Effect of remifentanil vs neuromuscular blockers during rapid sequence intubation on successful intubation without major complications among patients at risk for aspiration: a randomized clinical trial

ENGLISH TRANSLATION OF TRIAL PROTOCOL & STATISTICAL ANALYSIS

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REMICrush protocol

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"Evaluation *of REMIFENTANIL as a replacement for rapid-onset neuromuscular blockers for rapid sequence anesthetic induction in patients at risk of gastric fluid inhalation - Multicenter, prospective, controlled, randomized, single-blind, noninferiority study."*

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SIGNATURE PAGE

SIGNATURE OF THE PROMOTER

The sponsor undertakes to carry out this study in accordance with all the legislative and regulatory provisions to which the research may be subject and according to the protocol.		
Name and Function of Signatory Representative: **For the promoter and by a delegation of the Director-General, the Director of Medical Affairs and Research**	**Date:**	**Signature:**

SIGNATURE OF INVESTIGATORS

I have read all the pages of the clinical trial protocol, of which the CHU of Nantes is the sponsor. I confirm that it contains all the information necessary for the test conduct. I undertake to carry out the test in accordance with the protocol and the terms and conditions defined therein. I undertake to carry out the test respecting:

- the principles of the "Declaration of Helsinki,"
- international (ICH) and French rules and recommendations of good clinical practice (rules of good clinical practice for biomedical research on medicinal products for human use)
- European regulations and national legislation and regulations relating to clinical trials,

I also undertake that investigators and other qualified members of my team will have access to this protocol and to the documents relating to the Conduct of the trial to enable them to work in compliance with the provisions contained in these documents.

	Name:	**Date:**	**Signature:**
Coordinating Investigator	**Dr. GRILLOT Nicolas** Anesthesia and resuscitation department CHU de Nantes		
Principal Investigator	**Name and Institution:**	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

ANSM	National Agency for the Safety of Medicines and Health Products
MA	Marketing Authorization
BOW	Clinical Research Associate (monitor)
PCBs	Good Clinical Practices
bpm	Beat per minute
CPP	Committee for the Protection of Persons
CNIL	Commission Nationale de l'Informatique et des Libertés
CIS	Independent Service Committee
SOME	Specialized Study Diploma
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EtCO2	End Tidal CO2 (Fraction expirée de CO2)
EvIG	Serious Unwanted Event
ISG	Serious Adverse Reaction
EIGI	Unexpected serious adverse reaction
FC	Heart rate
FeO2	Exhaled oxygen fraction
FIH	First-in-Human = ^{1st} administration trial in humans
IADE	Nurse Anesthetist State Graduate
RSIA	Rapid Sequence Induction of Anesthesia
BMI	Body Mass Index
IVD	Direct Intravenous
TUE	Physician Anesthetist-Resuscitator
MR	CNIL Reference Methodology
PAD	Diastolic blood pressure
PAM	Average blood pressure
STEP	Systolic blood pressure
ENERGY	Positive Expiratory Pressure
RCP	Summary of Product Characteristics
SFAR	French Society of Anesthesia-Resuscitation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEC	Clinical Study Technician

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INTRODUCTION

Rapid sequence induction of anesthesia (RSIA) is the reference anesthetic technique for patients at risk of inhalation of gastric contents or with predictive criteria for intubation or difficult ventilation. It classically combines a hypnotic with a rapid-onset neuromuscular blocker. Suxamethonium (CELOCURINE®) is historically the recommended rapid-onset neuromuscular blocker in this indication because of its short time of action, its short duration of action, and the intensity of the neuromuscular block it generates (1). Nevertheless, its use may be responsible for serious side effects (2). The anaphylactic reaction is the most feared; prolonged neuromuscular blockade, malignant hyperthermia, or the occurrence of severe hyperkalemia (in patients with deregulation of acetylcholine receptors at the neuromuscular junction) are others. In patients with a contraindication to suxamethonium, rocuronium is an alternative (3,4). However, this molecule is known as allergenic as suxamethonium, and its very long duration of action limits the indications in this context. In addition, the 2012 French Per-Anesthetic Reactions Study Group survey results reported an increase in the incidence of anaphylactic reactions to suxamethonium and an increase in the incidence of the most severe forms of all recommended combined (5). Due to the risks associated with their use, and despite their effectiveness, rapid-onset neuromuscular blockers are used in only 31 to 55% of RSIA cases, according to international observational studies (6-9). Remifentanil is an opioid with interesting pharmacological properties in the context of RSIA. Indeed its time of action is short, about 60 seconds, its duration of action is short of 5 minutes (10), and several studies report that it provides good exposure conditions during intubation without rapid-onset neuromuscular blocker in regulated surgery (11-15). It also decreases the hemodynamic response during laryngoscopy (16-20). Finally, this treatment has marketing authorization in the indication of anesthetic induction. It is further recognized as an alternative to rapid-onset neuromuscular blockers for orotracheal intubation for anesthesia in pediatry (21).

In common practice, two RSIA protocols in adults are currently used: RSIA with or without rapid-onset neuromuscular blocker. The effectiveness of these two protocols is demonstrated, but no data are now available to compare the incidences of complications between these two strategies. Showing the noninferiority of remifentanil on the incidence of RSIA without major complications will change international recommendations and practices worldwide.

We hypothesize that the incidence of tracheal intubations without major complications is not lower at RSIA with remifentanil compared to RSIA with rapid-onset neuromuscular blockers. Therefore, we are conducting a multicenter, randomized, controlled, open-label, noninferiority trial.

1. JUSTIFICATION OF THE STUDY

1.1. SEARCH POSITIONING

Pulmonary inhalation of gastric fluid related to general anesthesia

For general anesthesia, securing the upper airway by placing an orotracheal intubation probe is a standard procedure and has been made mandatory in many situations. The first reason is to ensure adequate oxygenation throughout the time of surgery. The second is to protect the upper airways from the risk of inhalation of gastric contents.
In most cases, gastric fluid inhalation occurs at the time of induction of general anesthesia before securing the airways by the tracheal intubation probe. In 1993, Warner et al. (22) reported an incidence of gastric inhalation in 67 cases out of 215,488 anesthesia performed between 1985 and 1991. More recently, Sakai et al.(23) reported an incidence of 14 inhalations out of 99,441 anesthesia performed between 2001 and 2004, ranging from 1.5 to 3 per 10,000 anesthesia in adults. Morbidity-mortality from inhalation is not negligible with, in a recent study (24), a risk of pulmonary complications estimated at 1 event every 9753 anesthesia and risk of death related to inhalation every 23406 anesthesia. In this same study, the risk of inhalation is increased by 4.5 times in non-fasting patients. To reduce the risk of inhalation, the induction of anesthesia in non-fasting patients has been standardized: it is called rapid sequence induction of anesthesia. This anesthetic induction scheme is widespread. For example, it is used nearly 5000 times yearly (400 times a month) at the University Hospital of Nantes.

Rapid sequence anesthesia induction

The main objective of RSIA is to place the tracheal intubation probe in the shortest possible time and without having to ventilate the patient with a face mask (which would increase the risk of inhalation). In addition, it is helpful that the patient finds spontaneous ventilation quickly to limit the duration of ventilation with a face mask in case of difficulty setting up the orotracheal intubation probe. To achieve these two objectives, the drug agents used must therefore have a short time of action and a short duration or be able to be antagonized

Rapid sequence induction, therefore, classically associates a hypnotic with a depolarizing neuromuscular blocker: suxamethonium remains the reference molecule in this indication because of its short action time (30 to 60 seconds) and its short duration of action (5-15min). In addition, the intensity of the neuromuscular block it generates provides excellent conditions for exposure and tracheal intubation at a dose of 1 mg/kg accurate weight (1).
Nevertheless, its use exposes the patient to severe complications such as anaphylaxis ranging from a simple skin reaction to the cardio-respiratory arrest, severe hyperkalemia, or malignant hyperthermia (3). Hypersensitivity reactions involving suxamethonium have a frequency of 1/6500 anesthesia in France (25). The latest epidemiological data show that neuromuscular blockers remain the most frequently implicated in peri-anesthetic anaphylactic reactions since they are responsible for 54% of severe allergies. Suxamethonium is the leading cause of anaphylactic accidents of drug origin in the operating room (frequency of 37%).) In addition, the rate of grade 3 and 4 anaphylactic reactions (shock, cardiorespiratory arrest) is more significant with this molecule than with other neuromuscular blockers (26). These allergic reactions are therefore frequent and potentially severe. However, it is impossible to predict the allergic risk for a given patient, making it very difficult to measure the benefit/risk balance at the individual level. Finally, suxamethonium is contraindicated, among others, in chronic neuromuscular pathology (myopathy, myasthenia gravis, spinal cord injury ..) or situations at risk of hyperkalemia (major rhabdomyolysis, severe burn of more than 24 hours, etc ...).

In case of contraindication to suxamethonium, rocuronium bromide at a dose of 1 mg/kg ideal weight has been proposed as a satisfactory alternative (4). Nevertheless, this molecule risks an anaphylactic reaction like suxamethonium (27). In addition, this molecule has a prolonged duration of action, justifying having a stock of SUGAMMADEX, a specific antagonist molecule, in case of a possible complication.

Remifentanil

Pharmacology

In the recommendations on the induction of the non-fasting patient, the place of morphine has been little studied. Their use is conventionally ruled out because of the relatively long duration of action of the oldest morphine (sufentanil, fentanyl), which would delay the resumption of spontaneous ventilation in case of intubation failure. Nevertheless, during laryngoscopy, intubation without morphine is responsible for a hemodynamic response with tachycardia and hypertension by sympathetic stimulation that can be deleterious in the fragile patient (28,29).

Remifentanil is a morphine derivate developed in the early 2000s. It is a pure agonist specific to μ receptors from the anilidopiperidin family. It has structural relationships with fentanyl and its other derivatives. Its methyl-ester group is responsible for its unique pharmacological properties (30).
Its pKa is lower than plasma pH. It circulates in plasma mostly in its non-ionized form and quickly penetrates the blood-brain barrier allowing a rapid balance between plasma and brain concentrations. In addition, its initial distribution volume is low, which gives it a high speed of action (action time of about one minute). In addition, remifentanil is degraded by non-specific plasma and tissue esterases, providing it with a very short contextual half-life (3.2 minutes), allowing a rapid elimination of the product even after prolonged infusion. These pharmacokinetic characteristics are little altered by age and renal or hepatic impairment (31-33).

All these characteristics are responsible for the "on-off effect" attributed to this molecule, namely a short time of action allowing rapid and facilitated intubation and a short duration of action hence a brief respiratory depression.

The place of remifentanil in the induction of rapid sequence anesthesia

The benefit-risk balance of RSIA could be improved by replacing suxamethonium (or rocuronium), which has significant potential adverse effects, with another agent with better tolerance but which would retain similar pharmacodynamic properties (good intubation condition, short time to action, short duration of action). The "on-off" effect of remifentanil makes it a good candidate for rapid sequence induction.

Conditions of intubation without rapid-onset neuromuscular blocker but with remifentanil

Several studies report excellent intubation conditions when intubated with remifentanil without a rapid-onset neuromuscular blocker.
In pediatric anesthesia, using rapid-onset neuromuscular blockers for intubation is rare, and remifentanil has been proposed as an adjuvant to sevoflurane and propofol to enable tracheal intubation. In both cases, the ease of intubation was comparable to intubation with rapid-onset neuromuscular blockers, and the tolerance was excellent (21). The same is true in four studies in adult anesthesia, where induction of anesthesia by a hypnotic agent associated with remifentanil (2 to 4 μg/kg) provided excellent intubation conditions in nearly 95% of cases with an intubation success rate close to 100% (11,12,34,35). In two randomized studies, induction

of anesthesia with propofol and remifentanil 4 µg/kg provided tracheal intubation conditions comparable to rapid sequence induction with suxamethonium (13,36). At this dosage, the time to resume spontaneous ventilation was 8 minutes with remifentanil compared to 4 minutes with suxamethonium (14).

Hemodynamic tolerance of remifentanil

The hemodynamic tolerance of remifentanil is satisfactory during induction. The drop in blood pressure varies from 19 to 31% compared to the fundamental values, according to the studies. Heart rate decreases by 20-30% as well (33.36). On the other hand, RSIA with suxamethonium and without morphine is accompanied by an increase in heart rate and blood pressure of 20 to 30%(13).

No high-level studies comparing remifentanil with suxamethonium in the RSIA are currently available. Given the morbidity induced by suxamethonium and the lack of a validated alternative in this indication, it is crucial to look for an alternative procedure

In conclusion

The induction of anesthesia in a non-fasting patient seeks to limit the risk of significant complications, including pulmonary inhalation of gastric fluid. Pharmacological agents must therefore provide suitable conditions for tracheal intubation and have a short time to action and short duration. Current recommendations support using suxamethonium, which could decrease the risk of complications related to emergency intubation.

Significant problems with the tolerance of suxamethonium mean that nearly 50% of rapid sequence inductions are currently done without suxamethonium (6,7,37). Due to its pharmacokinetic characteristics, remifentanil is commonly used in the context of rapid sequence induction without its noninferiority on the incidence of uncomplicated intubations having been demonstrated compared to suxamethonium.

We hypothesize that the incidence of tracheal intubations without major complications is not lower at RSIA with remifentanil compared to RSIA with rapid-onset neuromuscular blockers. Therefore, we are conducting a multicenter, randomized, controlled, open-label, noninferiority trial to demonstrate the noninferiority of remifentanil compared to rapid-onset neuromuscular blockers to allow, in combination with a hypnotic, uncomplicated tracheal intubation during rapid sequence induction. The REMICrush study can potentially change international recommendations and the medical practice of a frequent procedure during anesthesia.

1.2. BENEFITS AND RISKS FOR THOSE WHO LEND THEMSELVES TO RESEARCH

1.2.1. Benefits

1.2.1.1. Individual benefit

At the individual level, the expected benefit of the induction of high-quality rapid sequence anesthesia is to reduce the risk of significant complications related to intubation, to reduce the incidence of postoperative respiratory complications, to reduce the incidence of complications

associated with the use of rapid-onset neuromuscular blocker or its non-use despite the formal indication of rapid sequence induction. Patients in the arm without rapid-onset neuromuscular blockers may benefit from a decrease in adverse effects related to the use of rapid-onset neuromuscular blockers (decreased risk of allergy, hyperkalemia, and prolonged neuromuscular blockade). The individual benefit can therefore be objectified by the patient himself and quantified by the statistical analysis of our study.

1.2.1.2. Collective benefit

The incidence of allergic events when using a neuromuscular blocker for anesthesiologist induction is non-zero and exposes these patients to a risk of death or severe complications, especially if a neuromuscular blocker is unnecessary for the surgical procedure. Conversely, the non-use of this therapeutic class despite a formal indication of the realization of a rapid sequence induction also exposes patients to the risks related to intubation difficulties such as traumatic injuries, the occurrence of a hypoxic event, inhalation of gastric contents, the occurrence of postoperative respiratory complications or death. If the use of a bolus of remifentanil allows the obtaining of a condition of intubation not inferior to the use of a rapid-onset neuromuscular blocker without associated significant side effects, this study would be likely to modify the modalities of management of these patients at the international level because this molecule is inexpensive and easy to use. This could also make it possible to reduce the costs of initial care, especially in the event of the need to use rocuronium (which requires a stock of SUGAMMADEX), and in the longer term to reduce the additional costs of hospitalization in connection with the occurrence of an allergic event or a postoperative respiratory complication.

1.2.2. Risks

1.2.2.1. Individual risk

- Risks and physical constraints

No

- Risks related to the disease

The most common risks during rapid sequence induction are inhalation of gastric contents, damage to the oropharyngeal tract, and respiratory complications

- Risks associated with trial treatments including comparator where appropriate (AR)

The most common risks with the study drug are low blood pressure and bradycardia.
The complete list of ARs can be found in the pharmacovigilance section (see below).

- Risks and psychological constraints

No

- Socio-economic risks

No

1.2.2.2. Collective risk

No

1.2.3. Balance of benefits and risks

The balance of benefits and risks is favorable because of the literature and medical context data. In case of noninferiority demonstrated in our study, the use of remifentanil in place of a rapid-onset neuromuscular blocker will allow, in an identical way to the latter, to practice quality intubation in rapid sequence induction with a drug of fast action and short duration while preventing the occurrence of major complications related to tracheal intubation.
The expected benefit with the use of remifentanil instead of rapid-onset neuromuscular blocker is the decreased risk of:
- an unpredictable severe allergic reaction (rate approximately 1 per 3000 patients),
- hyperkalemia and heart rhythm disorders
- muscle pain,
- postoperative lung infections and postoperative swallowing disorders,
- prolonged neuromuscular blockade.

The main risks associated with the use of remifentanil instead of rapid-onset neuromuscular blocker are:
- dose-dependent bradycardia which is temporary and quickly reversible.
- dose-dependent arterial hypotension, which is temporary and quickly reversible.

The bibliographical references are given in Annex 3 of the document.

2. OBJECTIVES AND CRITERIA OF JUDGMENT

2.1. OBJECTIVE AND PRIMARY ENDPOINT

2.1.1. Main objective

The main objective of the study is to demonstrate the noninferiority of a rapid-onset neuromuscular blocker-free rapid-sequence anesthetic induction with remifentanil in preventing major complications related to tracheal intubation compared to rapid sequence induction with rapid-onset neuromuscular blocker.

2.1.2. Primary Endpoint

The primary endpoint is the rate of tracheal intubation without major complications defined by the combination of the following criteria:

1) Tracheal intubation after ≤ 2 laryngoscopy
2) Absence of inhalation of gastric fluid through the vocal cords within 10 minutes of anesthetic induction
3) Absence of desaturation is defined by a SpO2 < 95% within 10 minutes of anesthetic induction
4) Absence of severe hemodynamic instability is defined as hypotension (PAM ≤ 50 mmHg) or hypertension (PAM ≥ 110 mmHg) within 10 minutes of anesthetic induction
5) Absence of sustained ventricular rhythm disorder (i.e., requiring pharmacological or electrical intervention to be reduced or for more than thirty seconds), ventricular fibrillation, or cardiac arrest within 10 minutes of anesthetic induction
6) No occurrence of Grade III or IV anaphylactic reaction from the HAS 2013 classification within 10 minutes of anesthetic induction

There is no recommendation for the choice of the primary endpoint in studies evaluating rapid sequence induction modalities in the operating room.

Standard sequence intubation has excellent efficacy, with close to 97% intubation at the first attempt (38). The effectiveness of intubation without rapid-onset neuromuscular blocker with remifentanil is already demonstrated (13-15). The main criterion for choosing between RSIA protocols is the frequency of major complications during intubation. We, therefore, wish to demonstrate the noninferiority of remifentanil on the incidence of uncomplicated intubations.

Rapid sequence induction is considered adequate only if:

- it prevents inhalation of gastric fluid. For the REMICrush study, we defined tracheal intubation without major complications by a composite endpoint adapted from studies evaluating emergency intubation in anesthesia and resuscitation (39-41,47) and based on the major complications associated with emergency anesthesia.
- It allows rapid intubation. An intubation time of fewer than 60 seconds has been proposed, but this threshold is medically objectionable (42). The number of laryngoscopies required for intubation (greater than 2) is recommended as a criterion for a long and complicated procedure (43).
- It avoids desaturation and ventilation with a face mask. According to the French recommendations on difficult intubation, mask ventilation should be initiated as soon as saturation is less than 95% (38,43).

- It does not cause severe hemodynamic instability.
- It does not cause an allergic manifestation whose symptoms threaten life.
- It does not result in death.

Therefore, we have chosen a clinically relevant criterion: the frequency of tracheal intubation without major complications, which covers the main complications feared by the anesthetists during emergency intubation.

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objective(s)

Secondary objectives are

1) Compare the effectiveness of rapid sequence intubation with or without rapid-onset neuromuscular blockers.
2) Compare the tolerance of rapid sequence induction with or without rapid-onset neuromuscular blockers.
3) Comparing the ability to prevent postoperative respiratory complications

2.2.2. Secondary endpoint(s)

The secondary endpoints are:

1. Intubation quality score (IDS-3 score) (see Appendix 10)
2. Cormack-Lehane and POGO score values (see Appendix 10)
3. The frequency of patients for whom a technique to assist tracheal intubation was required
4. The time between the administration of the hypnotic (beginning of anesthetic induction) and the achievement of the 6th capnography curve (effective tracheal intubation)
5. The frequency of patients who have experienced desaturation is between 95% and 80% and < to 80% SpO2 within 10 minutes of anesthetic induction.
6. The frequency of a patient with a severe hemodynamic disorder is defined as a heart rate of less than 45 bpm or a heart rate greater than 110 bpm or a SBP less than 80 mmHg or a SBP greater than 160 mmHg, or a PAM of less than 55 mmHg or an MPA greater than 100 mmHg within 10 minutes of anesthetic induction.
7. The frequency of patients who have had dental or tracheal lesions (endoscopic confirmation for the latter)
8. The frequency of patients who have had an allergic manifestation of grade I or II of the HAS 2013 classification (see Appendix 10) within 10 minutes of anesthetic induction.
9. Post score values in SSPI at one-hour post-extubation (estimation of laryngeal lesions in immediate postoperative) (see Appendix 10)

- The frequency of patients who have had postoperative pneumonia occurring on Day 7 of hospitalization and defined by the presence of a new or progressive infiltrate on chest X-ray or chest computed tomography, associated with one of the following symptoms: the appearance of purulent sputum, change in the formation of chronic sputum, fever ≥ 38 ° C, hyperleukocytosis (>12000 /mL) or leukopenia (<4000/mL), positive blood cultures or isolation of the pathogen on sputum, tracheal aspiration or bronchoalveolar lavage.
- The frequency of patients who presented with postoperative respiratory distress occurring on Day 7 of hospitalization and defined by the combination of a clinical picture of acute hypoxemic

respiratory failure, a PaO2 / FiO2 ratio < 300 mmHg, the presence of new bilateral pulmonary infiltrates on chest X-ray and the absence of an argument for a cardiac origin.
- intra-hospital mortality.

