcher for the Curasmur study at …… *(Name of centre)* hereby confirm having included :

on …… / …… / ……., the patient **I__I__I-I__I__I__I-I__I__I**, by using the emergency procedure.

Centre number – Patient number – Initials of patient

In fact, the patient is currently unable to comprehend the information relating to the study and it is not possible to inform nor to obtain consent from the family or support person representing him/her.

In accordance with Article L.1122-1-2 of the Public Health Code, I hereby commit myself to informing the patient, or the support person representing him, or the family as soon as possible and I will ask them their consent for the tracking of the research.

Date : …… Signature of Researcher : ……

This statement must be sent to the Resuscitation team that has the patient in their care. A copy of this statement will be kept by the researcher and another sent to the sponsor.

ANNEXE 6.5 : BRIEFING NOTE IN EMERGENCY SITUATIONS FOR THE REPRESENTATIVE OF A PERSON UNABLE TO EXPRESS THEIR CONSENT TO PARTICIPATE IN THE BIOMEDICAL RESEARCH PROJECT TITLED

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study: CURASMUR

Sponsor: CHR of Reunion Island

Dear Sir/Ma'am,

Due to his current condition and the level of emergency, in accordance with the law, we are approaching you for authorisation for the participation of Mrs., Miss, Mr. (cross out the titles that do not apply) (surname, first name) ……. in this biomedical research project.

Your family member is currently being treated by a SMUR (Mobile Emergency and Resuscitation Services) Unit as he/she is presenting with a vital distress. His/her condition requires a mechanical ventilation which will be done with a respirator. This mechanical ventilation cannot be performed without an intubation tube that will be inserted into the trachea.
In order to insert this intubation tube, sedation is necessary. A hypnotic drug, which has the purpose of making him/her unconscious at the time of intubation, will be administered to your family member intravenously. Another medication is necessary in order to do the intubation in optimal conditions, this is a curare that relaxes all the muscles for a few minutes, particularly those of the upper airways that control the vocal chords. The use of a curare makes intubation easier and minimises the risks that could be associated with it. The curare that is generally used is succinylcholine, which allows for an emergency intubation to be done in less than 1 minute and of which the duration of action is short (approximately 8 minutes), and which allows the patient to resume effective spontaneous breathing quickly should intubation prove to be impossible. This medication has some side effects that are rare but which could be severe: allergy, hyperkalaemia (fierce increase of concentration of potassium in blood) which could lead to cardiac rhythm difficulties, slowing heart rate. Another curare, rocuronium, has been used for a number of years in the operating room. At a dose that is slightly higher than that used in the operating room, it makes it possible to perform an intubation just as quickly as with succinylcholine. Up until now rocuronium has not been used often for emergency intubation as its duration of action (time during which the muscles are relaxed) is long (approximately one hour) and in the event where it is impossible to insert the intubation tube, spontaneous breathing does not resume quickly.

A counteracting drug to rocuronium has been available for some months. This medication is called sugammadex. It makes it possible to counteract the effects of rocuronium in a few minutes. Sugammadex is a medication which presents very few side effects, the most of which are not serious (sensation of metallic taste in the mouth, very rare allergic reactions). Sugammadex counteracts the effects of rocuronium in less than 2 minutes, when administered at a dose of 16 mg/kg. The fact that it can counteract rocuronium quickly in the case of difficult intubation makes

its use possible in emergency and it could replace succinylcholine, particularly when the latter is contraindicated. These two medications have already been compared in the operating room in patients needing to be anaesthetised outside of an emergency situation. Rocuronium, when used at a dose of 1,2 mg/kg has, in these circumstances, made intubation possible in the same conditions as those obtained with succinylcholine.

At present, rocuronium and succinylcholine have not been compared in emergency situations outside the hospital. Before the use of rocuronium can be recommended for performing emergency intubations, it needs to be determined whether this medication is equally effective as succinylcholine, which remains the curare of reference for now, for emergency intubations.

It is for this reason that we are proposing that your family member participate in this study titled "**Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study"**, where patients treated for a vital distress and in need of a tracheal intubation, receive, after a random draw, either succinylcholine or rocuronium to facilitate the insertion of the intubation tube to the trachea. Once this study has been completed, it will be possible to determine whether rocuronium could be used instead of succinylcholine in emergency medical treatment, and with the same efficacy.

This study has an expected duration of 3 years, which will allow for the inclusion of approximately 1300 patients.

The length of monitoring of your family member in this study will not exceed a few hours, correspondent to the period during which he/she will have been treated by the SMUR team.

