ICUNEB STUDY SYNOPSIS (VERSION 1.2)

Sponsor	Haute Ecole Arc Santé, Espace de l'Europe 11, 2000 Neuchâtel.
Study Title:	Inhaled drug delivery in patients with respiratory support: a prospective, multicenter, international observational study
Study category and Rationale	Research project involving human subjects Risk category A acc. to ordinance HRO Art.7 This study is strictly observational and involves no intervention beyond standard care. Data collection is limited to routinely available clinical and technical information related to aerosol therapy practices, without any modification of patient management.
Background and Rationale:	Aerosol therapy has become an integral component of respiratory care for critically ill patients receiving invasive mechanical ventilation (IMV), non-invasive ventilation (NIV), or high-flow nasal cannula (HFNC).[1,2] Over the past decade, the field has evolved considerably through advances in aerosol delivery technologies, the widespread adoption of non-invasive respiratory support, the emergence of novel inhaled therapies, and the publication of the first international expert recommendations dedicated to aerosol therapy during respiratory support.[3–5] Collectively, these developments have considerably expanded the evidence base supporting aerosol therapy and created new opportunities to optimize inhaled drug delivery in critically ill patients. Despite these advances, contemporary aerosol therapy practices remain poorly characterized at the international level. The latest international survey was conducted before many of these major developments and largely reflected European practice.[2] Subsequent surveys have provided valuable insights but were restricted to individual countries,[3,5] specific respiratory support modalities,[1] or selected inhaled therapies,[6,7] thereby offering only a partial picture of contemporary international practice. The ICUNEB study is a prospective, multicenter, international observational study designed to comprehensively characterize contemporary aerosol therapy practices during IMV, NIV and HFNC. Specifically, the study will describe the 14-day period prevalence of aerosol therapy, clinical indications, prescribed dosing regimens, and administration techniques across participating intensive care units worldwide. By capturing contemporary real-world practice across diverse healthcare systems, ICUNEB aims to generate robust international evidence to improve our understanding of aerosol therapy during respiratory support and provide valuable data to support future clinical research, educational initiatives, and the continued development of evidence-informed clinical practice.

Objectives:	**Primary descriptive objective** ▪ Determine the prevalence of aerosol therapy administration among patients receiving respiratory support during the 14-day observation period, reported separately for IMV, NIV and HFNC. **Secondary descriptive objectives** ▪ Identify the clinical indications for aerosol therapy during IMV, NIV and HFNC. ▪ Characterize the inhaled medications administered and their dosing regimens, including dose and administration frequency. ▪ Describe the aerosol administration techniques used during IMV, NIV and HFNC, and assess adherence of reported administration practices to current international recommendations, separately for each respiratory support modality.
Study design:	This study is a prospective, multicenter, observational, international project. Each participating center will conduct a single 14-day observation period within the predefined study window.
Eligibility criteria for participating centers	(1) Tertiary or non-tertiary care center with an adult intensive care or intermediate care unit (also referred to as high-dependency care, stepdown care, progressive care, transitional care unit), in which at least one of the following respiratory support modalities is routinely used: IMV, NIV, or HFNC; (2) represented by a co-investigator with at least three years of clinical experience in intensive or intermediate care; (3) willing to participate in the study. To ensure representation of the roles assigned to each healthcare profession across different countries, all professions will be encouraged to participate (i.e. physicians, nurses, physical therapists, etc.). For eligible Swiss centers, co-investigators must have completed GCP training modules 1 and 2, with certifications obtained after Jan 1, 2016.
Inclusion / Exclusion criteria:	**Inclusion criteria:** ▪ Patients hospitalized in the intensive care unit (ICU) or the intermediate care unit (IMCU, also called high-dependency care, stepdown care, progressive care, transitional care unit) at any time during the center-specific 14-day observation period of the participating center, regardless of the length of stay in the unit; ▪ aged 18 years or older; ▪ receiving IMV, NIV or HFNC at least once during the 14-day observation period; ▪ for whom consent has been obtained according to national law. In Switzerland, the informed consent will be signed by the patient or a legal representative. **No exclusion criteria** will be applied in this observational study of patients on respiratory support.

Measurements and procedures:	During the 14-day observation period, data will be collected through a secure REDCap® electronic case report form (eCRF) at each participating center. The co-investigator will perform daily unit screening to identify patients who require respiratory support and meet the other inclusion criteria. Demographic and clinical data will be collected for each patient immediately following study inclusion. Thereafter, daily follow-up data will be collected for each included patient until study completion, including whether respiratory support is being received and, when applicable, the respiratory support modality or modalities used. For patients receiving respiratory support, aerosol therapy administration will also be documented. When aerosol therapy is administered, additional data will be collected on the clinical indication, inhaled medication, dose and administration frequency, and aerosol administration technique according to the respiratory support modality (IMV, NIV, or HFNC).
Number of Participants with Rationale:	The study will seek to recruit the largest feasible number of participating centers internationally to capture aerosol therapy practices across diverse healthcare systems and geographical regions. The last observational international study obtained data from 81 centers across 22 countries and included approximately 1'215 intubated patients.[2] Based on this previous experience and the planned international recruitment strategy, we anticipate enrolling a comparable or larger study population.
Study Duration:	Each center will collect data during a single 14-day observation period. Participating centers will be able to select their 14-day observation period within the four-month study window.
Study Schedule:	Expected study window: September–December 2027
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Study Centers:	Multicenter international study; the final number of participating centers has not yet been determined.
Statistical Considerations:	Analyses will be primarily descriptive. Continuous variables will be summarized using appropriate measures of central tendency and dispersion, and categorical variables using counts and proportions. The prevalence of aerosol therapy will be determined separately for IMV, NIV, and HFNC. No hypothesis-driven comparative analyses are planned as primary analyses. Given the descriptive design, no formal hypothesis-testing sample size calculation was performed; the achieved sample size will determine the precision of the prevalence estimates and other descriptive outcomes.
GCP Statement:	This research project will be conducted in accordance with the protocol, the Declaration of Helsinki, the Human Research Act (HRA) and the Human Research Ordinance (HRO) as well as all national or local legal and regulatory requirements.