3. TREATMENTS USED DURING THE STUDY

3.1. DESCRIPTION OF THE NECESSARY TREATMENTS AND METHODS OF ADMINISTRATION

3.1.1. Investigational drug(s) / comparator

3.1.1.1. Identification of treatments

Suxamethonium chloride 50 mg/mL inj, ampoule 2 mL
MA for anesthetic induction
Excipients: sodium hydroxide, succinic acid, PPI water
Dosage: 1 mg/kg (actual weight if BMI ≥ 30), single IVD injection
Duration of treatment: single dose

Rocuronium bromide 10 mg/mL inj, 5 mL vial
MA for anesthetic induction
Excipients: sodium acetate, sodium chloride, glacial acetic acid, PPI water
Dosage: 1 mg/kg (ideal weight if BMI ≥ 30), single IVD injection
Duration of treatment: single dose

REMIFENTANIL MYL 1 mg powder for solution for injection or infusion
Active ingredient: Remifentanil hydrochloride, 1 mg, powder for solution for injection or infusion
Holder of the MA: MYLAN SAS laboratory
MA for anesthetic induction in 1997
Excipients: glycine, hydrochloric acid
Dosage: 3 to 4 µg/kg (lean weight if BMI ≥ 30), single IVD injection
Duration of treatment: single dose
Generic for use in the study: none as long as the drug is supplied to the centers by the sponsor.

3.1.1.2. Administration

Suxamethonium chloride: direct intravenous injection at a dosage of 1 mg/kg immediately after injection of the hypnotic. For an ampoule of 2 ml to 50 mg/ml of Suxamethonium Chloride, dilution with 0.9% sodium chloride in a 10 ml syringe, i.e., a final concentration of 10 mg/ml. Suxamethonium chloride should not be mixed in the same syringe with barbiturates or any other alkaline product.

Rocuronium bromide: direct intravenous injection at a dosage of 1 mg/kg immediately after injection of the hypnotic. For 5 ml to 10 mg/ml vials of Rocuronium bromide, administration without dilution is possible. If desired, Rocuronium can be diluted with 0.9% sodium chloride solute or 5% glucose solute or water for injections or Ringer-Lactate solute.

REMIFENTANIL: direct intravenous injection at a dosage of 3 to 4 µg/kg immediately after injection of the hypnotic. For a 1mg vial, dilute a 20 ml syringe to obtain a concentration of 50 µg/ml. One of the following solutions for injection should be used for dilution: water for injection, 5% glucose solution, and 0.9% sodium chloride solution for injection.

3.1.1.3. Dose adjustment

There is no dose adjustment

3.1.1.4. Reference documents

To the extent that investigational medicinal products are used commercially, the reference document for each of them is the SmPC.

3.1.2. Other treatments

3.1.2.1. Auxiliary drugs

The administration of auxiliary treatments is left to the discretion of the doctor in charge of the patient and documented in the observation book. All treatments usually used for the management of a patient in pre, per, and post-induction anesthetic are authorized, including the following non-exhaustive list:

- Injectable barbiturate and non-barbiturate drugs (Thiopental sodium, propofol, ketamine)
- Inhalation anesthetics (Sevoflurane and Desflurane)
- Morphine and non-morphine analgesics (Sufentanil, Alfentanil)
- Curarizing agents (atracurium besylate, cisatracurium besylate)

All treatments will be administered intravenously or by electric syringe push, except for halogenated gases (inhalation using a suitable evaporator).

An adaptation of the dosages may be necessary according to the clinical context by the anesthesiologist-resuscitator in charge of the patient

3.1.2.2. Other non-drug treatments

All medical devices necessary for anesthesia practice will be used per the regulations in force and according to local habits.

3.2. METHODS FOR MONITORING ADHERENCE TO TREATMENT

Since the experimental drugs are administered to a population of patients undergoing anesthesia, compliance can only be excellent. The products are injected directly intravenously by the anesthetist-resuscitator, the IADE, or the internal anesthesia-resuscitation in charge of the patient. The last report on the anesthesia file is the exact dose administered. This information is also reported in the patient's eCRF.

3.3. INVESTIGATIONAL DRUG CIRCUIT

3.3.1. General circuit

The medicines will be presented in their commercial form and original packaging.
Considering the study's design, the sponsor will provide the evaluated product, REMIFENTANIL, to all investigator centers. To do this, the pharmacy of the Nantes University Hospital (Hôtel-Dieu site) will be the coordinating pharmacy of the study. It will ensure the labeling of REMIFENTANIL per the regulations and the supply to pharmacies in the centers according to the rhythm of inclusions.
The center's pharmacy will ensure the reception, storage, and provision of the experimental product according to the center's practice (nominative dispensing or endowment) and traceability. Used and unused investigational products will be destroyed on-site after monitoring and agreement of the sponsor. As this is a commercial form, therapeutic units will not be re-labeled.
Regarding the comparator arm, the rapid-onset neuromuscular blockers will be used according to the practice of the center, taken from the stock of the establishment (SUXAMETHONIUM or ROCURONIUM).

3.3.2. Storage conditions for investigational medicinal products

3.3.2.1. Description of storage at the pharmacy

Storage is carried out at the pharmacy of the investigator center, in a cabinet monitored in temperature, locked (per the regulations of narcotics), with restricted access, and apart from drugs all coming. The product should be stored at a temperature not exceeding + 25 ° C.
The investigator's center will provide rapid-onset neuromuscular blockers (SUXAMETHONIUM or ROCURONIUM).

3.3.2.2. Description of storage in the service

In the department, storage is carried out in a secure cabinet placed in an air-conditioned environment at a constant temperature, locked (per the regulations on narcotics), with restricted access, and apart from all-coming medicines. The product should be stored at a temperature not exceeding + 25 ° C.

3.4. DRUGS AND TREATMENTS ALLOWED AND PROHIBITED

3.4.1. Permitted treatments

All treatments usually used for the management of a patient in pre-and post-induction anesthetic are authorized, including the following non-exhaustive list:

- Sympathomimetics IV

- Parasympatholytics
- Antibiotics and antifungal
- Hypnotic and sedative agents
- Antiemetics
- Glucocorticoid hormones
- Electrolyte solution and blood-derived products
- Antihypertensive

3.4.2. Unauthorized processing

No treatment is prohibited in the protocol

In case of difficult intubation not foreseen as defined by the protocol, the administration as rescue therapy of rapid-onset neuromuscular blockers or remifentanil is also authorized, at the discretion of the medical doctor in charge of the patient.

3.4.3. Emergency treatment

Emergency treatments include:

- In cardiac arrest, the implementation of resuscitation procedures is immediate and complies with local care procedures or defaults, the ILCOR recommendations of 2015. Treatments aimed at correcting anaphylactic shock, negative inotropic effects of anesthetic agents, underlying metabolic abnormalities (hyperkaliemia,) or collapse of ventilation are preferred.

- In the event of grade II or III anaphylactic manifestation, intravenous adrenaline will be administered urgently per local procedures and default according to SFAR's 2010 clinical practice guidelines. Emergency antagonization of ROCURONIUM by SUGAMMADEX may be used at a dose of 16mg/kg (ideal weight if Body Mass Index ≥ 30) in case of grade IV manifestation (drug available in the stocks of investigator centers)

- In case of difficulty of intubation, ventilation, or vomiting during the procedure, SUXAMETHONIUM and ROCURONIUM may be used in the REMIFENTANIL group (and vice versa) at the dosages indicated in the protocol. Emergency antagonization of ROCURONIUM by SUGAMMADEX may be used at a dose of 16mg/kg (ideal weight if BMI ≥ 30). In any case, the procedure will follow the 2006 SFAR expert conference updated in 2017.

- In case of poorly tolerated bradycardia, a parasympatholytic (ATROPINE) may be administered as an IVD.

- In case of hypotension, filling with a crystalloid or colloidal solute and administering sympathomimetic drugs (EPHEDRINE, NEOSYNEPHRINE, NORADRENALINE, ADRENALINE) may be used in IVD or electric syringe.

- In the case of hypertension, the choice of administering an IV antihypertensive will be left to the free choice of the anesthesiologist after the failure of the deepening of the anesthesia.

- In the case of malignant hyperthermia, treatment with DANTROLENE will be initiated per the recommendations of experts for the risk of malignant hyperthermia in anesthesia-resuscitation of the SFAR published in 2013.

All the treatments mentioned above are drugs immediately available in any operating room where acts under general anesthesia are performed.

4. STUDY POPULATION

4.1. DESCRIPTION OF THE POPULATION

The number of patients needed for statistical analyses is 1150.

The study population comprises hospitalized adult patients requiring rapid sequence induction in the operating room or shock room.

Participation in the study will be offered to the patient during the preoperative anesthesia consultation by the anesthetist, with the delivery of the information note and consent form. An emergency procedure will be used if it is impossible to deliver precise and fair information to the patient during the study's inclusion period.

Individuals participating in the research will not be able to participate simultaneously in another intervention research (excluding intervention research at minimal risk and constraint) for 24 hours following the RPIA.

4.2. INCLUSION CRITERIA

- Woman or man.
- Aged 18 to 80
- Procedure requiring general anesthesia with orotracheal intubation
- Anesthetic management with rapid sequence induction indication
- The risk of inhalation of gastric fluid is defined by, or less one of the following criteria: fasting period < 6:00 am, digestive occlusion, functional ileus, vomiting < 12:00 hours, orthopedic trauma < 12:00 hours, history of severe GERD for hiatal hernia or gastroparesis or dysautonomia or gastroesophageal surgery
- Existence of informed and signed consent of the patient, or failing that, emergency procedure

4.3. NON-INCLUSION CRITERIA

- Intubation impossible planned
- Known or suspected history of allergy to rapid-onset neuromuscular blockers or remifentanil
- History of neuromuscular disease contraindicating the use of rapid-onset neuromuscular blockers
- History of prolonged neuromuscular blockade.
- History of malignant hyperthermia
- Preoperative respiratory distress (SpO2 < 95% in ambient air)
- Preoperative shock (under vasopressor)
- Patient in cardiorespiratory arrest
- Women of childbearing potential with a progressive pregnancy or clinical signs suggestive of pregnancy or not having contraception or unprotected sex within 15 days of the last menstruation.

- Patients under guardianship or curatorship
- Intended use of ETOMIDATE for rapid sequence induction

5. DESIGN AND CONDUCT OF THE STUDY

5.1. STUDY SCHEDULE

STUDY CALENDAR

Actions	J0 (date of surgery)	J7
Patient Information*	X	
Informed consent or emergency consent	X	
Randomization	X	
Measurement of efficacy and safety per and post-induction anesthetic	X	
Effectiveness and safety measurement in SSPI	X	
Effectiveness and safety measurement on Day 7		X
Adverse events	X	X

5.2. GENERAL RESEARCH METHODOLOGY

The search has the following characteristics:
-Phase III drug
-Multicentric
-Prospective
-Controlled
-Randomized
-With stratification on the type of material used for intubation: (Macintosh laryngoscope or video-laryngoscope) and the leading risk factor for inhalation of gastric fluid (occlusive syndrome versus other causes)
-In parallel groups
-Single-blind
-Noninferiority

The scheme of the study is as follows:

Inclusion phase:

All patients admitted to the operating room or shock room requiring rapid sequence anesthetic induction for an act requiring general anesthesia with orotracheal intubation will be offered to participate in the study.

Screening is provided by the investigating physicians taking care of these patients during the anesthesia consultation. They select patients with all inclusion criteria (see inclusion criteria paragraphs 4.2 and 4.3) and seek consent to participate in the study (see information and collection of the consent). The investigating physician shall also determine the most appropriate anesthetic regimen for the patient to undergo the invasive procedure, in particular the risk factors for inhalation (time of the last meal, presence of recent nausea or vomiting, occlusive syndrome, the existence of reflux or hiatal hernia, history of gastroesophageal surgery) and the choice of the laryngeal exposure device, and evaluates the essential elements of the anesthesia consultation namely: medical-surgical history, allergies, weight, height, risks of ventilation with a complex mask and difficult intubation according to the recommendations of the SFAR, choice of hypnotic. The patient's wish is also considered when there is a possible choice between locoregional anesthesia and general anesthesia.

Randomization phase:

The investigating physician performs the randomization of the patient, which is done between 2 groups with stratification on the material used for intubation and the leading risk factor for inhalation of gastric fluid.
- The control group (GC): In addition to the hypnotic chosen by the investigator, suxamethonium or rocuronium is injected into IVD at a dose of 1mg/kg (actual weight and ideal weight, respectively, if BMI ≥ 30) immediately after administration of the hypnotic. Intubation occurs at the end of fasciculations with suxamethonium (30 to 60 seconds in the absence of fasciculation) or 30 to 60 seconds after rocuronium injection. An experienced person carries out the intubation: a qualified anesthetist doctor, a graduate IADE or an intern enrolled in the DES of anesthesia-resuscitation and having validated at least four semesters, including two in the anesthesia sector.

- The Remifentanil group (GR): In addition to the hypnotic chosen according to the clinical situation, remifentanil is injected into IVD at the dosage of 3 to 4µg/kg (lean weight if BMI ≥ 30) immediately after administration of the hypnotic. Intubation takes place 30 to 60 seconds after remifentanil administration by a graduate MAR, a graduate IADE or an intern enrolled in the DES

of anesthesia-resuscitation and having validated at least four semesters, including two in the anesthesia sector.

Rapid sequence anesthetic induction sequence

The rapid sequence induction sequence refers to the SFAR 2003 recommendations on airway management in adult anesthesia except for difficult intubation and SFAR 2017 on difficult intubation and extubation in adult anesthesia (available http://sfar.org/referentiels/). It consists in our study of the following steps:

- 1st step: Denitrogenation with a face mask with 100% FiO2 for 3 minutes or until theoretical obtaining a FeO2> 90%. The patient's installation is left to the free choice of the MAR in charge of the patient. In case of obesity, a denitrogenation in positive pressure or via a high-flow nasal oxygen therapy device will be left to the free choice of the MAR in charge of the patient.

- 2nd step: IVD injection of the hypnotic on a peripheral or central venous route previously controlled. The time between the beginning of pre-oxygenation and the administration of the hypnotic is the free choice of the MAR. Nevertheless, this period and the value of FeO2 will have to be filled in. In both groups, the realization of a Sellick maneuver is left to the discretion of the MAR in charge of the patient.

- 3rd step: injection of rapid-onset neuromuscular blockers (SUXAMETHONIUM or ROCURONIUM) or REMIFENTANIL immediately after hypnotic depending on the randomization group. The time between the administration of the hypnotic and the administration of rapid-onset neuromuscular blockers or remifentanil should be indicated.

- 4th step: At the end of fasciculations with suxamethonium (30 to 60 seconds in the absence of fasciculation) or after 30 to 60 seconds for ROCURONIUM or REMIFENTANIL, beginning of tracheal exposure with the laryngoscopy device chosen during randomization. The size and type of probe used for orotracheal intubation are left to the free choice of the MAR in charge of the patient. The time between the start of administration of the hypnotic and the orotracheal intubation defined by the presence of 6 cycles of EtCO2 on the scope should also be indicated.

In both randomization groups, in case of unforeseen intubation difficulty accompanied by desaturation (SpO2 <95%) and the need for ventilation with a face mask, a so-called rescue administration of SUXAMETHONIUM [1 mg/kg (actual weight if BMI ≥ 30)], ROCURONIUM [1 mg/kg (ideal weight if BMI ≥ 30)] or REMIFENTANIL [3 to 4 µg/kg (lean weight if BMI ≥ 30)] is left to the free choice of the anesthetist in charge of the patient. The rest of the procedure refers to the recommendations of the SFAR by following the unplanned difficult intubation algorithm.

It should be noted that:

In both groups, it is not permitted by the protocol to use in the operating room before the first laryngoscopy any other medicinal product for hypnotic, muscle relaxant, or intubation facilitating purposes (LIDOCAINE, CATAPRESSAN, morphine other than REMIFENTANIL in the REMIFENTANIL group, SEVOFLURANE, MIDAZOLAM). These drugs can be freely used by the MAR in charge of the patient during this first laryngoscopy if it is successful or beyond the 2nd laryngoscopy in case of unforeseen difficult intubation.

In both groups, the oral or IV administration of premedication and the use of morphine for analgesia purposes (and no anesthetic) before the initiation of anesthesia and left to the free choice of the MAR in charge of the patient and will have to be informed.

After intubation, patients are ventilated in controlled assisted ventilation with a current volume between 6 and 8ml/kg of ideal weight with a PEP of at least five cmH20, a ventilatory frequency for EtCO2 objectives between 35 and 45 mmHg, and a FiO2 for SpO2 goals between 95 and

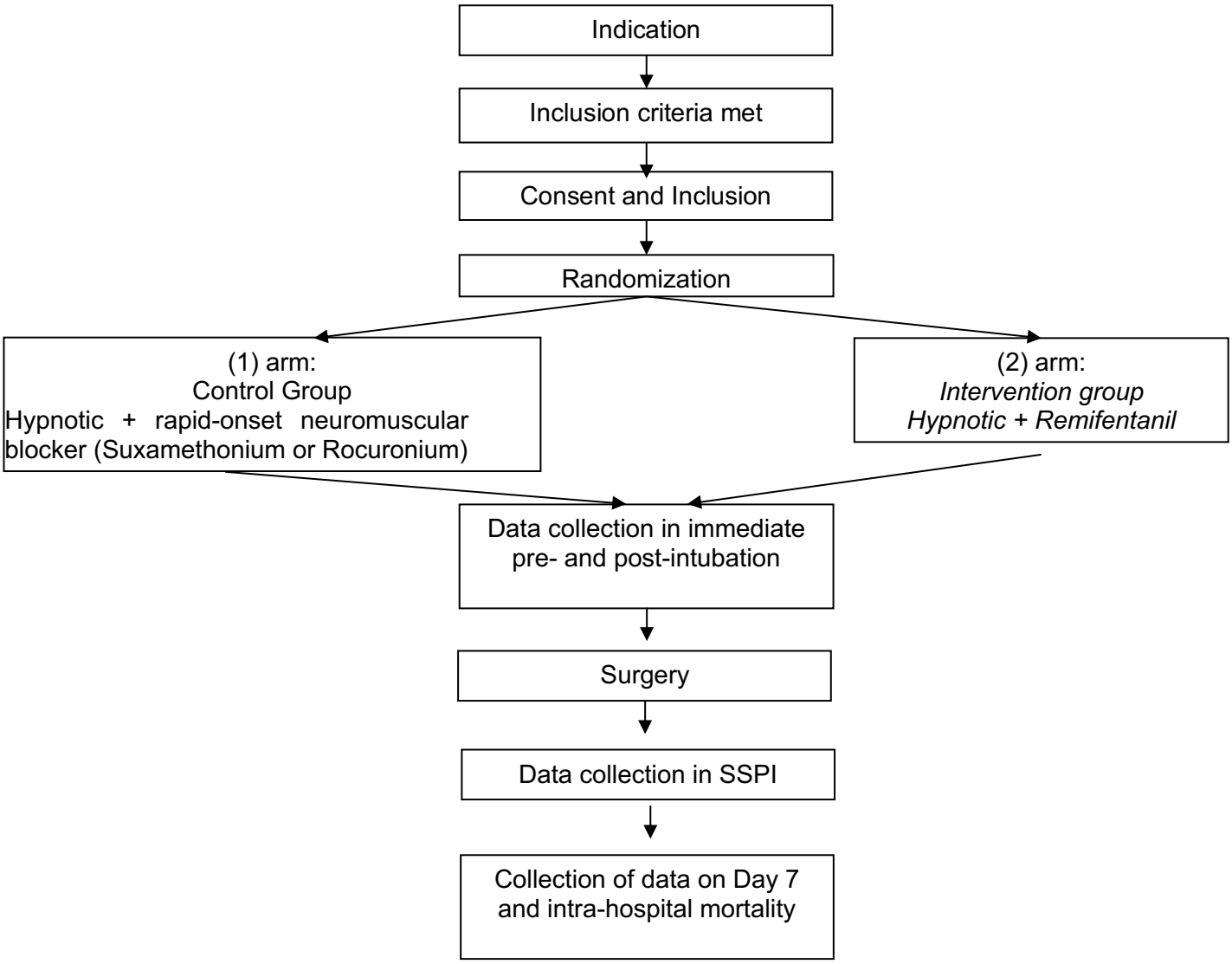
100%. The success of intubation is defined by six cycles of adequate ventilation (exhaled CO2 curves) and symmetrical bilateral pulmonary auscultation

Data collection.
Data collection is done on an eCRF. The source data are collected on a paper version of the eCRF.