Of course, the protocol does not in any way modify the nature of the patient's treatment which will be done according to the current recommendations.

The participation of Mrs., Miss, Mr. (cross out the titles that do not apply) (surname, first name) ……. in this biomedical research project will not generate any supplementary fees with respect to the existing ones associated with the standard monitoring of this illness. Nevertheless, in order to participate in this research project, he/she needs to be a main member or beneficiary of a medical aid scheme.

The CHR of Reunion Island, who has arranged for this biomedical research in the capacity of promoter, has contracted insurance in accordance with the legislative provisions, with SHAM.

This research project has received the favourable opinion of the Institutional Review Board (CPP) of the South-West and Overseas Region III, on the …. as well as the authorisation for implementation from the relevant health authority. It is possible that this research project will be interrupted, should the circumstances deem necessary, by the sponsor or at the request of the health authority.

In the context of the biomedical research project in which the CHR of Reunion Island is proposing that your parent or family member take place, a treatment of his personal data will be implemented in order to facilitate analysis of the research results with regard to the objective of said research as presented to you.

For this purpose, the medical data concerning your parent or family member and the data relating to his/her lifestyle habits will be sent to the sponsor of the research or to the persons or companies standing in on his behalf, in France or abroad. This data will be identified by a code number and his/her initials. This data could also, where the conditions guarantee confidentiality, be sent to the French or foreign health authorities, or to other CHR entities of Reunion Island. In accordance with the law relating to Information Technology, Data Files and Civil Liberties (CNIL) you will have to the right to access and rectification. You equally have the right to oppose to the transmission of data covered by professional secrecy that are likely to be used in the context of this research and be processed.

We hereby inform you that you are free to either agree to or not agree to the participation of your parent or family member in this research project.

You may at any point exercise your right to withdraw regarding the participation of this person.

Once it becomes medically possible, we will ask him/her directly for their opinion regarding the tracking of their participation in this research.

Once you have read this briefing note and have obtained answers to the questions you may have asked while consulting with the physician, you will be asked, if you agree, to give your written authorisation by signing the form prepared for this purpose.

ANNEXE 6.6 : CONSENT FORM FOR PARTICIPATION IN A BIOMEDICAL RESEARCH PROJECT IN AN EMERGENCY SITUATION BY THE REPRESENTATIVE OF A PERSON UNABLE TO GIVE THEIR CONSENT.

Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study: CURASMUR

Sponsor: CHR of Reunion Island

I, the undersigned,

Mrs., Miss, Mr. *(cross out the titles that do not apply)* (*surname, first name*)…….

freely and voluntarily accept, in my capacity as parent, support person* (*cross out the ones that do not apply*) that Mrs., Miss, Mr. (*cross out the titles that do not apply*) (**surname, first name**) ……

participate in this biomedical research project titled "Comparison of the usage of succinylcholine and rocuronium for intubation in pre-hospitalization emergencies. A multi-centric, non-inferiority, randomized, controlled and blind study" of which the Assistance Publique - Hôpitaux de Paris is the sponsor and which has been proposed to me by Doctor (*surname, first name, telephone number*) ……., physician in this research project.

Given that:

- The physician who informed me and answered all my questions, made it clear to me that I have the right to agree to or refuse that my parent or family member participate in this research.
- Before participating in this research, this person received a medical exam of which the results have been communicated to me,
- I will be able to communicate with the physician through the course of or at the publication of research information regarding his health, which he (the physician) possesses,
- I am fully aware that I can withdraw my consent for his/her participation in this research at any point, irrespective of my reasons and without any responsibility to do so, but I hereby agree to inform the physician in that event. The fact that he/she will no longer be participating in this research will not jeopardise my relationship with the physician who will be approaching me, if necessary, for another treatment for my parent or family member.

- Should I wish, I will be informed by the physician of the overall results of this research once it has been completed,
- My consent does not in any way release the physician and sponsor of all their responsibilities, and my parent or family member reserve their rights as per the law.
- The participation of this person in this research project implies that he/she will not be able to participate in another biomedical research project for a period of 60 days.

Relationship with person in question: ……
Signed at …….

Date : …… Signature

Signature of the physician who certifies having fully explained the goal, terms and conditions as well as potential risks of the research project to the person signing this document.

Date : …… Signature

** The support person needs to have been designated previously, in written form, by the patient (Art. L.1111-6 CSP).*

1. Jabre P, Galinski M, Ricard-Hibon A, et al. Out-of-hospital tracheal intubation with single-use versus reusable metal laryngoscope blades: a multicenter randomized controlled trial. *Annals of emergency medicine.* Mar 2011;57(3):225-231.