CLINICAL STUDY PROTOCOL

EXTUBE

EXtubation related complications - an international observational study **T**o **U**nderstand the impact and **BE**st practices in the operating room and intensive care unit

Study Design:	International, multicentre, prospective observational point prevalence study
Study Number:	EXTUBE (CTO#4850)
ClinicalTrials.Gov:	NCT06442930
Planned Clinical Start:	Quarter 1 2025
Planned Clinical End:	Quarter 4 2026
Date of Protocol:	19-June-2025
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PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

Matteo Parotto MD		June 19, 2025
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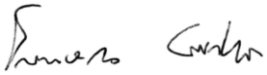
Francesco Cavallin MSc Statistics		June 19, 2025
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RATIONALE

Globally, it is estimated that over 200 million people each year require mechanical ventilation using an endotracheal tube, as part of general anesthesia for surgery or as a life-saving intervention in critical illnesses (for example, in severe respiratory failure due to pneumonia).[1,2] Once a patient has recovered, the endotracheal tube is removed, a process called 'extubation'. While routinely performed, extubation is a skilled and potentially high-risk procedure that should be performed only when physiologic, pharmacologic, and contextual conditions are optimal.[3] The decision of when and how to extubate a patient can be challenging because optimizing certain conditions can antagonize others. For example, extubation while the patient is fully anesthetized before upper airway reflexes return prevents laryngospasm but increases the risk of aspiration. Complications at this stage of patient care can result in decreased oxygen delivery to the brain and body, sometimes leading to serious adverse events such as cardiac arrest, brain damage, or death.[4] Indeed, in audits and safety reports, one quarter of airway complications that result in death or brain death occur at the time of extubation.[5] Each of the last 5 semi-annual safety bulletins of critical care incidents in England report serious adverse complications of extubation resulting in patients' death.[6-8]In all these cases, the experts' opinion reflected that these complications could have been prevented with proper planning and timing, adequate techniques and expertise at the bedside.[9]

Despite the frequency of extubation and the potential for life-threatening complications of extubation failure, we currently lack systematic data on the rate and circumstances under which these severe complications occur.[3] The limited data on complication rates indicate 10-30% of extubations may lead to severe complications, depending on the population and outcome definition.[5,10-16] However, the certainty of these estimates is severely limited because they are based on studies that are small,[11] mostly single-centre, based on clinician recall,[5,10] only capture a small portion of extubation complications,[14] or do not reflect current clinical practice.[12] Beyond these data, extubation complications and practices have not been thoroughly studied.[4] Yet extubation management decisions and outcomes depend on a complex interplay of patient and situational characteristics,[4] so a large, systematic study would be required to make conclusions about the best extubation technique in various patient populations and settings.[17]

Historically, extubation has received significantly less research attention than intubation[17-20] (i.e., the process of inserting the endotracheal tube at the start of mechanical ventilation), even though complications at extubation may occur as frequently as complications at intubation, but may have increased risk of severe patient harm.[6-8,12,18,21-25]

Promisingly, a recent focus on intubation complications, risk factors, and best-practices has decreased intubation related complications[26] – an evidence-based bundle of intubation strategies decreased airway complications by 26%[27] – suggesting that a similar program of research focusing on extubation could have a comparable impact on patient safety and outcomes.[28]

As a result, there have been calls for research to identify risks of extubation complications and effective extubation techniques.[5,7,19,20,28-30] In particular, high quality baseline data on complication rates are needed to evaluate future interventions and clinical practice

guidelines.[31] High quality data on patient risk factors for complications are needed because current guidelines specify that extubation algorithms should be selected based on patient risk level, but risk factors to date are based mainly on expert opinion. The algorithms themselves are based on case studies and expert opinion as there has been no large-scale study of the effectiveness of individual extubation techniques or guidelines,[4,20,28] so procedural factors associated with complications need to be elucidated. While adherence to clinical practice guidelines has not been formally evaluated, surveys of anesthesiology and critical care professionals show non-adherence to some best practices and considerable variation in practice.[5,10,32] Lack of adherence to best practices is frequently at the root cause of serious adverse outcomes of extubation, according to data from audits and medicolegal claims, suggesting that half of the complications are preventable.[17,23,24] For example, half of adverse events associated with extubation in a large audit had evidence of poor planning.[17] Therefore, data on the frequency and nature of extubation complications, patient and procedural risk factors for complications, and guideline adherence rates are needed before these preventable events can be addressed.