In the post-interventional monitoring room (SSPI)
The data collection is completed on the eCRF. Particular attention is paid to the achievement of a score estimating the laryngeal lesions in SSPI at 1 hour of extubation (POST Score), the use or not during the surgery of neuromuscular blockers, the use or not of a neuromuscular blockade monitoring as well as the occurrence of nausea/vomiting after extubating.

A Day 7:
The collection of data on the occurrence during hospitalization of an episode of postoperative pneumonia, postoperative respiratory distress, admission to intensive care or continuing care unit, or death.
In case of discharge from the hospital before J7, the patient will be considered free of these complications.

5.3. DIAGRAM OF THE STUDY



5.4. DESCRIPTION AND JUSTIFICATION OF THE TREATMENT REGIMEN

REMIFENTANIL is administered as ivd on a previously controlled peripheral or central venous route. Treatment is given only once at a dose of 3 to 4 µg/kg (lean weight if BMI ≥ 30). This dose-weight corresponds to the best benefit-risk ratio (benefit in terms of intubation quality, risk in adverse events, including hemodynamics) found in the medical literature (11-15, 19-21, 35).

Due to the need to secure the airways early, a slow intravenous bolus injection of 1 µg/kg suggested for non-urgent tracheal intubation cannot be respected.

5.5. IDENTIFICATION OF ALL SOURCE DATA NOT INCLUDED IN THE MEDICAL RECORD

The study-specific data that can be collected directly in the observation book are as follows:

- POST score (estimate of laryngeal lesions in immediate postoperative)
- The time between administration of the hypnotic and the 6th capnography curve (effective tracheal intubation)
- Intubation quality score (IDS-3 score)

5.6. RULES FOR STOPPING A PERSON'S PARTICIPATION

5.6.1. Criteria for premature termination of a person's participation in research

Study exits will only be effective after the investigator and sponsor confirm.
When a patient is discharged from the study, data about them will no longer be collected.

Withdrawal of patient consent:
This is a criterion for permanent cessation of participation in the study. Data obtained before it has been removed will be used. The data collected after the withdrawal of consent will not be used for this research and will remain intended for the strict use of the care. These patients will still be encouraged to continue the entire clinical follow-up to detect the possible occurrence of side effects. Pharmacovigilance data will be retained for the safety report of the study.

Violation of the Protocol:
- Failure to comply with the inclusion rules will not result in the termination of the protocol or the exclusion of patients. A *modified intention-to-treat analysis* will be performed (patients with all inclusion criteria and no non-inclusion criteria).

- Deviation of administration of the treatment: the treatment is administered only once during the anesthetic induction on a previously laid and controlled venous route. The observance will therefore be excellent. A deviation from the administration protocol will not result in the discontinuation of the protocol or the exclusion of patients. Deviations from treatment will be

collected. A *per-protocol analysis* will be performed (patients who received in 1st *intention the* treatment assigned by randomization).

The lost to follow-up:
Patients cannot be lost to follow-up during the perioperative phase. All means will be implemented to collect data on Day 7. In case of discharge from hospitalization before J7, without re-hospitalization during the first week, the patient will be considered free of complications. In case of hospitalization of more than seven days, only the date of the end of hospitalization or the date of death during the same hospitalization will be collected. Anesthesia reports and discharge letters will report the patient's inclusion in the REMICrush study.

Deaths:
The patient's death within seven days of the operation leads to a premature cessation of participation in the research. The data of these patients will be kept in the final analysis.

Use of rapid-onset neuromuscular blockers in the REMIFENTANIL group:
Patients in the "REMIFENTANIL" group who receive "rescue therapy" rapid-onset neuromuscular blockers will be followed clinically, and their data will be used in the intention-to-treat analysis and excluded from the per-protocol analysis. These patients will remain analyzed in the "REMIFENTANIL" group in which they were randomized. The frequency of patients receiving rescue therapy in the REMIFENTANIL group will be studied.

5.6.2. Procedures for premature termination of a person's participation in research

Data concerning exclusions and early terminations will be communicated to the promoter without delay in the event of a Serious Adverse Event or a new event.
This statement is made on the eCRF and must include the day of the protocol's termination concerning inclusion and the reasons for the termination of the protocol.
The investigator shall also complete the data collection book, particularly the part concerning deviations from the protocol where he justifies the discontinuation or exclusion of the patient.
The premature discharge of a patient from the study will not change his usual management concerning his pathology. He will not have the follow-up specific to the study (control on Day 7).
In case of exit following an adverse event, serious or not, an appropriate follow-up will be proposed.

Treatment-related side effects (local and general) are immediate and last only within hours of anesthetic induction. The investigator uses all the means at his disposal (mail, telephone) to ensure that side effects do not occur during the first 14 days after the injection of the treatment. In case of cessation of participation before the end of the routine follow-up provided by the study, the investigator ensures a clinical follow-up of the patient until regression of the possible side effects of the treatment under investigation.

5.6.3. Criteria for stopping some or all of the research (excluding biostatistical considerations)

The end of the research will correspond to the end of the participation of the last patient included in the study, after adjusting the number of subjects needed according to the number of patients lost to follow-up and excluded to maintain sufficient power of the study

Part or all of the study may be definitively or temporarily decided by the decision of the ANSM, the CPP, and the Sponsor of the study after consulting the CIS

In all cases:
- A written confirmation will be sent to the coordinating investigator of the study (specifying the reasons for premature discontinuation) as well as to the principal investigator of each center
-All patients in the study will be informed and have to carry out their preterm discharge visit.

5.7. MODALITY OF PATIENT CARE AT THE END OF THE RESEARCH

Not applicable

6. DATA MANAGEMENT AND STATISTICS

6.1. COLLECTION AND PROCESSING OF STUDY DATA

6.1.1. Collection, processing, and circulation of data

Data collection from each person suitable for research is carried out through an electronic observation book (CRF). Each person responsible for this collection (investigator, ARC monitoring, TEC ...):

- is identified in the delegation table of responsibilities of each center (kept in the investigator binder)
- will have a "user" account with the computer rights specific to his role (right to enter or modify data, right to lock, monitor, or sign an eCRF page)

The entry, consultation, or modification of the data will only be possible via the pages of the eCRF (input masks), on https://nantes-lrsy.hugo-online.fr/CSonline

This data is stored directly from the eCRF in a database hosted on a dedicated server, with controlled access (username/password) depending on the user's role. Any addition, modification, or deletion of data will be traced in a non-modifiable electronic file (the audit trail).

6.1.2. Participant Identification

The principal investigator and co-investigators undertake to keep confidential the identities of the persons suitable for research by assigning them a code.

This code is used for all eCRF, and all documents (reports of imaging examinations, biology, ...) are attached. This is the only information that allows you to make the correspondence with the participant.

The coding rule is as follows: 1st letter of the first name + 1st letter of the name + month and year of birth, Inclusion number

6.2. STATISTICS

It is planned to include 1150 patients.

The statistical analyses will be carried out by Fanny FEUILLET, biostatistician – Methodology and Biostatistics Platform of the Research Directorate (Nantes University Hospital) & INSERM U1246 SPHERE (University of Nantes).

Sas software (version 9.4 NC, USA) will be used for statistical analyses.

6.2.1. Description of the planned statistical methods, including the schedule of planned interim analyses

The statistical analysis will be carried out in line with the recommendations in force for the analysis of noninferiority trials *(Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006; 295: 1152-60).*

Qualitative data will be described for all patients and in each of the two groups in terms of the number and percentage of each modality. Quantitative data will be described in terms of mean/standard deviation or median/interquartile interval depending on their distribution.

For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. The confidence interval will be calculated by a logistic model considering stratification on the type of material used for intubation and bowel obstruction (yes vs. no) and will be adjusted on the center. According to the assumptions we have defined, the group without rapid-onset neuromuscular blockers (i.e., with remifentanil) will be considered non-inferior to the group with rapid-onset neuromuscular blockers if the upper bound of the 95% CI does not exceed 7% (margin of noninferiority).

Subgroup analyses will be carried out on the main criterion, following the same methodology:

- Stratification criteria:
  - *Type of equipment used for intubation (Macintosh laryngoscope vs. video-laryngoscope
  - *Primary risk factor for inhalation of gastric fluid (occlusive syndrome/bowel occlusion vs. other causes)
- Age groups (18-40; 40-60; 60-80)
- Mallampati score (I and II vs III and IV)
- Method of care (urgent or non-urgent gesture)
- BMI sup to 30 kg/m² (yes vs. no)
- ASA score (1-2 vs. 3-4)
- Choice of propofol as hypnotic (yes vs. no)

For secondary endpoints, the comparison between the two groups will be estimated by logistic models for binary variables (postoperative pneumonia, postoperative respiratory distress); by linear models for continuous variables (heart rates, systolic blood pressure, etc.); by Poisson models for the number of events (number of episodes of allergic manifestation, number of episodes of desaturation, etc.). All analyses will be adjusted on the stratification criteria.

6.2.2. Statistical justification of the number of inclusions

The incidence of severe complications in our population related to rapid sequence intubation with rapid-onset neuromuscular blockers is between 12 and 30%, depending on studies and definitions (40,40,44,45). In a monocentric retrospective analysis of the Nantes University Hospital database performed on 100,000 general anesthesia including 8500 rapid sequence inductions, we observed an incidence of significant complications of 20%.

We hypothesized an incidence of intubation without major complications of 80% in the rapid-onset neuromuscular blockers group. The noninferiority margin is set at 7% (i.e., 8.875% in relative risk) so as not to tolerate a change in relative risk of more than 10% (46). Therefore, it is appropriate to include 575 patients per group (1150 patients in total) to ensure a power of 80% with an alpha risk of 5%.

6.2.3. Expected statistical significance

The degree of statistical significance will be 5% for the final analysis of the primary and secondary endpoints. The noninferiority threshold for the primary outcome study is set at 7%.

6.2.4. Statistical criteria for stopping search

Not applicable

6.2.5. Method of accounting for missing, unused, or invalid data

Missing data will be described in terms of numbers and corresponding percentages for each group. The presence of possible imbalances in terms of the proportion of missing data between the two groups will be assessed by proportional comparison tests ($\chi 2$ tests or exact Fisher tests).

As the primary endpoint is identified within 10 minutes of anesthetic induction and death is included in the endpoint, no missing data are expected.

For the evaluation criteria at seven days postoperative, a pejorative imputation will be applied in case of missing data (death of the patient *or* other).

6.2.6. Managing changes to the initial strategy analysis plan

No interim analysis is planned.

A statistical analysis plan will be drawn up before the database is frozen and will detail any changes made to the statistical paragraph of the protocol.

The study may be stopped early by the decision of the sponsor if the frequency of SAEs is high.

6.2.7. Choosing who to include in analyses

The analyses will be applied to the per-protocol (PP) and intention-to-treat (ITT) populations.

ITT: All randomized patients. The data will be imputed for patients for whom the main criterion would not be available (withdrawal of consent).

PP: All randomized patients, except patients who do not verify the inclusion/non-inclusion criteria, patients for whom the primary endpoint is unavailable, and patients who have not received the treatment assigned to them by randomization.

6.2.8. Randomization

The randomization list will be created by the statistician of the Department of Research Promotion of the University Hospital of Nantes. Randomization will be stratified on the type of material used for intubation (Macintosh laryngoscope or video-laryngoscope) and the leading risk factor for inhalation of gastric fluid (occlusive syndrome vs. other causes). The list will be made in blocks according to a 1:1 ratio.

Randomization will then be done under the Clinsight software by connecting to the site: https://nantes-lrsy.hugo-online.fr/CSOnline/. The connection will be made through a login and a password (issued by the Clinical Research Promotion Unit of the Nantes University Hospital).

The following information must be provided:
-First initial of the name
-First initial of the first name
-Date of birth
-Compliance with inclusion and non-inclusion criteria (yes/no)
-Signature of informed consent (yes/no)

Randomization will be done by the center's principal investigator or their delegate (the person whose name will be mentioned in the delegation of responsibilities sheet of the investigator binder).

The number and randomization arm will be assigned automatically during randomization. Confirmation by email will be sent to the person who carried out the randomization and to all concerned people.

Randomization will be the responsibility of statisticians from the Clinical Research Promotion Unit of Nantes University Hospital. A Guide to Using Clinsight will be provided to each investigator.

7. PHARMACOVIGILANCE AND ADVERSE EVENT MANAGEMENT

7.1. DEFINITIONS

Vigilance	It is the monitoring of medicines, medical devices, and other health products. It also consists of preventing the risk of adverse effects resulting from their use, whether this risk is potential or proven.
Adverse Events (AE)	Any harmful manifestation occurring in a person who lends himself to research involving the human person, whether or not that manifestation is related to the study or the product on which the research relates.
The intensity of Adverse Events (AEi)	It will be rated according to the following criteria: *1 = benign* *2 = moderate* *3 = severe* *4 = life-threatening* *5 = death* In the particular case of anaphylaxis, the HAS 2013 classification will be applied, namely: Grade I Isolated mucocutaneous signs; Grade II Moderate multi-organ involvement (at least two functions affected), Grade III Severe multi-organ involvement, Grade IV Circulatory or respiratory arrest
Adverse reactions (AEs)	An undesirable event occurring in a person who is suitable for research involving the human person, where that event is related to the study or to the product to which the research relates.
Adverse reaction of an investigational medicinal product	Any harmful and unwanted reaction to an investigational drug regardless of the dose administered. (also applicable to cell therapy products)
Effects/ Serious Adverse Events (SAEs)/ (EvIG)	Any adverse reaction/event that: * entails death, * involves the vital prognosis, * results in temporary or permanent incapacity or invalidity, * requires or prolongs hospitalization of the patient, * leads to a congenital or neonatal anomaly, * is medically important (the EMA defines the list of medically important effects/events).
Unexpected Adverse Reactions (EIIs)	Any adverse reaction of the nature, severity or course does not agree with the information relating to the products, procedures, and methods used during the research.
New development	Any new data that may lead to a reassessment of the report of the benefits and risks of the research or the product being

	researched, to changes in the use of that product, in the Conduct of the study, or the research documents, or to suspend or discontinue or modify the protocol of the research or similar research. For trials of the first administration or use of a health product in people who do not have any conditions: any serious adverse reaction.
Abuse	Excessive intentional, persistent or sporadic drug use is accompanied by harmful physical or psychological reactions.
Overdose	Administration of an amount of the drug, given during administration or cumulatively, that is above the maximum recommended dose according to the rules of compliance or use of the product. Clinical judgment should always be applied. (real overdose: due to too much gross amount/relative overdose: due to the patient's predisposing factors such as renal failure, hypo-albuminemia ...)
Misuse or off-label use	Situation where the product is intentionally used in a manner that does not comply with the specifications of use of the product (e.g., route of administration/dosage or indication different from that listed in the reference document).
Quality defect	Non-compliance with the specifications described in the MA /CE marking/technical documentation dossier or deviation from Good Manufacturing Practices (GMP) / Good Distribution, Preservation, and Labelling Practices.
Medication Error (ME)	Corresponds to any unintentional, proven (or potential) omission or performance of an act that occurred during the care process, *in the circuit (from manufacture to administration)* involving a product that may cause a risk or adverse event for the patient. The risk of error or potential error concerns situations where the error did not occur, was intercepted but could have happened.

7.2. LIST OF EXPECTED AES

For this protocol, the most frequent expected AEs for the treatments under study are:

For REMIFENTANIL:
- Rigidity of the skeletal muscles
- Bradycardia
- Hypotension
- Postoperative hypertension
- Acute respiratory depression, apnea
- Nausea, vomiting
- Pruritus
- Postoperative chills

For SUXAMETHONIUM:
- Increased kalemia.
- Allergic or non-allergic anaphylactic reactions (non-specific histamine-liberation): pruritus, erythematous reactions at the injection site, or systemic reactions such as generalized erythema (often inaugural), cardiovascular disorders, bronchospasm, anaphylactic shock that can be severe (or even fatal).

- Bradycardia, rhythm disorders.
- Low blood pressure.
- Transient increase in intracranial pressure*.
- Transient increase in intraocular pressure*.
- Muscle pain, feeling of aches.
- Transient increase in intragastric pressure*.

For ROCURONIUM:
- Anaphylactic and anaphylactoid reactions and associated symptoms.
- Tachycardia
- Hypotension
- Reaction and pain at the injection site
- Prolonged neuromuscular block, lengthening of the recovery time after anesthesia

AEs expected to use REMIFENTANIL, ROCURONIUM, and SUXAMETHONIUM as part of their MAs are listed in their respective SMEs.

For this Protocol, the expected AEs for medicinal products and medical devices associated with anesthetic induction shall be listed in the respective SMRs of medicinal products and package leaflets of the instruments used in the context of their marketing authorizations.

For this Protocol, the expected AEs for the anesthetic induction procedure are:

- Desaturations < 95%,
- Hypotension or severe hypertension
- Cardiac arrests
- Deaths during intubation
- Unplanned difficult intubations
- Heart rhythm disorders
- Esophageal intubations
- Agitations
- Regurgitations/inhalations
- Dental breakage or tracheal lesions

In the context of this protocol, adverse events related to pathology or management in the operating room or shock room and which are those conventionally observed in this context will not be collected under this protocol, except for those related to the study drugs or its comparators which will be well managed and reported if necessary.

7.3. ADVERSE EVENT MANAGEMENT

7.3.1. AE Compendium

Any AE (unless otherwise specified in 9.2), whether expected or unexpected, serious or non-serious, should be collected in real-time in the study's eCRF.

7.3.2. Notification of EvIG/ISGs

Any Expected or Unexpected EvIG/SAE shall be notified to the sponsor without delay from the day the investigator becomes aware of it. The information provided and the attached documents must be complete, precise, clear (do not put an abbreviation...), and code. Pregnancy, overdose, misuse, errors or risk of errors, and quality defects are also notified to the sponsor even if there are no associated adverse events.

7.3.3. Notification period

Any EvIG/SAE, whether expected or unexpected, shall be notified to the sponsor if it occurs for a research participant from the date of signature of consent and the entire duration of the participant's follow-up in the trial.

7.3.4. Independent Oversight Committee (IIC)

The mission of the Independent Supervisory Committee is to monitor the clinical and biological tolerance of the study's treatments.

It is responsible for informing the Scientific Committee in its decisions to amend or discontinue the trial. The list of CIS and Scientific Committee members is attached as Annex 10.

7.4. MODALITIES AND DURATION OF FOLLOW-UP OF PEOPLE FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

7.4.1. Action to be taken for patients concerned by the AEs

Any adverse events, serious or non-serious, whether expected or unexpected, must be followed until healing, consolidation, or death (closed event).

8. ADMINISTRATIVE AND REGULATORY ASPECTS

8.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

The medical data of each patient will only be transmitted to the sponsor or any person duly authorized by him and, where appropriate, to the authorized health authorities, under conditions guaranteeing their confidentiality.
The sponsor and the supervisory authorities may request direct access to the medical record to verify the procedures and data of the clinical trial and within limits permitted by laws and regulations.
The data collected during the test will be subject to computer processing per the requirements of the CNIL (Compliance with the MR01).

8.2. TRIAL MONITORING

Monitoring will be carried out by the promotion department of the Research Directorate. A Clinical Research Associate (ARC) will regularly visit each site (investigator and pharmacy) to carry out quality control of the data reported in the observation books.

The protocol was classified according to the estimated level of risk to the patient undergoing research. It will be followed as follows:

Risk B: foreseeable risk close to that of usual care

The frequency and intensity of monitoring depend on the risk of the study. The level of risk should be determined in consultation with the coordinating investigator, the CRA and the project leader before the start of the study. A monitoring plan, validated by the investigator, the project manager, and the MONITORING ARC defines the data that will be monitored and the frequency of visits
On-site monitoring visits will be organized after an appointment with the investigator. The CRAs will have to be able to consult on each site:
- the patient data collection books included,
- patients' medical and nursing records,
- the investigator's binder
- places of storage and dispensing of medicinal products

8.3. INSPECTION / AUDIT

As part of this study, an inspection or audit may take place. The promoter and participating centers must be able to give access to the data to inspectors or auditors.

8.4. ETHICAL CONSIDERATIONS

8.4.1. Written informed consent

Rapid sequence anesthetic induction is a standard care procedure in the operating room.

The investigator, therefore, undertakes to obtain the free and informed consent of the person, collected in writing, after providing him with the protocol information (information note and consent collection form in Annexes 4, 6). He will give him a copy of the information note and a consent form. The person can only be included in the study after reading the information note and signing and dating the consent form after having had time to reflect. The investigator must also sign and date the consent form. This document will be issued on paper in at least two copies so that the patient and the investigator can keep a copy. The investigator's original will be filed in the investigator's filing cabinet. In case of duplicate signed consent, the investigator keeps the original, and the duplicate is given to the patient.

8.4.1. Procedures for obtaining consent in an emergency situation or for an adult unable to express consent

If the investigator can't provide clear and fair information to the patient within the maximum period of inclusion of the study (e.g., urgent surgical procedure, polytrauma, state of confusion), an emergency procedure will be made available to the investigator to facilitate the inclusion of the patient without delaying the medical-surgical management

- Situation N°1: a trusted person or close present

Information to the trusted person or relative via the specific information note (Annex 8). The written consent of the authorized person or relative will be obtained (Appendix 7). The investigator must also sign and date the consent form. This document will be issued on paper in at least two copies so that the patient and the investigator can keep a copy. The investigator's original will be filed in the investigator filing cabinet. In case of duplicate signed consent, the investigator keeps the original, and the duplicate is given to the patient.

- Situation N°2: trusted or close person who cannot be present within the maximum period of inclusion of the study

The investigating physician must complete, date, and sign the emergency procedure certificate (Annex 11). This document will be issued on paper in at least two copies so that the patient and the investigator can keep a copy. The investigator's original will be filed in the investigator filing cabinet. In case of a duplicate signed certificate, the investigator keeps the original, and the document is given to the patient.

Whatever the situation, the patient's free, informed, and written retrospective consent will be systematically sought a posteriori as soon as the patient can express his approval. Patients will thus be informed a posteriori comprehensively and fairly, in understandable terms, of the objectives and constraints of the study, of the possible risks involved, of the necessary monitoring and safety measures, of their rights to refuse to participate in the research or of the possibility of withdrawing at any time. All this information can be found on an information note, and the consent form is given to the patient (see Annexes 5 and 6). This retrospective consent will be obtained by the investigator or a physician representing them before final inclusion in the study. A copy of the

information and consent form signed by both parties will be given to the patient. The investigator will keep the original.

If death prevents fair consent, the patient's consent cannot be obtained. Still, the data collected from these patients will be used because their exclusion would significantly bias the study results, which aims, among other things, to compare the tolerance of rapid sequence induction with or without rapid-onset neuromuscular blockers.

8.4.2. Committee for the Protection of Persons

The promoter undertakes to submit the study project to the prior authorization of a Committee for the Protection of Persons (CPP).

8.5. DECLARATION TO THE COMPETENT AUTHORITIES

This protocol will be the subject of an application for authorization from the ANSM.

8.6. AMENDMENTS TO THE PROTOCOL

The promoter will send requests for substantial modifications for authorization to the ANSM and for authorization/information to the committee for the protection of persons concerned per the law in force and its implementing decrees.
The amended protocol must be the subject of a dated updated version.
The patient information and consent forms will be subject to change if necessary.

8.7. FINANCING AND INSURANCE

The promoter ensures the financing of the study and takes out an insurance policy guaranteeing the financial consequences of his civil liability under regulations.

8.8. PUBLICATION RULES

A copy of the publication will be given to the University Hospital of Nantes, the promoter of the study, which will necessarily be cited.

The editorial board is composed of the scientific committee. Signatories are the coordinating investigator (Dr. Grillot) and the principal investigator of the study (Pr Roquilly), and as such, respectively, the first and last signatories, the statistician-methodologist, and such penultimate signatory. The 2nd (*equally participated with the 1st author), 3rd places (and so on) will be

allocated to the centers outside Nantes, having achieved a minimum of 60 inclusions (in order of the most significant number to the smallest number of inclusions).

The sponsor will increment the European Union database of the clinical trial results as soon as the originator publication resulting from this work is effective and in order not to prejudice the protection of intellectual property.

8.9. ARCHIVING SOURCE DATA

The investigator must retain all information relating to the study for at least 15 years after the end of the study. At the end of the study, the investigator will receive a copy of each patient's data from their center sent by the sponsor.

LIST OF ANNEXES

Appendix 1: List of Investigators
Appendix 2: Protocol Summary
Appendix 3: Bibliographic References
Appendix 4: Patient Information Note (excluding emergency procedure)
Appendix 5: Patient Information Note (Lawsuit)
Appendix 6: Patient Consent Collection Form
Appendix 7: Consent Collection Form – Relative/Trusted Person
Appendix 8: Information Note Close/Trusted Person
Annex 9: Composition of the Independent Oversight Committee and the Scientific Committee
Appendix 10: Scores and classifications used in the study
Appendix 11: Emergency Procedure Certificate

REMICrush protocol

EudraCT number: 2019-000753-31

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"Evaluation *of REMIFENTANIL as a replacement for rapid-onset neuromuscular blockers for rapid sequence anesthetic induction in patients at risk of gastric fluid inhalation - Multicenter, prospective, controlled, randomized, single-blind, noninferiority study."*

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SIGNATURE PAGE

SIGNATURE OF THE PROMOTER

The sponsor undertakes to carry out this study in accordance with all the legislative and regulatory provisions to which the research may be subject and according to the protocol.		
Name and Function of Signatory Representative: **For the promoter and by a delegation of the Director-General, the Director of Medical Affairs and Research**	**Date:**	**Signature:**

SIGNATURE OF INVESTIGATORS

I have read all the pages of the clinical trial protocol, of which the CHU of Nantes is the sponsor. I confirm that it contains all the information necessary for the test conduct. I undertake to carry out the test in accordance with the protocol and the terms and conditions defined therein. I undertake to carry out the test respecting:

- the principles of the "Declaration of Helsinki,"
- international (ICH) and French rules and recommendations of good clinical practice (rules of good clinical practice for biomedical research on medicinal products for human use)
- European regulations and national legislation and regulations relating to clinical trials,

I also undertake that investigators and other qualified members of my team will have access to this protocol and to the documents relating to the Conduct of the trial to enable them to work in compliance with the provisions contained in these documents.

	Name:	**Date:**	**Signature:**
Coordinating Investigator	**Dr. GRILLOT Nicolas** Anesthesia and resuscitation department CHU de Nantes		
Principal Investigator	**Name and Institution:**	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

ANSM	National Agency for the Safety of Medicines and Health Products
MA	Marketing Authorization
BOW	Clinical Research Associate (monitor)
PCBs	Good Clinical Practices
bpm	Beat per minute
CPP	Committee for the Protection of Persons
CNIL	Commission Nationale de l'Informatique et des Libertés
CIS	Independent Service Committee
SOME	Specialized Study Diploma
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EtCO2	End Tidal CO2 (Fraction expirée de CO2)
EvIG	Serious Unwanted Event
ISG	Serious Adverse Reaction
EIGI	Unexpected serious adverse reaction
FC	Heart rate
FeO2	Exhaled oxygen fraction
FIH	First-in-Human = ^{1st} administration trial in humans
IADE	Nurse Anesthetist State Graduate
RSIA	Rapid Sequence Induction of Anesthesia
BMI	Body Mass Index
IVD	Direct Intravenous
TUE	Physician Anesthetist-Resuscitator
MR	CNIL Reference Methodology
PAD	Diastolic blood pressure
PAM	Average blood pressure
STEP	Systolic blood pressure
ENERGY	Positive Expiratory Pressure
RCP	Summary of Product Characteristics
SFAR	French Society of Anesthesia-Resuscitation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEC	Clinical Study Technician

TABLE OF CONTENTS

INTRODUCTION

Rapid sequence induction of anesthesia (RSIA) is the reference anesthetic technique for patients at risk of inhalation of gastric contents or with predictive criteria for intubation or difficult ventilation. It classically combines a hypnotic with a rapid-onset neuromuscular blocker. Suxamethonium (CELOCURINE®) is historically the recommended rapid-onset neuromuscular blocker in this indication because of its short time of action, its short duration of action, and the intensity of the neuromuscular block it generates (1). Nevertheless, its use may be responsible for serious side effects (2). The anaphylactic reaction is the most feared; prolonged neuromuscular blockade, malignant hyperthermia, or the occurrence of severe hyperkalemia (in patients with deregulation of acetylcholine receptors at the neuromuscular junction) are others. Rocuronium is an alternative for patients with a contraindication to suxamethonium (3,4). However, this molecule is known as allergenic as suxamethonium, and its very long duration of action limits the indications in this context. In addition, the 2012 French Per-Anesthetic Reactions Study Group survey results reported an increase in the incidence of anaphylactic reactions to suxamethonium and an increase in the incidence of the most severe forms of all recommended combined (5). Due to the risks associated with their use, and despite their effectiveness, rapid-onset neuromuscular blockers are used in only 31 to 55% of RSIA cases, according to international observational studies (6-9). Remifentanil is an opioid with interesting pharmacological properties in the context of RSIA. Indeed its time of action is short, about 60 seconds, its duration of action is short of 5 minutes (10), and several studies report that it provides good exposure conditions during intubation without rapid-onset neuromuscular blocker in regulated surgery (11-15). It also decreases the hemodynamic response during laryngoscopy (16-20). Finally, this treatment has marketing authorization in the indication of anesthetic induction. It is further recognized as an alternative to rapid-onset neuromuscular blockers for orotracheal intubation for anesthesia in pediatry (21).

In common practice, two RSIA protocols in adults are currently used: RSIA with or without rapid-onset neuromuscular blocker. The effectiveness of these two protocols is demonstrated, but no data are now available to compare the incidences of complications between these two strategies. Showing the noninferiority of remifentanil on the incidence of RSIA without major complications will change international recommendations and practices worldwide.

We hypothesize that the incidence of tracheal intubations without major complications is not lower at RSIA with remifentanil compared to RSIA with rapid-onset neuromuscular blockers. Therefore, we conducted a multicenter, randomized, controlled, open-label, noninferiority trial.

1. JUSTIFICATION OF THE STUDY

1.1. SEARCH POSITIONING

Pulmonary inhalation of gastric fluid related to general anesthesia

For general anesthesia, securing the upper airway by placing an orotracheal intubation probe is a standard procedure and has been made mandatory in many situations. The first reason is to ensure adequate oxygenation throughout the time of surgery. The second is to protect the upper airways from the risk of inhalation of gastric contents.
In most cases, gastric fluid inhalation occurs at the time of induction of general anesthesia before securing the airways by the tracheal intubation probe. In 1993, Warner et al. (22) reported an incidence of gastric inhalation in 67 cases out of 215,488 anesthesia performed between 1985 and 1991. More recently, Sakai et al.(23) reported an incidence of 14 inhalations out of 99,441 anesthesia performed between 2001 and 2004, ranging from 1.5 to 3 per 10,000 anesthesia in adults. Morbidity-mortality from inhalation is not negligible with, in a recent study (24), a risk of pulmonary complications estimated at 1 event every 9753 anesthesia and risk of death related to inhalation every 23406 anesthesia. In this same study, the risk of inhalation is increased by 4.5 times in non-fasting patients. To reduce the risk of inhalation, the induction of anesthesia in non-fasting patients has been standardized: it is called rapid sequence induction of anesthesia. This anesthetic induction scheme is widespread. For example, it is used nearly 5000 times yearly (400 times a month) at the University Hospital of Nantes.

Rapid sequence anesthesia induction

The main objective of RSIA is to place the tracheal intubation probe in the shortest possible time and without having to ventilate the patient with a face mask (which would increase the risk of inhalation). In addition, it is helpful that the patient finds spontaneous ventilation quickly to limit the duration of ventilation with a face mask in case of difficulty setting up the orotracheal intubation probe. To achieve these two objectives, the drug agents used must therefore have a short time of action and a short duration or be able to be antagonized

Rapid sequence induction, therefore, classically associates a hypnotic with a depolarizing neuromuscular blocker: suxamethonium remains the reference molecule in this indication because of its short action time (30 to 60 seconds) and its short duration of action (5-15min). In addition, the intensity of the neuromuscular block it generates provides excellent conditions for exposure and tracheal intubation at a dose of 1 mg/kg accurate weight (1).
Nevertheless, its use exposes the patient to severe complications such as anaphylaxis ranging from a simple skin reaction to the cardio-respiratory arrest, severe hyperkalemia, or malignant hyperthermia (3). Hypersensitivity reactions involving suxamethonium have a frequency of 1/6500 anesthesia in France (25). The latest epidemiological data show that neuromuscular blockers remain the most frequently implicated in peri-anesthetic anaphylactic reactions since they are responsible for 54% of severe allergies. Suxamethonium is the leading cause of anaphylactic accidents of drug origin in the operating room (frequency of 37%).) In addition, the rate of grade 3 and 4 anaphylactic reactions (shock, cardiorespiratory arrest) is more significant with this molecule than with other neuromuscular blockers (26). These allergic reactions are therefore frequent and potentially severe. However, it is impossible to predict the allergic risk for a given patient, making it very difficult to measure the benefit/risk balance at the individual level. Finally, suxamethonium is contraindicated, among others, in chronic neuromuscular pathology (myopathy, myasthenia gravis, spinal cord injury ..) or situations at risk of hyperkalemia (major rhabdomyolysis, severe burn of more than 24 hours, etc ...).

In case of contraindication to suxamethonium, rocuronium bromide at a dose of 1 mg/kg ideal weight has been proposed as a satisfactory alternative (4). Nevertheless, this molecule risks an anaphylactic reaction like suxamethonium (27). In addition, this molecule has a prolonged duration of action, justifying having a stock of SUGAMMADEX, a specific antagonist molecule, in case of a possible complication.

Remifentanil

Pharmacology

In the recommendations on the induction of the non-fasting patient, the place of morphine has been little studied. Their use is conventionally ruled out because of the relatively long duration of action of the oldest morphine (sufentanil, fentanyl), which would delay the resumption of spontaneous ventilation in case of intubation failure. Nevertheless, during laryngoscopy, intubation without morphine is responsible for a hemodynamic response with tachycardia and hypertension by sympathetic stimulation that can be deleterious in the fragile patient (28,29).

Remifentanil is a morphine derivate developed in the early 2000s. It is a pure agonist specific to μ receptors from the anilidopiperidin family. It has structural relationships with fentanyl and its other derivatives. Its methyl-ester group is responsible for its unique pharmacological properties (30).
Its pKa is lower than plasma pH. It circulates in plasma mostly in its non-ionized form and quickly penetrates the blood-brain barrier allowing a rapid balance between plasma and brain concentrations. In addition, its initial distribution volume is low, which gives it a high speed of action (action time of about one minute). In addition, remifentanil is degraded by non-specific plasma and tissue esterases, providing it with a very short contextual half-life (3.2 minutes), allowing a rapid elimination of the product even after prolonged infusion. These pharmacokinetic characteristics are little altered by age and renal or hepatic impairment (31-33).

All these characteristics are responsible for the "on-off effect" attributed to this molecule, namely a short time of action allowing rapid and facilitated intubation and a short duration of action hence a brief respiratory depression.

The place of remifentanil in the induction of rapid sequence anesthesia

The benefit-risk balance of RSIA could be improved by replacing suxamethonium (or rocuronium), which has significant potential adverse effects, with another agent with better tolerance but which would retain similar pharmacodynamic properties (good intubation condition, short time to action, short duration of action). The "on-off" effect of remifentanil makes it a good candidate for rapid sequence induction.

Conditions of intubation without rapid-onset neuromuscular blocker but with remifentanil

Several studies report excellent intubation conditions when intubated with remifentanil without a rapid-onset neuromuscular blocker.
In pediatric anesthesia, using rapid-onset neuromuscular blockers for intubation is rare, and remifentanil has been proposed as an adjuvant to sevoflurane and propofol to enable tracheal intubation. In both cases, the ease of intubation was comparable to intubation with rapid-onset neuromuscular blockers, and the tolerance was excellent (21). The same is true in four studies in adult anesthesia, where induction of anesthesia by a hypnotic agent associated with remifentanil (2 to 4 μg/kg) provided excellent intubation conditions in nearly 95% of cases with an intubation success rate close to 100% (11,12,34,35). In two randomized studies, induction

of anesthesia with propofol and remifentanil 4 µg/kg provided tracheal intubation conditions comparable to rapid sequence induction with suxamethonium (13,36). At this dosage, the time to resume spontaneous ventilation was 8 minutes with remifentanil compared to 4 minutes with suxamethonium (14).

Hemodynamic tolerance of remifentanil

The hemodynamic tolerance of remifentanil is satisfactory during induction. The drop in blood pressure varies from 19 to 31% compared to the fundamental values, according to the studies. Heart rate decreases by 20-30% as well (33.36). On the other hand, RSIA with suxamethonium and without morphine is accompanied by an increase in heart rate and blood pressure of 20 to 30%(13).

No high-level studies comparing remifentanil with suxamethonium in the RSIA are currently available. Given the morbidity induced by suxamethonium and the lack of a validated alternative in this indication, it is crucial to look for an alternative procedure

In conclusion

The induction of anesthesia in a non-fasting patient seeks to limit the risk of significant complications, including pulmonary inhalation of gastric fluid. Pharmacological agents must therefore provide suitable conditions for tracheal intubation and have a short time to action and short duration. Current recommendations support using suxamethonium, which could decrease the risk of complications related to emergency intubation.

Significant problems with the tolerance of suxamethonium mean that nearly 50% of rapid sequence inductions are currently done without suxamethonium (6,7,37). Due to its pharmacokinetic characteristics, remifentanil is commonly used in the context of rapid sequence induction without its noninferiority on the incidence of uncomplicated intubations having been demonstrated compared to suxamethonium.

We hypothesize that the incidence of tracheal intubations without major complications is not lower at RSIA with remifentanil compared to RSIA with rapid-onset neuromuscular blockers. Therefore, we are conducting a multicenter, randomized, controlled, open-label, noninferiority trial to demonstrate the noninferiority of remifentanil compared to rapid-onset neuromuscular blockers to allow, in combination with a hypnotic, uncomplicated tracheal intubation during rapid sequence induction. The REMICrush study can potentially change international recommendations and the medical practice of a frequent procedure during anesthesia.

1.2. BENEFITS AND RISKS FOR THOSE WHO LEND THEMSELVES TO RESEARCH

1.2.1. Benefits

1.2.1.1. Individual benefit

At the individual level, the expected benefit of the induction of high-quality rapid sequence anesthesia is to reduce the risk of significant complications related to intubation, to reduce the incidence of postoperative respiratory complications, to reduce the incidence of complications

associated with the use of rapid-onset neuromuscular blocker or its non-use despite the formal indication of rapid sequence induction. Patients in the arm without rapid-onset neuromuscular blockers may benefit from a decrease in adverse effects related to the use of rapid-onset neuromuscular blockers (decreased risk of allergy, hyperkalemia, and prolonged neuromuscular blockade). The individual benefit can therefore be objectified by the patient himself and quantified by the statistical analysis of our study.

1.2.1.2. Collective benefit

The incidence of allergic events when using a neuromuscular blocker for anesthesiologist induction is non-zero and exposes these patients to a risk of death or severe complications, especially if a neuromuscular blocker is unnecessary for the surgical procedure. Conversely, the non-use of this therapeutic class despite a formal indication of the realization of a rapid sequence induction also exposes patients to the risks related to intubation difficulties such as traumatic injuries, the occurrence of a hypoxic event, inhalation of gastric contents, the occurrence of postoperative respiratory complications or death. If the use of a bolus of remifentanil allows the obtaining of a condition of intubation not inferior to the use of a rapid-onset neuromuscular blocker without associated significant side effects, this study would be likely to modify the modalities of management of these patients at the international level because this molecule is inexpensive and easy to use. This could also make it possible to reduce the costs of initial care, especially in the event of the need to use rocuronium (which requires a stock of SUGAMMADEX), and in the longer term to reduce the additional costs of hospitalization in connection with the occurrence of an allergic event or a postoperative respiratory complication.

1.2.2. Risks

1.2.2.1. Individual risk

- Risks and physical constraints

No

- Risks related to the disease

The most common risks during rapid sequence induction are inhalation of gastric contents, damage to the oropharyngeal tract, and respiratory complications

- Risks associated with trial treatments including comparator where appropriate (AR)

The most common risks with the study drug are low blood pressure and bradycardia.
The complete list of ARs can be found in the pharmacovigilance section (see below).

- Risks and psychological constraints

No

- Socio-economic risks

No

1.2.2.2. Collective risk

No

1.2.3. Balance of benefits and risks

The balance of benefits and risks is favorable because of the literature and medical context data. In case of noninferiority demonstrated in our study, the use of remifentanil in place of a rapid-onset neuromuscular blocker will allow, in an identical way to the latter, to practice quality intubation in rapid sequence induction with a drug of fast action and short duration while preventing the occurrence of major complications related to tracheal intubation.
The expected benefit with the use of remifentanil instead of rapid-onset neuromuscular blocker is the decreased risk of:
- an unpredictable severe allergic reaction (rate approximately 1 per 3000 patients),
- hyperkalemia and heart rhythm disorders
- muscle pain,
- postoperative lung infections and postoperative swallowing disorders,
- prolonged neuromuscular blockade.

The main risks associated with the use of remifentanil instead of rapid-onset neuromuscular blocker are:
- dose-dependent bradycardia which is temporary and quickly reversible.
- dose-dependent arterial hypotension, which is temporary and quickly reversible.

The bibliographical references are given in Annex 3 of the document.

2. OBJECTIVES AND CRITERIA OF JUDGMENT

2.1. OBJECTIVE AND PRIMARY ENDPOINT

2.1.1. Main objective

The main objective of the study is to demonstrate the noninferiority of a rapid-onset neuromuscular blocker-free rapid-sequence anesthetic induction with remifentanil in preventing major complications related to tracheal intubation compared to rapid sequence induction with rapid-onset neuromuscular blocker.