We propose the EXTUBE study, the first systematic, large, international prospective cohort study evaluating the incidence, risk factors, and outcomes of extubation-related complications and describing clinical practices related to extubation. We will use an innovative, point prevalence design that we recently adopted to successfully conduct the INTUBE study – the largest ever study on endotracheal intubation in critically ill patients.[33] These data will provide a precise understanding of current extubation practices and associated complications, and will be fundamental in informing targeted interventions to improve patient safety.

METHODS

Study Design

EXTUBE is an international, multicentre, prospective observational point prevalence study in patients who require extubation after general anesthesia or after critical illness in the operating room (OR), out of OR anesthesia location or intensive care unit (ICU). This study is designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines.[34]

Study Centres

To meet our target sample size (n=3,000), we have established a network of at least 60 broadly representative academic and non-academic hospitals worldwide that will report on patient data for this study. We will collect information about each study centre at the time of enrollment (e.g., community vs academic hospital, unit type [ICU, post-anesthesia care unit], number of beds in the hospital, number of beds in the unit). Each centre will be assigned a two-week enrollment window between January 2025 to December 2026, during which they will collect data on all eligible patients up to a maximum of 50 patients per centre.

Any future collaborations and transfer of data from/to UHN will be submitted for Research Ethics Board (REB) review via future amendment submission.

Patients

All potentially eligible patients will be identified by local investigators by screening all in-hospital extubations occurring in the ORs, out of OR anesthesia locations and ICUs during the enrollment window. Potentially eligible patients undergoing general anesthesia will be identified by screening daily preoperative assessment clinic lists, operating room booking lists, incoming patient lists on surgical wards, and monitoring operating room and out of OR procedure lists for add-on surgeries cases. Potentially eligible patients in the ICU will be identified by screening ICU census lists.

Inclusion Criteria

All adult patients (≥18 years old) undergoing extubation of an endotracheal tube (including index extubation and re-extubations) after general anesthesia in the OR, out of OR anesthesia location or ICU during the specified enrollment window will be included.

Exclusion Criteria

Patients will be excluded if the extubation is:

(i) performed in the context of withdrawal of life support measures or

(ii) performed for tracheostomy decannulation.

For each patient who is not included, reasons for exclusion will be reported.

Ethical Considerations

The study will be conducted in accordance with Good Clinical Practice guidelines[35] and the Declaration of Helsinki.[36] Additionally, the research will be conducted in compliance with local REB requirements at each centre.

We are requesting a waiver of consent (i.e., patient consent is not requested for their data to be included in this study). This study satisfies all of the criteria for alteration to consent as outlined in Article 3.7a of the Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans.[37] First, the research involves very minimal risk to patients as this is an observational study where patient care will not be modified, data will be collected from routine data sources, and patients will not be contacted. Second, waiver of consent will not affect the welfare of the patient. Third, this research question, which is fundamental to improve patient safety, is best answered with a waiver of consent, as collecting all consecutive patients are needed to provide an unbiased estimate of the prevalence of complications and asking for consent would make this impossible. Overall, the potential benefits of conducting this study outweigh the foreseeable risks to patients.

Data Collection

Data will be collected on paper case report forms (CRFs). Local investigators are expected to transcribe all collected data into an internet-based electronic CRF (eCRF, Research Electronic Data Capture – REDCap). Each local investigator will be trained in how to use the eCRF and will receive a personalized username and password. Each patient will be coded through a patient identification number (PIN) generated by the eCRF and no patient names or initials will be present on the paper CRF. Data will be handled confidentially and the paper CRF

will be stored behind a lock at each local site. Each centre should keep data stored for the length of the study and the time foreseen by local rules but at least 10 years from the date of study completion.

Data Quality and Security

To ensure data quality, training sessions will be provided to all research personnel involved in the trial. Standardized case report forms will be created in REDCap for collecting outcome data, with real-time checks for validity and completeness. To maximize usability and minimize missing data, the eCRF will use branching logic. To minimize missing data, the eCRF cannot be submitted with missing data. Coordinating centre personnel will perform quality checks on all data as it is received to screen for and verify potentially erroneous data (e.g., outliers) and review monthly reports of data quality and completeness. To ensure we capture all eligible patients during the enrollment window, we have included investigators from anesthesia and critical care at each study centre, and each day, we will record reason for exclusion for every patient in the ICU and undergoing general anesthesia who is not included in the study.

Data will be stored in a password-protected, encrypted, database on UHN's validated REDCap server. All patients will be identified in the database by a unique study ID. Identifying information will be encrypted and stored in a separate database.