2.1.2. Primary Endpoint

The primary endpoint is the rate of tracheal intubation without major complications defined by the combination of the following criteria:

1) Tracheal intubation after < 2 laryngoscopies (i.e. success intubation on the first attempt)
2) Absence of inhalation of gastric fluid through the vocal cords within 10 minutes of anesthetic induction
3) Absence of desaturation, which is defined by a SpO2 < 95% within 10 minutes of anesthetic induction or in case of mask-facial ventilation to treat desaturation.
4) Absence of severe hemodynamic instability is defined as hypotension (PAM ≤ 50 mmHg) or hypertension (PAM ≥ 110 mmHg) within 10 minutes of anesthetic induction
5) Absence of sustained ventricular rhythm disorder (i.e., requiring pharmacological or electrical intervention to be reduced or for more than thirty seconds), ventricular fibrillation, or cardiac arrest within 10 minutes of anesthetic induction
6) No occurrence of Grade III or IV anaphylactic reaction from the HAS 2013 classification within 10 minutes of anesthetic induction

There is no recommendation for the choice of the primary endpoint in studies evaluating rapid sequence induction modalities in the operating room.

Standard sequence intubation has excellent efficacy, with close to 97% intubation at the first attempt (38). The effectiveness of intubation without rapid-onset neuromuscular blocker with remifentanil is already demonstrated (13-15). The main criterion for choosing between RSIA protocols is the frequency of major complications during intubation. We, therefore, wish to demonstrate the noninferiority of remifentanil on the incidence of uncomplicated intubations.

Rapid sequence induction is considered adequate only if:

- it prevents inhalation of gastric fluid. For the REMICrush study, we defined tracheal intubation without major complications by a composite endpoint adapted from studies evaluating emergency intubation in anesthesia and resuscitation (39-41,47) and based on the major complications associated with emergency anesthesia.
- It allows rapid intubation. An intubation time of fewer than 60 seconds has been proposed, but this threshold is medically objectionable (42). The number of laryngoscopies required for intubation (greater than 2) is recommended as a criterion for a long and complicated procedure (43).
- It avoids desaturation and ventilation with a face mask. According to the French recommendations on difficult intubation, mask ventilation should be initiated as soon as saturation is less than 95% (38,43).

- It does not cause severe hemodynamic instability.
- It does not cause an allergic manifestation whose symptoms threaten life.
- It does not result in death.

Therefore, we have chosen a clinically relevant criterion: the frequency of tracheal intubation without major complications, covering the main complications feared by the anesthetists during emergency intubation.

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objective(s)

Secondary objectives are

1) Compare the effectiveness of rapid sequence intubation with or without rapid-onset neuromuscular blockers.
2) Compare the tolerance of rapid sequence induction with or without rapid-onset neuromuscular blockers.
3) Comparing the ability to prevent postoperative respiratory complications

2.2.2. Secondary endpoint(s)

The secondary endpoints are:

1. The type of pre-oxygenation used and the maximum exhaled oxygen fraction obtained during pre-oxygenation.
2. The position of the patient and head during the first laryngoscopy
3. The frequency of use of gastric ultrasound or nasogastric tube in the pre-induction period
4. Intubation quality score (IDS-3 score) (see Appendix 10)
5. Cormack-Lehane and POGO score values (see Appendix 10)
6. The frequency of patients for whom a technique to assist tracheal intubation was required
7. The time between preoxygenation initiation, the administration of the hypnotic (beginning of anesthetic induction), administration of study intervention, the first laryngoscopy, and the achievement of the 6th capnography curve (effective tracheal intubation)
8. The SpO2 lowest value, the frequency of patients who have experienced desaturation is between 95% and 80% and < to 80% SpO2 within 10 minutes of anesthetic induction.
9. The frequency of a patient with a severe hemodynamic disorder is defined as a heart rate of less than 45 bpm or a heart rate greater than 110 bpm or a SBP less than 80 mmHg or a SBP greater than 160 mmHg, or a MAP of less than 55 mmHg or an MAP greater than 100 mmHg within 10 minutes of anesthetic induction.
10. The frequency of patients who have had dental or tracheal lesions (endoscopic confirmation for the latter), the rate of patients with a cough requiring the deepening of anesthesia
11. The frequency of patients who have had an allergic manifestation of grade I or II of the HAS 2013 classification (see Appendix 10) within 10 minutes of anesthetic induction.
12. During the 2 hours after the surgical procedure: the frequencies of neuromuscular blockade monitoring, neuromuscular blocker antagonization, nausea/vomiting,

inhalation of gastric fluid, laryngeal dyspnea requiring aerosol or intravenous drug intervention, desaturations less than 80% or 92% before or after extubating, of non-invasive mechanical ventilation, of extubating failure, discharge to intensive care unit due to a complication related to anesthetic induction

13. Post score values and pharyngeal visual analogic score (from 0 to 100)in the post-operating monitoring room (estimation of laryngeal lesions in immediate postoperative) (see Appendix 10)

- The frequency of patients who have had postoperative pneumonia occurring on Day 7 of hospitalization and defined by the presence of a new or progressive infiltrate on chest X-ray or chest computed tomography, associated with one of the following symptoms: the appearance of purulent sputum, change in the formation of chronic sputum, fever ≥ 38 ° C, hyperleukocytosis (>12000 /mL) or leukopenia (<4000/mL), positive blood cultures or isolation of the pathogen on sputum, tracheal aspiration or bronchoalveolar lavage.
- The frequency of patients who presented with postoperative respiratory distress occurring on Day 7 of hospitalization and defined by the combination of a clinical picture of acute hypoxemic respiratory failure, a PaO2 / FiO2 ratio < 300 mmHg, the presence of new bilateral pulmonary infiltrates on chest X-ray and the absence of an argument for a cardiac origin.
- intra-hospital mortality.

3. TREATMENTS USED DURING THE STUDY

3.1. DESCRIPTION OF THE NECESSARY TREATMENTS AND METHODS OF ADMINISTRATION

3.1.1. Investigational drug(s) / comparator

3.1.1.1. Identification of treatments

Suxamethonium chloride 50 mg/mL inj, ampoule 2 mL
MA for anesthetic induction
Excipients: sodium hydroxide, succinic acid, PPI water
Dosage: 1 mg/kg (actual weight if BMI ≥ 30), single IVD injection
Duration of treatment: single dose

Rocuronium bromide 10 mg/mL inj, 5 mL vial
MA for anesthetic induction
Excipients: sodium acetate, sodium chloride, glacial acetic acid, PPI water
Dosage: 1 mg/kg (lean weight if BMI ≥ 30), single IVD injection
Duration of treatment: single dose

Remifentanil mg powder for solution for injection or infusion
Active ingredient: Remifentanil hydrochloride, 1 mg, powder for solution for injection or infusion
Excipients: glycine, hydrochloric acid
Dosage: 3 to 4 µg/kg (lean weight if BMI ≥ 30), single IVD injection
Duration of treatment: single dose
Supplied to the centers by the sponsor.

3.1.1.2. Administration

Suxamethonium chloride: direct intravenous injection at a dosage of 1 mg/kg immediately after injection of the hypnotic. For an ampoule of 2 ml to 50 mg/ml of Suxamethonium Chloride, dilution with 0.9% sodium chloride in a 10 ml syringe, i.e., a final concentration of 10 mg/ml. Suxamethonium chloride should not be mixed in the same syringe with barbiturates or any other alkaline product.

Rocuronium bromide: direct intravenous injection at a dosage of 1 mg/kg immediately after injection of the hypnotic. For 5 ml to 10 mg/ml vials of Rocuronium bromide, administration without dilution is possible. If desired, Rocuronium can be diluted with 0.9% sodium chloride solute or 5% glucose solute or water for injections or Ringer-Lactate solute.

Remifentanil: direct intravenous injection at a dosage of 3 to 4 µg/kg immediately after injection of the hypnotic. For a 1mg vial, dilute a 20 ml syringe to obtain a concentration of 50 µg/ml. One of the following solutions for injection should be used for dilution: water for injection, 5% glucose solution, and 0.9% sodium chloride solution for injection.

3.1.1.3. Dose adjustment

There is no dose adjustment

3.1.1.4. Reference documents

To the extent that investigational medicinal products are used commercially, the reference document for each of them is the SmPC.

3.1.2. Other treatments

3.1.2.1. Auxiliary drugs

The administration of auxiliary treatments is left to the discretion of the doctor in charge of the patient and documented in the observation book. All treatments usually used for the management of a patient in pre, per, and post-induction anesthetic are authorized, including the following non-exhaustive list:

- Injectable barbiturate and non-barbiturate drugs (Thiopental sodium, propofol, ketamine)
- Inhalation anesthetics (Sevoflurane and Desflurane)
- Morphine and non-morphine analgesics (Sufentanil, Alfentanil)
- Curarizing agents (atracurium besylate, cisatracurium besylate)

All treatments will be administered intravenously or by electric syringe push, except for halogenated gases (inhalation using a suitable evaporator).

An adaptation of the dosages may be necessary according to the clinical context by the anesthesiologist-resuscitator in charge of the patient

3.1.2.2. Other non-drug treatments

All medical devices necessary for anesthesia practice will be used per the regulations in force and according to local habits.

3.2. METHODS FOR MONITORING ADHERENCE TO TREATMENT

Since the experimental drugs are administered to a population of patients undergoing anesthesia, compliance can only be excellent. The products are injected directly intravenously by the anesthetist-resuscitator, the IADE, or the internal anesthesia-resuscitation in charge of the patient. The last report on the anesthesia file is the exact dose administered. This information is also reported in the patient's eCRF.

3.3. INVESTIGATIONAL DRUG CIRCUIT

3.3.1. General circuit

The medicines will be presented in their commercial form and original packaging.
Considering the study's design, the sponsor will provide the evaluated product, Remifentanil, to all investigator centers. To do this, the pharmacy of the Nantes University Hospital (Hôtel-Dieu site) will be the coordinating pharmacy of the study. It will ensure the labeling of Remifentanil per the regulations and the supply to pharmacies in the centers according to the rhythm of inclusions.
The center's pharmacy will ensure the reception, storage, and provision of the experimental product according to the center's practice (nominative dispensing or endowment) and traceability. Used and unused investigational products will be destroyed on-site after monitoring and agreement of the sponsor. As this is a commercial form, therapeutic units will not be re-labeled.
Regarding the comparator arm, the rapid-onset neuromuscular blockers will be used according to the practice of the center, taken from the stock of the establishment (SUXAMETHONIUM or ROCURONIUM).

3.3.2. Storage conditions for investigational medicinal products

3.3.2.1. Description of storage at the pharmacy

Storage is carried out at the pharmacy of the investigator center, in a cabinet monitored in temperature, locked (per the regulations of narcotics), with restricted access, and apart from drugs all coming. The product should be stored at a temperature not exceeding + 25 ° C.
The investigator's center will provide rapid-onset neuromuscular blockers (SUXAMETHONIUM or ROCURONIUM).

3.3.2.2. Description of storage in the service

In the department, storage is carried out in a secure cabinet placed in an air-conditioned environment at a constant temperature, locked (per the regulations on narcotics), with restricted access, and apart from all-coming medicines. The product should be stored at a temperature not exceeding + 25 ° C.

3.4. DRUGS AND TREATMENTS ALLOWED AND PROHIBITED

3.4.1. Permitted treatments

All treatments usually used for the management of a patient in pre-and post-induction anesthetic are authorized, including the following non-exhaustive list:

- Sympathomimetics IV

- Parasympatholytics
- Antibiotics and antifungal
- Hypnotic and sedative agents
- Antiemetics
- Glucocorticoid hormones
- Electrolyte solution and blood-derived products
- Antihypertensive

3.4.2. Unauthorized processing

No treatment is prohibited in the protocol

In case of difficult intubation not foreseen as defined by the protocol, the administration as rescue therapy of rapid-onset neuromuscular blockers or remifentanil is also authorized, at the discretion of the medical doctor in charge of the patient.

3.4.3. Emergency treatment

Emergency treatments include:

- In cardiac arrest, the implementation of resuscitation procedures is immediate and complies with local care procedures or defaults, the ILCOR recommendations of 2015. Treatments aimed at correcting anaphylactic shock, negative inotropic effects of anesthetic agents, underlying metabolic abnormalities (hyperkaliemia,) or collapse of ventilation are preferred.

- In the event of grade II or III anaphylactic manifestation, intravenous adrenaline will be administered urgently per local procedures and default according to SFAR's 2010 clinical practice guidelines. Emergency antagonization of ROCURONIUM by SUGAMMADEX may be used at a dose of 16mg/kg (ideal weight if Body Mass Index ≥ 30) in case of grade IV manifestation (drug available in the stocks of investigator centers)

- In case of difficulty of intubation, ventilation, or vomiting during the procedure, SUXAMETHONIUM and ROCURONIUM may be used in the REMIFENTANIL group (and vice versa) at the dosages indicated in the protocol. Emergency antagonization of ROCURONIUM by SUGAMMADEX may be used at a dose of 16mg/kg (ideal weight if BMI ≥ 30). In any case, the procedure will follow the 2006 SFAR expert conference updated in 2017.

- In case of poorly tolerated bradycardia, a parasympatholytic (ATROPINE) may be administered as an IVD.

- In case of hypotension, filling with a crystalloid or colloidal solute and administering sympathomimetic drugs (EPHEDRINE, NEOSYNEPHRINE, NORADRENALINE, ADRENALINE) may be used in IVD or electric syringe.

- In the case of hypertension, the choice of administering an IV antihypertensive will be left to the free choice of the anesthesiologist after the failure of the deepening of the anesthesia.

- In the case of malignant hyperthermia, treatment with DANTROLENE will be initiated per the recommendations of experts for the risk of malignant hyperthermia in anesthesia-resuscitation of the SFAR published in 2013.

All the treatments mentioned above are drugs immediately available in any operating room where acts under general anesthesia are performed.

4. STUDY POPULATION

4.1. DESCRIPTION OF THE POPULATION

The number of patients needed for statistical analyses is 1150.

The study population comprises hospitalized adult patients requiring rapid sequence induction in the operating room or shock room.

Participation in the study will be offered to the patient during the preoperative anesthesia consultation by the anesthetist, with the delivery of the information note and consent form. An emergency procedure will be used if it is impossible to deliver precise and fair information to the patient during the study's inclusion period.

Individuals participating in the research will not be able to participate simultaneously in another intervention research (excluding intervention research at minimal risk and constraint) for 24 hours following the RPIA.

4.2. INCLUSION CRITERIA

- Woman or man.
- Aged 18 to 80
- Procedure requiring general anesthesia with orotracheal intubation
- Anesthetic management with rapid sequence induction indication
- The risk of inhalation of gastric fluid is defined by, or less one of the following criteria: fasting period < 6:00 am, digestive occlusion, functional ileus, vomiting < 12:00 hours, orthopedic trauma < 12:00 hours, history of severe GERD for hiatal hernia or gastroparesis or dysautonomia or gastroesophageal surgery
- Existence of informed and signed consent of the patient, or failing that, emergency procedure

4.3. NON-INCLUSION CRITERIA

- Intubation impossible planned
- Known or suspected history of allergy to rapid-onset neuromuscular blockers or remifentanil
- History of neuromuscular disease contraindicating the use of rapid-onset neuromuscular blockers
- History of prolonged neuromuscular blockade.
- History of malignant hyperthermia
- Preoperative respiratory distress (SpO2 < 95% in ambient air)
- Preoperative shock (Mean Arterial Pressure ≤65 mmHg or under vasopressor)
- Patient in cardiorespiratory arrest
- Women of childbearing potential with a progressive pregnancy or clinical signs suggestive of pregnancy or not having contraception or unprotected sex within 15 days of the last menstruation.

- Patients under guardianship or curatorship
- Intended use of ETOMIDATE for rapid sequence induction

5. DESIGN AND CONDUCT OF THE STUDY

5.1. STUDY SCHEDULE

STUDY CALENDAR

Actions	J0 (date of surgery)	J7
Patient Information*	X	
Informed consent or emergency consent	X	
Randomization	X	
Measurement of efficacy and safety per and post-induction anesthetic	X	
Effectiveness and safety measurement in SSPI	X	
Effectiveness and safety measurement on Day 7		X
Adverse events	X	X

5.2. GENERAL RESEARCH METHODOLOGY

The search has the following characteristics:
-Phase III drug
-Multicentric
-Prospective
-Controlled
-Randomized
-With stratification on the type of material used for intubation: (Macintosh laryngoscope or video-laryngoscope) and the leading risk factor for inhalation of gastric fluid (occlusive syndrome versus other causes)
-In parallel groups
-Single-blind
-Noninferiority

The scheme of the study is as follows:

Inclusion phase:

All patients admitted to the operating room or shock room requiring rapid sequence anesthetic induction for an act requiring general anesthesia with orotracheal intubation will be offered to participate in the study.

Screening is provided by the investigating physicians taking care of these patients during the anesthesia consultation. They select patients with all inclusion criteria (see inclusion criteria paragraphs 4.2 and 4.3) and seek consent to participate in the study (see information and collection of the consent). The investigating physician shall also determine the most appropriate anesthetic regimen for the patient to undergo the invasive procedure, in particular the risk factors for inhalation (time of the last meal, presence of recent nausea or vomiting, occlusive syndrome, the existence of reflux or hiatal hernia, history of gastroesophageal surgery) and the choice of the laryngeal exposure device, and evaluates the essential elements of the anesthesia consultation namely: medical-surgical history, allergies, weight, height, risks of ventilation with a complex mask and difficult intubation according to the recommendations of the SFAR, choice of hypnotic. The patient's wish is also considered when there is a possible choice between locoregional anesthesia and general anesthesia.

Randomization phase:

The investigating physician performs the randomization of the patient, which is done between 2 groups with stratification on the material used for intubation and the leading risk factor for inhalation of gastric fluid.
- The control group (GC): In addition to the hypnotic chosen by the investigator, suxamethonium or rocuronium is injected into IVD at a dose of 1mg/kg (actual weight and lean weight, respectively, if BMI ≥ 30) immediately after administration of the hypnotic. Intubation occurs at the end of fasciculations with suxamethonium (30 to 60 seconds in the absence of fasciculation) or 30 to 60 seconds after rocuronium injection. An experienced person carries out the intubation: a qualified anesthetist doctor, a graduate IADE or an intern enrolled in the DES of anesthesia-resuscitation and having validated at least four semesters, including two in the anesthesia sector.

- The Remifentanil group (GR): In addition to the hypnotic chosen according to the clinical situation, remifentanil is injected into IVD at the dosage of 3 to 4µg/kg (lean weight if BMI ≥ 30) immediately after administration of the hypnotic. Intubation takes place 30 to 60 seconds after remifentanil administration by a graduate MAR, a graduate IADE or an intern enrolled in the DES

of anesthesia-resuscitation and having validated at least four semesters, including two in the anesthesia sector.

Rapid sequence anesthetic induction sequence

The rapid sequence induction sequence refers to the SFAR 2003 recommendations on airway management in adult anesthesia except for difficult intubation and SFAR 2017 on difficult intubation and extubation in adult anesthesia (available http://sfar.org/referentiels/). It consists in our study of the following steps:

-1st step: Denitrogenation with a face mask with 100% FiO2 for 3 minutes or until theoretical obtaining a FeO2> 90%. The patient's installation is left to the free choice of the MAR in charge of the patient. In case of obesity, a denitrogenation in positive pressure or via a high-flow nasal oxygen therapy device will be left to the free choice of the MAR in charge of the patient.

- 2nd step: IVD injection of the hypnotic on a peripheral or central venous route previously controlled. The time between the beginning of pre-oxygenation and the administration of the hypnotic is the free choice of the MAR. Nevertheless, this period and the value of FeO2 will have to be filled in. In both groups, the realization of a Sellick maneuver is left to the discretion of the MAR in charge of the patient.

-3rd step: injection of rapid-onset neuromuscular blockers (SUXAMETHONIUM or ROCURONIUM) or REMIFENTANIL immediately after hypnotic depending on the randomization group. The time between the administration of the hypnotic and the administration of rapid-onset neuromuscular blockers or remifentanil should be indicated.

-4th step: At the end of fasciculations with suxamethonium (30 to 60 seconds in the absence of fasciculation) or after 30 to 60 seconds for ROCURONIUM or REMIFENTANIL, beginning of tracheal exposure with the laryngoscopy device chosen during randomization. The size and type of probe used for orotracheal intubation are left to the free choice of the MAR in charge of the patient. The time between the start of administration of the hypnotic and the orotracheal intubation defined by the presence of 6 cycles of EtCO2 on the scope should also be indicated.

In both randomization groups, in case of unforeseen intubation difficulty accompanied by desaturation (SpO2 <95%) and the need for ventilation with a face mask, a so-called rescue administration of SUXAMETHONIUM [1 mg/kg (actual weight if BMI ≥ 30)], ROCURONIUM [1 mg/kg (lean weight if BMI ≥ 30)] or REMIFENTANIL [3 to 4 µg/kg (lean weight if BMI ≥ 30)] is left to the free choice of the anesthetist in charge of the patient. The rest of the procedure refers to the recommendations of the SFAR by following the unplanned difficult intubation algorithm.

It should be noted that:

In both groups, it is not permitted by the protocol to use in the operating room before the first laryngoscopy any other medicinal product for hypnotic, muscle relaxant, or intubation facilitating purposes (LIDOCAINE, CATAPRESSAN, morphine other than REMIFENTANIL in the REMIFENTANIL group, SEVOFLURANE, MIDAZOLAM). These drugs can be freely used by the MAR in charge of the patient during this first laryngoscopy if it is successful or beyond the 2nd laryngoscopy in case of unforeseen difficult intubation.

In both groups, the oral or IV administration of premedication and the use of morphine for analgesia purposes (and no anesthetic) before the initiation of anesthesia and left to the free choice of the MAR in charge of the patient and will have to be informed.

After intubation, patients are ventilated in controlled assisted ventilation with a current volume between 6 and 8ml/kg of ideal weight with a PEP of at least five cmH20, a ventilatory frequency for EtCO2 objectives between 35 and 45 mmHg, and a FiO2 for SpO2 goals between 95 and

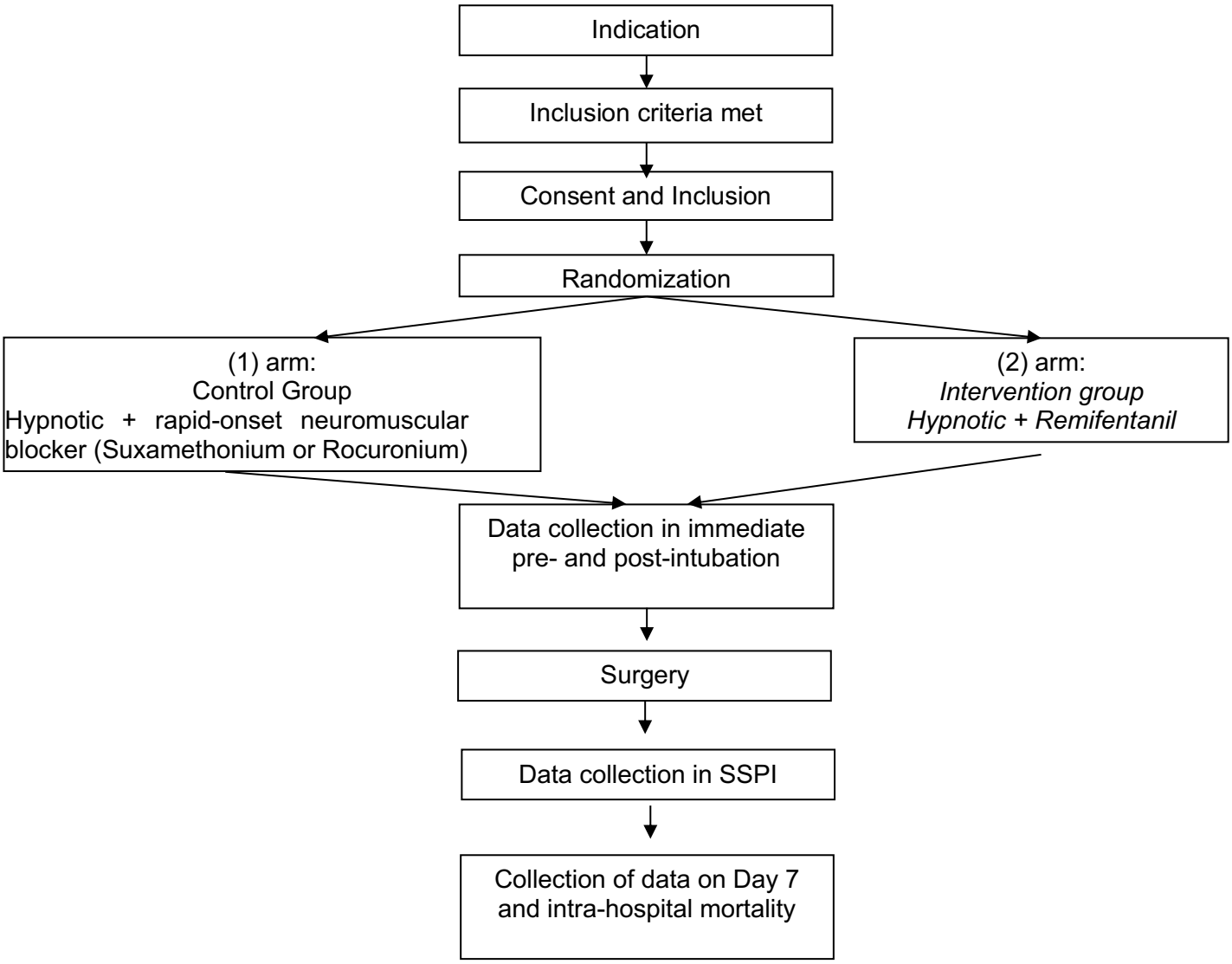
100%. The success of intubation is defined by six cycles of adequate ventilation (exhaled CO2 curves) and symmetrical bilateral pulmonary auscultation

Data collection.
Data collection is done on an eCRF. The source data are collected on a paper version of the eCRF.

In the post-interventional monitoring room (SSPI)
The data collection is completed on the eCRF. Particular attention is paid to the achievement of a score estimating laryngeal discomfort after extubating (POST Score), and pharyngeal pain score with the Visual Analogic Scale (from 0 to 100), the use or not during the surgery of neuromuscular blockers, the use or not of a neuromuscular blockade monitoring as well as the occurrence of nausea/vomiting after extubating.

A Day 7:
The collection of data on the occurrence during hospitalization of an episode of postoperative pneumonia, postoperative respiratory distress, admission to intensive care or continuing care unit, or death.
In case of discharge from the hospital before J7, the patient will be considered free of these complications.

5.3. DIAGRAM OF THE STUDY



5.4. DESCRIPTION AND JUSTIFICATION OF THE TREATMENT REGIMEN

REMIFENTANIL is administered as ivd on a previously controlled peripheral or central venous route. Treatment is given only once at a dose of 3 to 4 µg/kg (lean weight if BMI ≥ 30). This dose-weight corresponds to the best benefit-risk ratio (benefit in terms of intubation quality, risk in adverse events, including hemodynamics) found in the medical literature (11-15, 19-21, 35).

Due to the need to secure the airways early, a slow intravenous bolus injection of 1 µg/kg suggested for non-urgent tracheal intubation cannot be respected.

5.5. IDENTIFICATION OF ALL SOURCE DATA NOT INCLUDED IN THE MEDICAL RECORD

The study-specific data that can be collected directly in the observation book are as follows:

- POST score (estimate of laryngeal lesions in immediate postoperative)
- The time between administration of the hypnotic and the 6th capnography curve (effective tracheal intubation)
- Intubation quality score (IDS-3 score)

5.6. RULES FOR STOPPING A PERSON'S PARTICIPATION

5.6.1. Criteria for premature termination of a person's participation in research

Study exits will only be effective after the investigator and sponsor confirm.
When a patient is discharged from the study, data about them will no longer be collected.

Withdrawal of patient consent:
This is a criterion for permanent cessation of participation in the study. Data obtained before it has been removed will be used. The data collected after the withdrawal of consent will not be used for this research and will remain intended for the strict use of the care. These patients will still be encouraged to continue the entire clinical follow-up to detect the possible occurrence of side effects. Pharmacovigilance data will be retained for the safety report of the study.

Violation of the Protocol:
- Failure to comply with the inclusion rules will not result in the termination of the protocol or the exclusion of patients. A *modified intention-to-treat analysis* will be performed (patients with all inclusion criteria and no non-inclusion criteria).

- Deviation of administration of the treatment: the treatment is administered only once during the anesthetic induction on a previously laid and controlled venous route. The observance will therefore be excellent. A deviation from the administration protocol will not result in the discontinuation of the protocol or the exclusion of patients. Deviations from treatment will be

collected. A *per-protocol analysis* will be performed (patients who received in 1st *intention the* treatment assigned by randomization).

The lost to follow-up:
Patients cannot be lost to follow-up during the perioperative phase. All means will be implemented to collect data on Day 7. In case of discharge from hospitalization before J7, without re-hospitalization during the first week, the patient will be considered free of complications. In case of hospitalization of more than seven days, only the date of the end of hospitalization or the date of death during the same hospitalization will be collected. Anesthesia reports and discharge letters will report the patient's inclusion in the REMICrush study.

Deaths:
The patient's death within seven days of the operation leads to a premature cessation of participation in the research. The data of these patients will be kept in the final analysis.

Use of rapid-onset neuromuscular blockers in the REMIFENTANIL group:
Patients in the "REMIFENTANIL" group who receive "rescue therapy" rapid-onset neuromuscular blockers will be followed clinically, and their data will be used in the intention-to-treat analysis and excluded from the per-protocol analysis. These patients will remain analyzed in the "REMIFENTANIL" group in which they were randomized. The frequency of patients receiving rescue therapy in the REMIFENTANIL group will be studied.

5.6.2. Procedures for premature termination of a person's participation in research

Data concerning exclusions and early terminations will be communicated to the promoter without delay in the event of a Serious Adverse Event or a new event.
This statement is made on the eCRF and must include the day of the protocol's termination concerning inclusion and the reasons for the termination of the protocol.
The investigator shall also complete the data collection book, particularly the part concerning deviations from the protocol where he justifies the discontinuation or exclusion of the patient.
The premature discharge of a patient from the study will not change his usual management concerning his pathology. He will not have the follow-up specific to the study (control on Day 7).
In case of exit following an adverse event, serious or not, an appropriate follow-up will be proposed.

Treatment-related side effects (local and general) are immediate and last only within hours of anesthetic induction. The investigator uses all the means at his disposal (mail, telephone) to ensure that side effects do not occur during the first 14 days after the injection of the treatment. In case of cessation of participation before the end of the routine follow-up provided by the study, the investigator ensures a clinical follow-up of the patient until regression of the possible side effects of the treatment under investigation.

5.6.3. Criteria for stopping some or all of the research (excluding biostatistical considerations)

The end of the research will correspond to the end of the participation of the last patient included in the study, after adjusting the number of subjects needed according to the number of patients lost to follow-up and excluded to maintain sufficient power of the study

Part or all of the study may be definitively or temporarily decided by the decision of the ANSM, the CPP, and the Sponsor of the study after consulting the CIS

In all cases:
- A written confirmation will be sent to the coordinating investigator of the study (specifying the reasons for premature discontinuation) as well as to the principal investigator of each center
-All patients in the study will be informed and have to carry out their preterm discharge visit.

5.7. MODALITY OF PATIENT CARE AT THE END OF THE RESEARCH

Not applicable

6. DATA MANAGEMENT AND STATISTICS

6.1. COLLECTION AND PROCESSING OF STUDY DATA

6.1.1. Collection, processing, and circulation of data

Data collection from each person suitable for research is carried out through an electronic observation book (CRF). Each person responsible for this collection (investigator, ARC monitoring, TEC ...):

- is identified in the delegation table of responsibilities of each center (kept in the investigator binder)
- will have a "user" account with the computer rights specific to his role (right to enter or modify data, right to lock, monitor, or sign an eCRF page)

The entry, consultation, or modification of the data will only be possible via the pages of the eCRF (input masks), on https://nantes-lrsy.hugo-online.fr/CSonline

This data is stored directly from the eCRF in a database hosted on a dedicated server, with controlled access (username/password) depending on the user's role. Any addition, modification, or deletion of data will be traced in a non-modifiable electronic file (the audit trail).

6.1.2. Participant Identification

The principal investigator and co-investigators undertake to keep confidential the identities of the persons suitable for research by assigning them a code.

This code is used for all eCRF, and all documents (reports of imaging examinations, biology, ...) are attached. This is the only information that allows you to make the correspondence with the participant.

The coding rule is as follows: 1st letter of the first name + 1st letter of the name + month and year of birth, Inclusion number

6.2. STATISTICS

It is planned to include 1150 patients.

The statistical analyses will be carried out by Fanny FEUILLET, biostatistician – Methodology and Biostatistics Platform of the Research Directorate (Nantes University Hospital) & INSERM U1246 SPHERE (University of Nantes).

Sas software (version 9.4 NC, USA) will be used for statistical analyses.

6.2.1. Description of the planned statistical methods, including the schedule of planned interim analyses

The statistical analysis will be carried out in line with the recommendations in force for the analysis of noninferiority trials (Mauri L, D'Agostino R B, Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med 2017; 377:1357-1367).

Qualitative data will be described for all patients and in each of the two groups in terms of the number and percentage of each modality. Quantitative data will be described in terms of mean/standard deviation or median/interquartile interval depending on their distribution.

For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. The confidence interval will be calculated by a logistic model considering stratification on the type of material used for intubation and bowel obstruction (yes vs. no) and will be adjusted on the center. The principal analysis will be carried out in intention-to-treat and per-protocol populations. The non-inferiority of the remifentanil will be demonstrated if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority) in these two populations. Subgroup analyses will be carried out on the main criterion, following the same methodology:

- Stratification criteria:
  - *Type of equipment used for intubation (Macintosh laryngoscope vs. video-laryngoscope
  - *Primary risk factor for inhalation of gastric fluid (occlusive syndrome/bowel occlusion vs. other causes)
- Age groups (18-40; 40-60; 60-80)
- Mallampati score (I and II vs III and IV)
- Method of care (urgent or non-urgent gesture)
- BMI sup to 30 kg/m² (yes vs. no)
- ASA score (1-2 vs. 3-4)
- Choice of propofol as hypnotic (yes vs. no)

For secondary endpoints, the comparison between the two groups will be estimated by logistic models for binary variables (postoperative pneumonia, postoperative respiratory distress); by linear models for continuous variables (heart rates, systolic blood pressure, etc.); by Poisson models for the number of events (number of episodes of allergic manifestation, number of episodes of desaturation, etc.). All analyses will be adjusted on the stratification criteria.

6.2.2. Statistical justification of the number of inclusions

The incidence of severe complications in our population related to rapid sequence intubation with rapid-onset neuromuscular blockers is between 12 and 30%, depending on studies and definitions (40,40,44,45). In a monocentric retrospective analysis of the Nantes University Hospital database performed on 100,000 general anesthesia including 8500 rapid sequence inductions, we observed an incidence of significant complications of 20%.

We hypothesized an incidence of intubation without major complications of 80% in the rapid-onset neuromuscular blockers group. The noninferiority margin is set at 7% (i.e., 8.875% in relative risk) so as not to tolerate a change in relative risk of more than 10% (46). Therefore, it is appropriate to include 575 patients per group (1150 patients in total) to ensure a power of 80% with an alpha risk of 5%.

6.2.3. Expected statistical significance

The degree of statistical significance will be 5% for the final analysis of the primary and secondary endpoints. The noninferiority threshold for the primary outcome study is set at 7%.

If the non-inferiority of remifentanil compared to rapid-onset neuromuscular blockers is demonstrated, the superiority of remifentanil will be tested by a logistic model (minimum expected efficacy difference = 10%) in the intention-to-treat population. The degree of statistical significance will be 5%. This hierarchical approach will preserve alpha risk.

6.2.4. Statistical criteria for stopping search

Not applicable

6.2.5. Method of accounting for missing, unused, or invalid data

Missing data will be described in terms of numbers and corresponding percentages for each group. The presence of possible imbalances in terms of the proportion of missing data between the two groups will be assessed by proportional comparison tests ($\chi 2$ tests or exact Fisher tests).

As the primary endpoint is identified within 10 minutes of anesthetic induction and death is included in the endpoint, no missing data are expected.

For the evaluation criteria at seven days postoperative, a pejorative imputation will be applied in case of missing data (death of the patient *or* other).

6.2.6. Managing changes to the initial strategy analysis plan

No interim analysis is planned.

A statistical analysis plan will be drawn up before the database is frozen and will detail any changes made to the statistical paragraph of the protocol.

The study may be stopped early by the decision of the sponsor if the frequency of SAEs is high.

6.2.7. Choosing who to include in analyses

According to the current recommendations for the analysis of non-inferiority trials (48-49), The analyses will be applied to the per-protocol (PP) and intention-to-treat (ITT) populations.

ITT: All randomized patients. The data will be imputed for patients for whom the main criterion would not be available (withdrawal of consent).

PP: All randomized patients, except patients who do not verify the inclusion/non-inclusion criteria, patients for whom the primary endpoint is unavailable, and patients who have not received the treatment assigned to them by randomization.

6.2.8. Randomization

The randomization list will be created by the statistician of the Department of Research Promotion of the University Hospital of Nantes. Randomization will be stratified on the type of material used for intubation (Macintosh laryngoscope or video-laryngoscope) and the leading risk factor for inhalation of gastric fluid (occlusive syndrome vs. other causes). The list will be made in blocks according to a 1:1 ratio.

Randomization will then be done under the Clinsight software by connecting to the site: https://nantes-lrsy.hugo-online.fr/CSOnline/. The connection will be made through a login and a password (issued by the Clinical Research Promotion Unit of the Nantes University Hospital).

The following information must be provided:
-First initial of the name
-First initial of the first name
-Date of birth
-Compliance with inclusion and non-inclusion criteria (yes/no)
-Signature of informed consent (yes/no)

Randomization will be done by the center's principal investigator or their delegate (the person whose name will be mentioned in the delegation of responsibilities sheet of the investigator binder).

The number and randomization arm will be assigned automatically during randomization. Confirmation by email will be sent to the person who carried out the randomization and to all concerned people.

Randomization will be the responsibility of statisticians from the Clinical Research Promotion Unit of Nantes University Hospital. A Guide to Using Clinsight will be provided to each investigator.

7. PHARMACOVIGILANCE AND ADVERSE EVENT MANAGEMENT

7.1. DEFINITIONS

Vigilance	It is the monitoring of medicines, medical devices, and other health products. It also consists of preventing the risk of adverse effects resulting from their use, whether this risk is potential or proven.
Adverse Events (AE)	Any harmful manifestation occurring in a person who lends himself to research involving the human person, whether or not that manifestation is related to the study or the product on which the research relates.
The intensity of Adverse Events (AEi)	It will be rated according to the following criteria: *1 = benign* *2 = moderate* *3 = severe* *4 = life-threatening* *5 = death* In the particular case of anaphylaxis, the HAS 2013 classification will be applied, namely: Grade I Isolated mucocutaneous signs; Grade II Moderate multi-organ involvement (at least two functions affected), Grade III Severe multi-organ involvement, Grade IV Circulatory or respiratory arrest
Adverse reactions (AEs)	An undesirable event occurring in a person who is suitable for research involving the human person, where that event is related to the study or to the product to which the research relates.
Adverse reaction of an investigational medicinal product	Any harmful and unwanted reaction to an investigational drug regardless of the dose administered. (also applicable to cell therapy products)
Effects/ Serious Adverse Events (SAEs)/ (EvIG)	Any adverse reaction/event that: * entails death, * involves the vital prognosis, * results in temporary or permanent incapacity or invalidity, * requires or prolongs hospitalization of the patient, * leads to a congenital or neonatal anomaly, * is medically important (the EMA defines the list of medically important effects/events).
Unexpected Adverse Reactions (EIIs)	Any adverse reaction of the nature, severity or course does not agree with the information relating to the products, procedures, and methods used during the research.
New development	Any new data that may lead to a reassessment of the report of the benefits and risks of the research or the product being

	researched, to changes in the use of that product, in the Conduct of the study, or the research documents, or to suspend or discontinue or modify the protocol of the research or similar research. For trials of the first administration or use of a health product in people who do not have any conditions: any serious adverse reaction.
Abuse	Excessive intentional, persistent or sporadic drug use is accompanied by harmful physical or psychological reactions.
Overdose	Administration of an amount of the drug, given during administration or cumulatively, that is above the maximum recommended dose according to the rules of compliance or use of the product. Clinical judgment should always be applied. (real overdose: due to too much gross amount/relative overdose: due to the patient's predisposing factors such as renal failure, hypo-albuminemia ...)
Misuse or off-label use	Situation where the product is intentionally used in a manner that does not comply with the specifications of use of the product (e.g., route of administration/dosage or indication different from that listed in the reference document).
Quality defect	Non-compliance with the specifications described in the MA /CE marking/technical documentation dossier or deviation from Good Manufacturing Practices (GMP) / Good Distribution, Preservation, and Labelling Practices.
Medication Error (ME)	Corresponds to any unintentional, proven (or potential) omission or performance of an act that occurred during the care process, *in the circuit (from manufacture to administration)* involving a product that may cause a risk or adverse event for the patient. The risk of error or potential error concerns situations where the error did not occur, was intercepted but could have happened.

7.2. LIST OF EXPECTED AES

For this protocol, the most frequent expected AEs for the treatments under study are:

For REMIFENTANIL:
- Rigidity of the skeletal muscles
- Bradycardia
- Hypotension
- Postoperative hypertension
- Acute respiratory depression, apnea
- Nausea, vomiting
- Pruritus
- Postoperative chills

For SUXAMETHONIUM:
- Increased kalemia.
- Allergic or non-allergic anaphylactic reactions (non-specific histamine-liberation): pruritus, erythematous reactions at the injection site, or systemic reactions such as generalized erythema (often inaugural), cardiovascular disorders, bronchospasm, anaphylactic shock that can be severe (or even fatal).