OUTCOME MEASURES

Primary Outcomes

The *primary outcome* will be the occurrence of at least one of the following (composite outcome) occurring within 60 minutes after the end of extubation:

i. Severe hypoxemia (oxygen saturation as measured by pulse oximetry falls below SpO2 < 80% for > 5 minutes)
ii. Cardiac arrest
iii. Need for airway management (reintubation, insertion of a supraglottic airway, bag-mask ventilation).

Secondary Outcomes

Secondary outcomes will include the new occurrence of the following complications within 60 minutes of extubation:

i) Difficult airway (i.e., experienced difficulty by an experienced airway manager with any or all of laryngoscopy or tracheal intubation, supraglottic airway use, face-mask ventilation, or front-of-neck airway) and complications related to airway management (e.g., esophageal intubation) if reintubation is required,
ii) Planned and unplanned non-invasive respiratory support or high flow nasal cannula
iii) Emergency front of neck airway
iv) Cardiac arrhythmia requiring chemical or electrical treatment
v) Severe hypotension (systolic arterial pressure < 65 mmHg recorded at any time or systolic arterial pressure < 90 mmHg for > 30 minutes or new need/increase of vasopressor and/or fluid load > 15 mL/kg)
vi) Severe hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg),
vii) Aspiration of gastric contents (gastric contents inhaled into the larynx and the respiratory tract),
viii) Pneumothorax/pneumo-mediastinum,
ix) Dental injury (notable change to the patient's dentition attributable to extubation or to reintubation, should this be required),
x) Airways injury (e.g., vocal cord damage, arytenoid dislocation).

We will also collect the following outcomes:

xi) In-hospital mortality within 7 days after extubation
xii) Re-intubation within 48 hours of extubation

STATISTICAL ANALYSIS

Sample Size and Number of Study Centres

The sample size calculation is based on the primary objective (to estimate the incidence of immediate complications related to extubation in adult patients after general anesthesia and/or after critical illness). Based on estimates from current literature,[6-8] we expect an incidence of such complications around 8% (80 per 1,000 patients). Assuming such incidence, 2,827 patients need to be included to estimate a 95% confidence interval not wider than 2% (20 per 1,000 patients). Assuming approximately 5% of patients will be missing primary outcome data, we aim to collect data on 3,000 patients to meet our target sample size of 2,827. This sample size will also allow the inclusion of 15-22 candidate factors in the secondary objectives (i.e., investigation of the risk factors for the occurrence of the primary outcome).

Since we aim to estimate the overall incidence of the primary outcome in the population of interest (rather than the expected incidence in a centre), all eligible patients could be included during the enrollment window without any limitations on the number of enrolled patients in each centre. We estimate we will need to recruit at least 60 centres to achieve the target sample size, assuming an average of 50 extubation procedures in each centre in the

enrollment window. If the number of extubations per centre is lower than anticipated, we will continue to recruit centres until we reach our target sample size.

Interim Analysis

We plan an interim analysis with the data from the first 10 centres to complete their enrollment window to check if the magnitude of the primary outcome is broadly in line with the expected incidence. If the real incidence is different than expected incidence, or if we observe marked difference between populations in the OR and in the ICU, the sample size calculation may be updated, and the number and type of participating centres may be increased and diversified as needed. As this is an observational study, the interim analysis will not drive decisions about stopping for harm or futility.

Statistical Analysis

Descriptive statistics will be used to describe the patient characteristics. Continuous data will be expressed as mean and standard deviation or median and interquartile range, and categorical data as number and percentage. Bivariable analyses will be conducted using $\chi 2$ or Fisher exact test for categorical variables, and the Mann-Whitney or t test for continuous variables. A complete case analysis (with no assumptions made for missing data) will be performed. For the primary objective, the incidence of primary and secondary outcome measures (with 95% confidence interval) will be estimated overall, and within clinically relevant strata (e.g., sex, age, extubation in OR vs. ICU, low vs. high-risk extubation, global region, comorbidities, indication for intubation, complications at the time of original intubation, etc.).

For secondary objectives, (1) to identify risk factors for post-extubation complications, multivariable models (which may include logistic regression, Poisson regression, negative binomial regression, according to the nature of the data) adjusting for patient and surgical characteristics will be conducted. (2) Kaplan-Meier curves and Cox regression may be implemented to analyze survival data, if appropriate. (3) Exploratory analysis will be conducted to understand the current practice related to extubation and adherence. Given the multicentre enrollment, all analyses will be performed using multi-level models (with patients nested within study centre). All tests will be 2-sided and a p-value less than 0.05 will be considered statistically significant. Statistical analysis will be performed using R software (R Foundation for Statistical Computing, Vienna, Austria).

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