- Bradycardia, rhythm disorders.
- Low blood pressure.
- Transient increase in intracranial pressure*.
- Transient increase in intraocular pressure*.
- Muscle pain, feeling of aches.
- Transient increase in intragastric pressure*.

For ROCURONIUM:
- Anaphylactic and anaphylactoid reactions and associated symptoms.
- Tachycardia
- Hypotension
- Reaction and pain at the injection site
- Prolonged neuromuscular block, lengthening of the recovery time after anesthesia

AEs expected to use REMIFENTANIL, ROCURONIUM, and SUXAMETHONIUM as part of their MAs are listed in their respective SMEs.

For this Protocol, the expected AEs for medicinal products and medical devices associated with anesthetic induction shall be listed in the respective SMRs of medicinal products and package leaflets of the instruments used in the context of their marketing authorizations.

For this Protocol, the expected AEs for the anesthetic induction procedure are:

- Desaturations < 95%,
- Hypotension or severe hypertension
- Cardiac arrests
- Deaths during intubation
- Unplanned difficult intubations
- Heart rhythm disorders
- Esophageal intubations
- Agitations
- Regurgitations/inhalations
- Dental breakage or tracheal lesions

In the context of this protocol, adverse events related to pathology or management in the operating room or shock room and which are those conventionally observed in this context will not be collected under this protocol, except for those related to the study drugs or its comparators which will be well managed and reported if necessary.

7.3. ADVERSE EVENT MANAGEMENT

7.3.1. AE Compendium

Any AE (unless otherwise specified in 9.2), whether expected or unexpected, serious or non-serious, should be collected in real-time in the study's eCRF.

7.3.2. Notification of EvIG/ISGs

Any Expected or Unexpected EvIG/SAE shall be notified to the sponsor without delay from the day the investigator becomes aware of it. The information provided and the attached documents must be complete, precise, clear (do not put an abbreviation...), and code. Pregnancy, overdose, misuse, errors or risk of errors, and quality defects are also notified to the sponsor even if there are no associated adverse events.

7.3.3. Notification period

Any EvIG/SAE, whether expected or unexpected, shall be notified to the sponsor if it occurs for a research participant from the date of signature of consent and the entire duration of the participant's follow-up in the trial.

7.3.4. Independent Oversight Committee (IIC)

The mission of the Independent Supervisory Committee is to monitor the clinical and biological tolerance of the study's treatments.

It is responsible for informing the Scientific Committee in its decisions to amend or discontinue the trial. The list of CIS and Scientific Committee members is attached as Annex 10.

7.4. MODALITIES AND DURATION OF FOLLOW-UP OF PEOPLE FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

7.4.1. Action to be taken for patients concerned by the AEs

Any adverse events, serious or non-serious, whether expected or unexpected, must be followed until healing, consolidation, or death (closed event).

8. ADMINISTRATIVE AND REGULATORY ASPECTS

8.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

The medical data of each patient will only be transmitted to the sponsor or any person duly authorized by him and, where appropriate, to the authorized health authorities, under conditions guaranteeing their confidentiality.
The sponsor and the supervisory authorities may request direct access to the medical record to verify the procedures and data of the clinical trial and within limits permitted by laws and regulations.
The data collected during the test will be subject to computer processing per the requirements of the CNIL (Compliance with the MR01).

8.2. TRIAL MONITORING

Monitoring will be carried out by the promotion department of the Research Directorate. A Clinical Research Associate (ARC) will regularly visit each site (investigator and pharmacy) to carry out quality control of the data reported in the observation books.

The protocol was classified according to the estimated level of risk to the patient undergoing research. It will be followed as follows:

Risk B: foreseeable risk close to that of usual care

The frequency and intensity of monitoring depend on the risk of the study. The level of risk should be determined in consultation with the coordinating investigator, the CRA and the project leader before the start of the study. A monitoring plan, validated by the investigator, the project manager, and the MONITORING ARC defines the data that will be monitored and the frequency of visits
On-site monitoring visits will be organized after an appointment with the investigator. The CRAs will have to be able to consult on each site:
- the patient data collection books included,
- patients' medical and nursing records,
- the investigator's binder
- places of storage and dispensing of medicinal products

8.3. INSPECTION / AUDIT

As part of this study, an inspection or audit may take place. The promoter and participating centers must be able to give access to the data to inspectors or auditors.

8.4. ETHICAL CONSIDERATIONS

8.4.1. Written informed consent

Rapid sequence anesthetic induction is a standard care procedure in the operating room.

The investigator, therefore, undertakes to obtain the free and informed consent of the person, collected in writing, after providing him with the protocol information (information note and consent collection form in Annexes 4, 6). He will give him a copy of the information note and a consent form. The person can only be included in the study after reading the information note and signing and dating the consent form after having had time to reflect. The investigator must also sign and date the consent form. This document will be issued on paper in at least two copies so that the patient and the investigator can keep a copy. The investigator's original will be filed in the investigator's filing cabinet. In case of duplicate signed consent, the investigator keeps the original, and the duplicate is given to the patient.

8.4.1. Procedures for obtaining consent in an emergency situation or for an adult unable to express consent

If the investigator can't provide clear and fair information to the patient within the maximum period of inclusion of the study (e.g., urgent surgical procedure, polytrauma, state of confusion), an emergency procedure will be made available to the investigator to facilitate the inclusion of the patient without delaying the medical-surgical management

- Situation N°1: a trusted person or close present

Information to the trusted person or relative via the specific information note (Annex 8). The written consent of the authorized person or relative will be obtained (Appendix 7). The investigator must also sign and date the consent form. This document will be issued on paper in at least two copies so that the patient and the investigator can keep a copy. The investigator's original will be filed in the investigator filing cabinet. In case of duplicate signed consent, the investigator keeps the original, and the duplicate is given to the patient.

- Situation N°2: trusted or close person who cannot be present within the maximum period of inclusion of the study

The investigating physician must complete, date, and sign the emergency procedure certificate (Annex 11). The investigator's original will be filed in the investigator filing cabinet.

Whatever the situation, the patient's free, informed, and written retrospective consent will be systematically sought a posteriori as soon as the patient can express his approval. Patients will thus be informed a posteriori comprehensively and fairly, in understandable terms, of the objectives and constraints of the study, of the possible risks involved, of the necessary monitoring and safety measures, of their rights to refuse to participate in the research or of the possibility of withdrawing at any time. All this information can be found on an information note, and the consent form is given to the patient (see Annexes 5 and 6). This retrospective consent will be obtained by the investigator or a physician representing them before final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient. The investigator will keep the original.

If death prevents fair consent, the patient's consent cannot be obtained. Still, the data collected from these patients will be used because their exclusion would significantly bias the study results,

which aims, among other things, to compare the tolerance of rapid sequence induction with or without rapid-onset neuromuscular blockers.

At the end of the research (day 7), if the investigators can not obtain the consent of the patient or a trusted person/relative, and provided that all reasonable means have been applied for the search for this consent, the data collected will be used for the statistical analyses.

8.4.2. Committee for the Protection of Persons

The promoter undertakes to submit the study project to the prior authorization of a Committee for the Protection of Persons (CPP).

8.5. DECLARATION TO THE COMPETENT AUTHORITIES

This protocol will be the subject of an application for authorization from the ANSM.

8.6. AMENDMENTS TO THE PROTOCOL

The promoter will send requests for substantial modifications for authorization to the ANSM and for authorization/information to the committee for the protection of persons concerned per the law in force and its implementing decrees.
The amended protocol must be the subject of a dated updated version.
The patient information and consent forms will be subject to change if necessary.

8.7. FINANCING AND INSURANCE

The promoter ensures the financing of the study and takes out an insurance policy guaranteeing the financial consequences of his civil liability under regulations.

8.8. PUBLICATION RULES

A copy of the publication will be given to the University Hospital of Nantes, the promoter of the study, which will necessarily be cited.

The editorial board is composed of the scientific committee. Signatories are the coordinating investigator (Dr. Grillot) and the principal investigator of the study (Pr Roquilly), and as such, respectively, the first and last signatories, the statistician-methodologist, and such penultimate signatory. The 2nd (*equally participated with the 1st author), 3rd places (and so on) will be allocated to the centers outside Nantes, having achieved a minimum of 60 inclusions (in order of the most significant number to the smallest number of inclusions).

The sponsor will increment the European Union database of the clinical trial results as soon as the originator publication resulting from this work is effective and in order not to prejudice the protection of intellectual property.

8.9. ARCHIVING SOURCE DATA

The investigator must retain all information relating to the study for at least 15 years after the end of the study. At the end of the study, the investigator will receive a copy of each patient's data from their center sent by the sponsor.

LIST OF ANNEXES

Appendix 1: List of Investigators
Appendix 2: Protocol Summary
Appendix 3: Bibliographic References
Appendix 4: Patient Information Note (excluding emergency procedure)
Appendix 5: Patient Information Note (Lawsuit)
Appendix 6: Patient Consent Collection Form
Appendix 7: Consent Collection Form – Relative/Trusted Person
Appendix 8: Information Note Close/Trusted Person
Annex 9: Composition of the Independent Oversight Committee and the Scientific Committee
Appendix 10: Scores and classifications used in the study
Appendix 11: Emergency Procedure Certificate

Registration number: 2019-000753-31 CPP ref: 2-19-052

List of modifications of the study protocol from Version 1.1 (28 June 2019) to Version 2 (25 November 2019)

OLDER VERSION	NEW VERSION	JUSTIFICATION
Version n°1.1 of 28/06/2019	**Version n°2.0 of 25/11/2019**	
Name and Function of Signatory Representative: For the promoter and by the delegation of the Director-General, the Director of Medical Affairs and Research	Name and Function of Signatory Representative: For the promoter and by the delegation of the Director-General, the Director ~~of Medical Affairs and Research~~, Research, and Innovation	Change in the organization chart of Nantes University Hospital
2.1.2 Primary Endpoint (page 12) 1/ Tracheal intubation after ≤ 2 laryngoscopies [...] 3/ Absence of desaturation defined by a SpO2 < 95% within 10 minutes of anesthetic induction	**2.1.2 Primary Endpoint** 1/ Tracheal intubation after < 2 laryngoscopies (i.e. success on the first attempt) [...] 3/ Absence of desaturation, which is defined by a SpO2 < 95% within 10 minutes of anesthetic induction or in case of mask-facial ventilation to treat desaturation.	The typing error in the criteria 1 was corrected (and now it matches with the registered criteria on clinicaltrial.gov) We changed the formulation of the criteria 3 for greater clarity and consideration of the cases of mask-facial ventilation to prevent desaturation during an unplanned difficult intubation.
2.2.2 Secondary Endpoints (pages 13-14) 1. Intubation quality score (IDS-3 score) (see Appendix 10) 2. Cormack-Lehane and POGO score values (see Appendix 10) 3. The frequency of patients for whom a technique to assist tracheal intubation was required 4. The time between the administration of the hypnotic (beginning of anesthetic induction) and the achievement of the 6th capnography curve (effective tracheal intubation) 5. The frequency of patients who have experienced desaturation is between 95% and 80% and < to	**2.2.2 Secondary Endpoints** 1. The type of pre-oxygenation used, and the maximum exhaled oxygen fraction obtained during pre-oxygenation. 2. The position of the patient and head during the first laryngoscopy 3. The frequency of use of gastric ultrasound or nasogastric tube in the pre-induction period 4. The intubation quality score (IDS-3 score) (see Appendix 10) 5. Cormack-Lehane and POGO score values (see Appendix 10) 6. The frequency of patients for whom a technique to assist tracheal intubation was required 7. The time between preoxygenation initiation, the administration of hypnotic (beginning of anesthetic induction), the administration of study intervention,	We are adding secondary endpoints to enable the analyses of the immediate pre and post-intervention periods.

80% SpO2 within 10 minutes of anesthetic induction. 6. The frequency of a patient with a severe hemodynamic disorder is defined as a heart rate of less than 45 bpm or a heart rate greater than 110 bpm or a SBP less than 80 mmHg or a SBP greater than 160 mmHg, or a PAM of less than 55 mmHg or an MPA greater than 100 mmHg within 10 minutes of anesthetic induction. 7. The frequency of patients who have had dental or tracheal lesions (endoscopic confirmation for the latter) 8. The frequency of patients who have had an allergic manifestation of grade I or II of the HAS 2013 classification (see Appendix 10) within 10 minutes of anesthetic induction. 9. Post score values in SSPI at one-hour post-extubation (estimation of laryngeal lesions in immediate postoperative) (see Appendix 10)	the first laryngoscopy, and the achievement of the 6th capnography curve (effective tracheal intubation) 8. The SpO2 lowest value, the frequency of patients who have experienced desaturation between 95% and 80% and < to 80% SpO2 within 10 minutes of anesthetic induction. 9. The frequency of a patient with a severe hemodynamic disorder is defined as a heart rate of less than 45 bpm or a heart rate greater than 110 bpm or a SBP less than 80 mmHg or a SBP greater than 160 mmHg, or a MAP of less than 55 mmHg or a MAP greater than 100 mmHg within 10 minutes of anesthetic induction. 10. The frequency of patients who have had dental or tracheal lesions (endoscopic confirmation for the latter), the rate of patients with a cough requiring the deepening of anesthesia 11. The frequency of patients who have had an allergic manifestation of grade I or II of the HAS 2013 classification (see Appendix 10) within 10 minutes of anesthetic induction. 12. During the 2 hours after the surgical procedure: the frequencies of neuromuscular blockade monitoring, neuromuscular blocker antagonization, nausea/vomiting, inhalation of gastric fluid, laryngeal dyspnea requiring aerosol or intravenous drug intervention, desaturations less than 80% or 92% before or after extubating, of non-invasive mechanical ventilation, of extubating failure, discharge to intensive care unit due to a complication related to anesthetic induction 13. The values of POST Score and pharyngeal visual analogic score (from 0 to 100) in post-operating monitoring room I ~~at 1h post-extubation~~ (estimation ~~of lesions~~ of laryngeal discomfort in immediate post-operative) (see Appendix 10)	
Pages 15, 23 and 24 Rocuronium dosage: 1 mg/kg (ideal weight if Body Mass Index ≥ 30),	**Pages 15, 23 and 24** Rocuronium dosage: 1 mg/kg (~~ideal~~ lean weight if BMI ≥ 30),	We corrected a recurrent error: rocuronium bromide dosage is well calculated on lean

		weight if the patient's Body Mass Index is ≥ 30
4.3 Non-inclusion criteria (page 20) Preoperative shock (under vasopressor)	**4.3 Non-inclusion criteria** - Preoperative shock (Mean Arterial Pressure ≤65 mmHg or vasopressor)	This information was added to respond to questions from participating centers, and a clarification of the non-inclusion criterion regarding the definition of preoperative shock was added.
5.2 General Research Methodology (page 25) [...] In the post-interventional monitoring room (SSPI) The data collection is completed on the eCRF. Particular attention is paid to the achievement of a score estimating the laryngeal lesions in SSPI at 1 hour of extubation (POST Score), the use or not during the surgery of neuromuscular blockers, the use or not of a neuromuscular blockade monitoring as well as the occurrence of nausea/vomiting after extubating.	**5.2 General Research Methodology** [...] In the post-interventional monitoring room (SSPI) The data collection is completed on the eCRF. Particular attention is paid to the achievement of a score estimating laryngeal discomfort after extubating (POST Score), and pharyngeal pain score with the Visual Analogic Scale (from 0 to 100), the use or not during the surgery of neuromuscular blockers, the use or not of a neuromuscular blockade monitoring as well as the occurrence of nausea/vomiting after extubating.	This modification was necessary to match the new secondary outcomes

6.2.1 Description of planned statistical methods, including the schedule of planned interim analyses For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. The confidence interval will be calculated by a logistic model considering stratification on the type of hypnotic used and the type of material used for intubation. According to the assumptions we have defined, the group without rapid-onset neuromuscular blockers (i.e., with remifentanil) will be considered non-inferior to the group with rapid-onset neuromuscular blockers if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority).	**6.2.1 Description of planned statistical methods, including the schedule of planned interim analyses** For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. The confidence interval will be calculated by a logistic model considering stratification on the type of hypnotic used and the type of material used for intubation. According to the assumptions we have defined, the group without rapid-onset neuromuscular blockers (i.e., with remifentanil) will be considered non-inferior to the group with rapid-onset neuromuscular blockers if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority). If the non-inferiority of remifentanil is demonstrated, its superiority will be tested (minimum expected difference in efficacy = 10%). This hierarchical approach will preserve the consummation of the alpha risk.	We added a superiority analysis which will be performed only if the non-inferiority is demonstrated. The analyses could be useful to test the hypothesis that remifentanil is more efficient than rapid onset neuromuscular blockers in the same study, without reducing the statistical power of the primary aim.

8.4.1. Procedures for obtaining consent in an emergency situation or for an adult unable to express consent	**8.4.1. Procedures for obtaining consent in an emergency situation or for an adult unable to express consent**	
• Situation N°2: trusted or close person who cannot be present within the maximum period of inclusion of the study	• Situation N°2: trusted or close person who cannot be present within the maximum period of inclusion of the study	We are correcting an error: only one copy of the emergency consent form is signed by the investigator.
The investigating physician must complete, date, and sign the emergency procedure certificate (Annex 11). This document will be issued on paper in at least two copies so that the patient and the investigator can keep a copy. The investigator's original will be filed in the investigator filing cabinet. In case of a duplicate signed certificate, the investigator keeps the original, and the document is given to the patient. [...]	The investigating physician must complete, date and sign the emergency procedure certificate (Annex 11). ~~This document will be issued on paper in at least 2 copies so that the patient and the investigator can each keep a copy.~~ The investigator's original will be filed in the investigator filing cabinet. ~~In case of a duplicate signed certificate, the investigator keeps the original, the duplicate is given to the patient.~~ [...]	
If death prevents fair consent, the patient's consent cannot be obtained. Still, the data collected from these patients will be used because their exclusion would significantly bias the study results, which aims, among other things, to compare the tolerance of rapid sequence induction with or without rapid-onset neuromuscular blockers.	In the event of death preventing fair consent, the patient's consent cannot be obtained but the data collected from these patients will be used because their exclusion would significantly bias the results of the study which aims, among other things, to compare the tolerance of rapid sequence induction with or without fast-acting curares. At the end of the research (day 7), if the investigators can not obtain the consent of the patient or a trusted person/relative, and provided that all reasonable means have been applied for the search for this consent, the data collected will be used.	We add this precision which limits the risk of bias.

List of investigators

OLDER VERSION	NEW VERSION	JUSTIFICATION
Version n°1.0 of 25/04/2019	**Version n°2.0 of 25/11/2019**	
	Addition of the CHU Nantes – Laennec, CHRU de Lille - Centre Salengro, AP-HP-Henri Mondor and CHU de Toulouse	Improve recruitment

Annex 9 CIS and Scientific Committee

OLDER VERSION	NEW VERSION	JUSTIFICATION
Version n°1.0 of 25/04/2019	**Version n°2.0 of 25/11/2019**	
• Pr Benoit PLAUD (AP/HP): resuscitator anesthesiologist • Pr Denis FRASCAS (Poitiers): anaesthetist resuscitator/statistician	• Pr Benoit PLAUD (AP/HP): resuscitator anesthesiologist • Pr Denis FRASCAS (Poitiers): anaesthetist resuscitator/statistician • Dr Laura LEO (CHU Grenoble Alpes) : Pharmacovigilante	Dr. Leo has agreed to be part of the DSMB.

Registration number: 2019-000753-31 CPP ref: 2-19-052

List of modifications of the study protocol from Version 2 (25 November 2019) to Version 3 (03 August 2020)

Justification of the modification

As the Sponsor, we provide the investigational product. Until now, we have been supplying generic REMIFENTANIL from the MYLAN laboratory. Following a change of market at the Nantes University Hospital, ULTIVA from ASPEN PHARMA replaces REMIFENTANIL from MYLAN.

OLD VERSION OF THE PROTOCOL	NEW VERSION OF THE PROTOCOL
Version n°2.0 of 25/11/2019	**Version n°3.0 of 03/08/2020**
3.1.1.1. Identification of treatments **REMIFENTANIL** MYL 1 mg powder for solution for injection or infusion Active ingredient: Remifentanil hydrochloride, 1 mg, powder for solution for injection or infusion Holder of the MA: MYLAN SAS laboratory MA for anesthetic induction in 1997 Excipients: glycine, hydrochloric acid Dosage: 3 to 4 µg/kg (lean weight if BMI ≥ 30), single IVD injection Duration of treatment: single dose Generic for use in the study: none as long as the drug is supplied to the centers by the sponsor. [...] **REMIFENTANIL:** direct intravenous injection at a dosage of 3 to 4 µg/kg immediately after injection of the hypnotic. For a 1mg vial, dilute a 20 ml syringe to obtain a concentration of 50 µg/ml. One of the following solutions for injection should be used for dilution: water for injection, 5% glucose solution, and 0.9% sodium chloride solution for injection.	**3.1.1.1. Identification of treatments** **Remifentanil** mg powder for solution for injection or infusion Active ingredient: Remifentanil hydrochloride, 1 mg, powder for solution for injection or infusion Excipients: glycine, hydrochloric acid Dosage: 3 to 4 µg/kg (lean weight if BMI ≥ 30), single IVD injection Duration of treatment: single dose Supplied to the centers by the sponsor. [...] **Remifentanil:** direct intravenous injection at a dosage of 3 to 4 µg/kg immediately after injection of the hypnotic. For a 1mg vial, dilute a 20 ml syringe to obtain a concentration of 50 µg/ml. One of the following solutions for injection should be used for dilution: water for injection, 5% glucose solution, and 0.9% sodium chloride solution for injection.

3.3.1. General circuit The medicines will be presented in their commercial form and original packaging. Considering the study's design, the sponsor will provide the evaluated product, REMIFENTANIL, to all investigator centers. To do this, the pharmacy of the Nantes University Hospital (Hôtel-Dieu site) will be the coordinating pharmacy of the study. It will ensure the labeling of REMIFENTANIL per the regulations and the supply to pharmacies in the centers according to the rhythm of inclusions. The center's pharmacy will ensure the reception, storage, and provision of the experimental product according to the center's practice (nominative dispensing or endowment) and traceability. Used and unused investigational products will be destroyed on-site after monitoring and agreement of the sponsor. As this is a commercial form, therapeutic units will not be re-labeled. Regarding the comparator arm, the *rapid-onset neuromuscular blockers* will be used according to the practice of the center, taken from the stock of the establishment (SUXAMETHONIUM or ROCURONIUM).	**3.3.1. General circuit** The medicines will be presented in their commercial form and original packaging. Considering the study's design, the sponsor will provide the evaluated product, Remifentanil, to all investigator centers. To do this, the pharmacy of the Nantes University Hospital (Hôtel-Dieu site) will be the coordinating pharmacy of the study. It will ensure the labeling of Remifentanil per the regulations and the supply to pharmacies in the centers according to the rhythm of inclusions. The center's pharmacy will ensure the reception, storage, and provision of the experimental product according to the center's practice (nominative dispensing or endowment) and traceability. Used and unused investigational products will be destroyed on-site after monitoring and agreement of the sponsor. As this is a commercial form, therapeutic units will not be re-labeled. Regarding the comparator arm, the rapid-onset neuromuscular blockers will be used according to the practice of the center, taken from the stock of the establishment (SUXAMETHONIUM or ROCURONIUM).

Registration number: 2019-000753-31 CPP ref: 2-19-052

List of modifications of the study protocol from Version 3 (03 August 2020) to Version 4 (12 November 2020)

Justification of the modifications to the study protocol

Amendments to paragraph 6.2.1(page 31). We have updated the bibliographic reference on recommendations for analysis of non-inferiority studies since a more recent text was published in 2017. Following this text, we have chosen to reword the definition of the non-inferiority criterion for greater clarity, even though there is no change in the substance (same values of the non-inferiority endpoints). Finally, following the exact text, we specified that the two analysis populations have the same importance for the demonstration of the non-inferiority of the tested intervention (intention to treat taking into account all the randomized patients; and intention to treat taking into account only the patients having all the inclusion criteria and without deviation from the study treatment) Finally, an adjustment to the primary center analysis was added to account for a possible difference in intervention effects between participating departments. These changes in statistical design did not change the number of patients to be included.

Amendments to 6.2.3 (Page 32). Assuming the demonstration of the non-inferiority is achieved, the following medical question is whether or not the intervention being tested is superior to standard care. To answer this question without increasing the number of patients to be included and thus exposed to the intervention, we added a superiority analysis. A hierarchical approach (this superiority analysis is performed on the primary endpoint only if non-inferiority is demonstrated) allows us to control the alpha risk of the first kind and therefore does not impact our power calculation. This protocol modification will consequently enable us to answer a more significant number of scientific questions without modifying the risk for the patients.

Amendments to 6.2.7 (page 33). Update of references supporting the analysis populations.

Amendments to 8.8 (page 43). Given the workload of the coordinating investigator of the study after the inclusion of the first 800 patients (i.e., 70% of the recruitment), the notion "2nd author has equally participated in this work" would be false and has therefore been removed from the study protocol.

PAST VERSION OF THE PROTOCOL	NEW VERSION OF THE PROTOCOL
Version n°3.0 of 03/08/2020	**Version n°4.0 of 12/11/2020**
Page 31 **6.2.1 Description of planned statistical methods, including the schedule of planned interim analyses** The statistical analysis will be carried out in line with the recommendations in force for the analysis of non-inferiority trials (Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006; 295 : 1152-60). Qualitative data will be described for all patients and in each of the two groups in terms of the number and percentage of each modality. Quantitative data will be described in terms of mean/standard deviation or median/interquartile interval depending on their distribution. For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. According to the assumptions we have defined, the group without curare (i.e. with remifentanil) will be considered non-inferior to the group with curare if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority). The confidence interval will be estimated by a logistic model taking into account stratification on the type of hypnotic used and the type of material used for intubation. If the non-inferiority of remifentanil compared to curare is demonstrated, a superiority of remifentanil over curares for the primary endpoint will be tested (minimum expected difference in efficacy = 10%). This hierarchical approach will preserve alpha risk. [...]	**Page 31** **6.2.1 Description of planned statistical methods, including the schedule of planned interim analyses** The statistical analysis will be carried out in line with the recommendations in force for the analysis of noninferiority trials (Mauri L, D'Agostino R B, Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med 2017; 377:1357-1367). Qualitative data will be described for all patients and in each of the two groups in terms of the number and percentage of each modality. Quantitative data will be described in terms of mean/standard deviation or median/interquartile interval depending on their distribution. For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. The confidence interval will be calculated by a logistic model considering stratification on the type of hypnotic used and the type of material used for intubation and will be adjusted on the center. The principal analysis will be carried out in intention-to-treat and per-protocol populations. The non-inferiority of the remifentanil will be demonstrated if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority) in these two populations. [...]

Page 32 **6.2.3 Expected statistical significance** The degree of statistical significance will be 5% for the final analysis of the primary and secondary endpoints. The non-inferiority threshold for the analysis of the primary outcome is set at 7%.	**Page 32** **6.2.3 Expected statistical significance** The degree of statistical significance will be 5% for the final analysis of the primary and secondary endpoints. The noninferiority threshold for the primary outcome study is set at 7%. If the non-inferiority of remifentanil compared to rapid-onset neuromuscular blockers is demonstrated, the superiority of remifentanil will be tested by a logistic model (minimum expected efficacy difference = 10%) in the intention-to-treat population. The degree of statistical significance will be 5%. This hierarchical approach will preserve alpha risk.
Page 33 **6.2.7 Selection of persons to be included in the analyses** The analyses will be applied to the per-protocol (PP) and intention-to-treat (ITT) populations.	**Page 33** **6.2.7 Selection of persons to be included in the analyses** According to the current recommendations for the analysis of non-inferiority trials (48-49), The analyses will be applied to the per-protocol (PP) and intention-to-treat (ITT) populations.
Page 43 **8.8 Publication Rules** A copy of the publication will be given to the University Hospital of Nantes, the promoter of the study, which will necessarily be cited. The editorial board is composed of the scientific committee. Signatories are the coordinating investigator (Dr. Grillot) and the principal investigator of the study (Pr Roquilly), and as such, respectively, the first and last signatories, the statistician-methodologist, and such penultimate signatory. The 2nd (*equally participated with the 1st author), 3rd places (and so on) will be allocated to the centers outside Nantes, having achieved a minimum of 60 inclusions (in order of the most significant number to the smallest number of inclusions).	**Page 43** **8.8 Publication Rules** A copy of the publication will be given to the University Hospital of Nantes, the promoter of the study, which will necessarily be cited. The editorial board is composed of the scientific committee. Signatories are the coordinating investigator (Dr. Grillot) and the principal investigator of the study (Pr Roquilly), and as such, respectively, the first and last signatories, the statistician-methodologist, and such penultimate signatory. The 2nd, 3rd places (and so on) will be allocated to the centers outside Nantes, having achieved a minimum of 60 inclusions (in order of the most significant number to the smallest number of inclusions).

Original Statistical Plan Analysis (English translation)	
Title **PHASE CLINIQUE INDICATION(S) (CIBLE)**	Evaluation of REMIFENTANIL as a replacement for curare for rapid sequence anesthetic induction in patients at risk of gastric fluid inhalation - Multicenter, prospective, controlled, randomized, single-blind, non-inferiority study Phase 3 - Anesthesiology
INVESTIGATEUR COORDINATEUR	Dr Nicolas Grillot
Version	Version n°1

1.1. STATISTICS

It is planned to include 1150 patients.

The statistical analyses will be carried out by Fanny FEUILLET, biostatistician – Methodology and Biostatistics Platform of the Research Directorate (Nantes University Hospital) & INSERM U1246 SPHERE (University of Nantes).

Sas software (version 9.4 NC, USA) will be used for statistical analyses.

1.1.1. Description of the planned statistical methods, including the schedule of planned interim analyses

The statistical analysis will be carried out in line with the recommendations in force for the analysis of non-inferiority trials *(Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006; 295: 1152-60).*

Qualitative data will be described for all patients and in each of the two groups in terms of the number and percentage of each modality. Quantitative data will be described in terms of mean/standard deviation or median/interquartile interval depending on their distribution.

For the primary endpoint (rate of tracheal intubation without major complications), the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. According to the assumptions we have defined, the group without curare (i.e., with remifentanil) will be considered non-inferior to the group with curare if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority). The confidence interval will be calculated by a logistic model taking into account stratification (device for laryngoscopy and bowel obstruction).

Subgroup analyses will be carried out on the main criterion, following the same methodology:

- Stratification criteria:
    - *Type of equipment used for intubation (Macintosh laryngoscope vs video-laryngoscope
    - *Primary risk factor for inhalation of gastric fluid (occlusive syndrome/bowel occlusion vs. other causes)
- Age groups (18-40; 40-60; 60-80)
- Mallampati score (I and II vs III and IV)
- Method of care (urgent or non-urgent gesture)
- BMI sup to 30 kg/m² (yes vs no)
- ASA score (1-2 vs 3-4)
- Choice of propofol as hypnotic (yes vs no)

For secondary endpoints, the comparison between the two groups will be estimated by logistic models for binary variables (post-operative pneumonia, post-operative respiratory distress); by linear models for continuous variables (heart rates, systolic blood pressure, etc.); by Poisson models for the number of events (number of episodes of allergic manifestation, number of episodes of desaturation etc.). All analyses will be adjusted on the stratification criteria.

1.1.2. Statistical justification of the number of inclusions

The incidence of serious complications found in our population related to rapid sequence intubation with neuromuscular blockers is between 12 and 30% depending on studies and definitions (40,40,44,45). In a monocentric retrospective analysis of the Nantes University Hospital database performed on 100,000 general anesthesia including 8500 rapid sequence inductions, we observed an incidence of serious complications of 20%.

We hypothesize an uncomplicated incidence of intubation of 80% in the curare group. The margin of non-inferiority is set at 7% (i.e. 8.875% in relative risk) so as not to tolerate a change in relative risk of more than 10% (46). It is therefore appropriate to include 575 patients per group (1150 patients in total) to ensure a power of 80% with an alpha risk of 5%.

1.1.3. Expected statistical significance

The degree of statistical significance will be 5% for the final analysis of the primary and secondary endpoints

The non-inferiority threshold for the analysis of the primary outcome is set at 7%.

1.1.4. Statistical criteria for stopping search

Not applicable

1.1.5. Method of accounting for missing, unused or invalid data

Missing data will be described in terms of numbers and corresponding percentages by group. The presence of possible imbalances in terms of the proportion of missing data between the two groups will be assessed by proportional comparison tests ($\chi 2$ tests or exact Fisher tests).

As the primary endpoint is identified within 10 minutes of anesthetic induction and death is included in the endpoint, no missing data are expected.

For the evaluation criteria at 7 days post-operative, in case of missing data (death of the patient *or* other) a pejorative imputation will be applied.

1.1.6. Managing changes to the initial strategy analysis plan

No interim analysis is planned.

A statistical analysis plan will be drawn up before the database is frozen and will detail any changes made to the statistical paragraph of the protocol.

The study may be stopped early by decision of the sponsor if the frequency of SAEs is high.

1.1.7. Choosing who to include in analyses

The analyses will be applied to the per-protocol (PP) and intention-to-treat (ITT) populations.

ITT: All randomized patients. For patients for whom the main criterion would not be available (withdrawal of consent), the data will be imputed.

PP: All randomized patients, except patients who do not verify the inclusion/non-inclusion criteria, patients for whom the primary endpoint is not available, patients who have not received the treatment assigned to them by randomization.

1.1.8. Randomization

The randomization list will be created by the statistician of the Department of Research Promotion of the University Hospital of Nantes. Randomization will be stratified on the type of material used for intubation (Macintosh laryngoscope or video-laryngoscope) and the main risk factor for inhalation of gastric fluid (occlusive syndrome vs. other causes). The list will be made in blocks according to a 1:1 ratio.

Randomization will then be carried out under the Clinsight software by connecting to the site: https://nantes-lrsy.hugo-online.fr/CSOnline/ The connection will be made through a login and a password (issued by the Clinical Research Promotion Unit of the Nantes University Hospital).

The following information must be provided:
-First initial of the name
-First initial of the first name
-Date of birth
-Compliance with inclusion and non-inclusion criteria (yes/no)
-Signature of informed consent (yes/no)

Randomisation will be carried out by the centre's principal investigator or by his/her delegate (the person whose name will be mentioned in the delegation of responsibilities sheet of the investigator binder).

The number and randomization arm will be assigned automatically during randomization. A confirmation by email will be sent to the person who carried out the randomization as well as to all the people concerned.

Randomization will be the responsibility of statisticians from the Clinical Research Promotion Unit of Nantes University Hospital. A Guide to Using Clinsight will be provided to each investigator.

Final Statistical Plan Analysis (English Translation)	
Title **PHASE CLINIQUE INDICATION(S) (CIBLE)**	Evaluation of REMIFENTANIL as a replacement for curare for rapid sequence anesthetic induction in patients at risk of gastric fluid inhalation - Multicenter, prospective, controlled, randomized, single-blind, non-inferiority study Phase 3 - Anesthesiology
INVESTIGATEUR COORDINATEUR	Dr Nicolas Grillot
Version	Version n°2 (12 nov 2020)

1.1. STATISTICS

It is planned to include 1150 patients.

The statistical analyses will be carried out by Fanny FEUILLET, biostatistician – Methodology and Biostatistics Platform of the Research Directorate (Nantes University Hospital) & INSERM U1246 SPHERE (University of Nantes).

Sas software (version 9.4 NC, USA) will be used for statistical analyses.

1.1.1. Description of the planned statistical methods, including the schedule of planned interim analyses

The statistical analysis will be carried out in line with the recommendations in force for the analysis of non-inferiority trials *(Mauri L, D'Agostino R B, Challenges in the Design and Interpretation of Noninferiority Trials. N Engl J Med 2017; 377:1357-1367*).

Qualitative data will be described for all patients and in each of the two groups in terms of the number and percentage of each modality. Quantitative data will be described in terms of mean/standard deviation or median/interquartile interval depending on their distribution.

For the primary endpoint (rate of successful tracheal intubation on the first attempt without major complications), the difference in proportions between the two treatment arms and the 95% bilateral confidence interval will be calculated. The confidence interval will be calculated by a logistic model taking into account stratification (device for laryngoscopy and bowel obstruction), and will be adjusted on the center.
The main analysis will be carried out in intention-to-treat and per-protocol. The non-inferiority of the remifentanil arm will be retained if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority) in these two analysis populations.

Subgroup analyses will be carried out on the main criterion, following the same methodology:

- Stratification criteria:
  - *Type of equipment used for intubation (Macintosh laryngoscope vs video-laryngoscope)
  - *Primary risk factor for inhalation of gastric fluid (occlusive syndrome vs. other causes)
- Age groups (18-40; 40-60; 60-80)
- Mallampati score (I and II vs III and IV)
- Method of care (urgent or non-urgent gesture)
- BMI sup to 30 kg/m² (yes vs no)
- ASA score (1-2 vs 3-4)
- Choice of propofol as hypnotic (yes vs no)

For secondary endpoints, the comparison between the two groups will be estimated by logistic models for binary variables (post-operative pneumonia, post-operative respiratory distress); by linear models for continuous variables (heart rates, systolic blood pressure, etc.); by Poisson models for the number of events (number of episodes of allergic manifestation, number of episodes of desaturation etc.). All analyses will be adjusted on the stratification criteria and on the centre.

1.1.2. Statistical justification of the number of inclusions

The incidence of serious complications found in our population related to rapid sequence intubation with neuromuscular blockers is between 12 and 30% depending on studies and definitions (40,40,44,45). In a monocentric retrospective analysis of the Nantes University Hospital database performed on 100,000 general anesthesia including 8500 rapid sequence inductions, we observed an incidence of serious complications of 20%.

We hypothesize an uncomplicated incidence of intubation of 80%. The margin of non-inferiority is set at 7% (absolute difference) (46). It is therefore appropriate to include 575 patients per group (1150 patients in total) to ensure a power of 80% with an alpha risk of 2.5%.

1.1.3. Expected statistical significance

The degree of statistical significance will be 5% for the final analysis of secondary endpoints

The non-inferiority threshold for the analysis of the primary outcome is set at 7%.

If the non-inferiority of remifentanil compared to curare is demonstrated, a superiority of remifentanil over curares for the primary endpoint will be tested by a logistic model (minimum expected efficacy difference = 10%) over the intention-to-treat population. The degree of statistical significance will be 5%. This hierarchical approach will preserve alpha risk.

1.1.4. Statistical criteria for stopping search

Not applicable

1.1.5. Method of accounting for missing, unused or invalid data

Missing data will be described in terms of numbers and corresponding percentages by group. The presence of possible imbalances in terms of the proportion of missing data between the two groups will be assessed by proportional comparison tests (χ2 tests or exact Fisher tests).

As the primary endpoint was identified within 10 minutes of anesthetic induction and death was included in the endpoint, a small number of missing datawas expected. In case of missing data, multiple imputation based on demographic criteria and available data will be used.

For the evaluation criteria at 7 days post-operative, in case of missing data (death of the patient *or* other) a pejorative imputation will be applied.

1.1.6. Managing changes to the initial strategy analysis plan

No interim analysis is planned.

A statistical analysis plan will be drawn up before the database is frozen and will detail any changes made to the statistical paragraph of the protocol.

The study may be stopped early by decision of the sponsor if the frequency of SAEs is high.

1.1.7. Choosing who to include in analyses

According to the current recommendations for the analysis of non-inferiority trials (*48-49),* the analyses *will be applied to the* per-protocol (PP) population and the intention-to-treat (ITT) population.

ITT: All randomized patients. For patients for whom the main criterion would not be available (withdrawal of consent), the data will be imputed.

PP: All randomized patients, except patients who did not verify the inclusion/non-inclusion criteria, patients for whom the primary endpoint is not available, patients who did not receive the treatment assigned to them by randomization

1.1.8. Randomization

The randomization list will be created by the statistician of the Department of Research Promotion of the University Hospital of Nantes. Randomization will be stratified on the type of material used for intubation (Macintosh laryngoscope or video-laryngoscope) and the main risk factor for inhalation of gastric fluid (occlusive syndrome vs. other causes). The list will be made in blocks according to a 1:1 ratio.

Randomization will then be carried out under the Clinsight software by connecting to the site: https://nantes-lrsy.hugo-online.fr/CSOnline/ The connection will be made through a login and a password (issued by the Clinical Research Promotion Unit of the Nantes University Hospital).

The following information must be provided:
-First initial of the name
-First initial of the first name
-Date of birth
-Compliance with inclusion and non-inclusion criteria (yes/no)
-Signature of informed consent (yes/no)

Randomisation will be carried out by the centre's principal investigator or by his/her delegate (the person whose name will be mentioned in the delegation of responsibilities sheet of the investigator binder).

The number and randomization arm will be assigned automatically during randomization. A confirmation by email will be sent to the person who carried out the randomization as well as to all the people concerned.

Randomization will be the responsibility of statisticians from the Clinical Research Promotion Unit of Nantes University Hospital. A Guide to Using Clinsight will be provided to each investigator.

Summary of changes in the statistical analysis plan	
Title	Evaluation of REMIFENTANIL as a replacement for curare for rapid sequence anesthetic induction in patients at risk of gastric fluid inhalation - Multicenter, prospective, controlled, randomized, single-blind, non-inferiority study
Coordinator	Dr Nicolas Grillot
Summary of changes between version 1 and 2	

Clarification of the analysis of the primary outcome

"Analysis of the main endpoint: the difference in proportion between the two treatment arms and the bilateral 95% confidence interval will be estimated. ~~According to the assumptions we have defined, the group without curare will be considered non-inferior to the group with curare if the upper bound of the 95% CI does not exceed 7% (margin of non-inferiority).~~ The confidence interval will be ~~estimated~~ calculated by a logistic model taking into account stratification (device for laryngoscopy and bowel obstruction), and will be adjusted on the center."

Clarification of the list of secondary outcomes

1. The type of pre-oxygenation used and the maximum exhaled oxygen fraction obtained during pre-oxygenation.
2. The position of the patient and head during the first laryngoscopy
3. The frequency of use of gastric ultrasound or a nasogastric tube in pre-induction