Recruitment Procedure

The Steering Committee and National Coordinators will seek to recruit centers internationally, with the support of the European Society of Intensive Care Medicine (ESICM). The recruitment strategy will seek broad geographical representation across participating regions, including representation from low- and middle-income settings.

Patient recruitment will be conducted by the co-investigator at each center. The co-investigator will be responsible for screening patients who meet the inclusion criteria and for obtaining informed consent from the patient or, in cases of impaired decision-making capacity, from a legally authorized representative in accordance with applicable national or local laws and regulations, prior to study participation.

Study Procedure/Flowchart with Timelines

The following two tables provide an overview of the project timeline and the data collection phase.

Steps		Months						
		0	4	11	12 - 15	20	22	24
0	Swiss participating centers identified and confirmed	X						
1	Protocol submitted to the CER-VD	X						
2	Favorable opinion obtained from CER-VD		X					
3	International centers identified		X					
4	Favorable opinions obtained from the ethics committees of all participating centers			X				
5	eCRF REDCap® tested and finalized			X				
6	Data collection by participating centers (Periods of 14-day observation)				X			
7	Data analysis					X		
8	Submission of the final report						X	
9	Manuscript submission							X

Time	T1	Daily until study completion**
Visit	Screening, ICF and data collection at inclusion	Data collection
Screening of patients	x	
Check eligibility criteria	x	
Oral and written information	x*	
Obtain written informed consent	x*	
Demographic and clinical data	x	
Daily follow-up data: respiratory support status and modality/modalities, and aerosol therapy administration, when applicable.	x	x
Data on clinical indications, inhaled medications and dosing regimens throughout follow-up, when applicable.	x	x
Data on aerosol administration techniques throughout follow-up, according to respiratory support modality, when applicable.	x	x

ICF, Informed Consent Form.

* Oral and written information will be given to the patient or, in cases of impaired decision-making capacity, to a legally authorized representative in accordance with applicable national or local laws and regulations to obtain written consent prior to study participation. If the patient regains decision-making capacity during the study period, their consent must be sought.

** Study completion is defined as the occurrence of any of the following: (1) the end of the 14-day observation period at the participating center; (2) discharge from or transfer to a unit not participating in the study; (3) withdrawal of informed consent by the patient or their legally authorized representative; or (4) the patient's death. Temporary or permanent discontinuation of respiratory support does not constitute study completion. If IMV, NIV, or HFNC is subsequently resumed during the observation period, respiratory support and aerosol therapy data collection will resume as applicable.

Risks/ Inconveniences, which are Study specific:

This study is strictly non-interventional. The study does not involve any intervention, modification of standard clinical care, or additional procedures for participants. All data are collected from routine clinical practice.

Coverage of Damages:

Haute école Arc Santé acts as the international sponsor of the study and is responsible for the overall initiation, coordination and management of the research project.
For participating centers in Switzerland, the project is classified as a Category A research project under the Swiss Human Research Ordinance (HRO) and is therefore exempt from the requirement for specific liability insurance or equivalent coverage. Any potential damage occurring in Switzerland is covered by HE-Arc's liability insurance.

For participating centers outside Switzerland, liability and insurance requirements shall be governed by the applicable national legislation and institutional requirements.

Publication

Study findings will be submitted for publication in a high-impact peer-reviewed critical care journal and submitted for presentation at the annual ESICM Congress.

Scientific contributions will be recognized according to participation, recruitment and scientific contribution to the study, in accordance with the recommendations of the International Committee of Medical Journal Editors (ICMJE) and the editorial policy of the target journal. Each participating center will designate one local co-investigator who will be recognized as a member of the ICUNEB Study Group, cited at the end of the co-author list, in accordance with the editorial policy of the target journal. All investigators will be acknowledged. Depending on the final size of the collaboration, the journal's editorial policy, and fulfilment of the ICMJE authorship criteria, participating investigators may also be considered for co-authorship of the primary publication.

As this is an investigator-initiated international observational study involving many participating countries, no financial compensation is available for participating centers.

Storage of Data for Future Research Aims:

The collected data may be made available for future research in accordance with participants' consent, applicable data-protection legislation, and study governance procedures. Where data are shared, this will be done in accordance with the FAIR principles (Findable, Accessible, Interoperable, and Reusable) and with appropriate access controls. Any secondary use of study data will comply with applicable ethical and regulatory requirements. For participating centers in Switzerland, written informed consent for the secondary use of study data will be obtained from participants, or where applicable from their legally authorized representative, through the study informed consent form.

Ethical Considerations:

The primary scientific value of this study lies in providing a comprehensive and contemporary description of aerosol therapy practices during respiratory support across diverse intensive care settings worldwide. By documenting current practices and their variability, the ICUNEB study will address important knowledge gaps regarding the real-world use of aerosol therapy during IMV, NIV, and HFNC.

The study also has strong knowledge translation potential. Observed administration practices will be interpreted in the context of contemporary evidence and international recommendations. This

analysis will be conducted at the study-population level to identify practice patterns and potential priorities for future research and education, rather than to assess or rank individual participating centers. The findings may therefore inform educational initiatives, future clinical research, and the continued development of evidence-informed clinical practice and international recommendations.

Although participation from all countries and all intensive care units cannot be achieved, the planned international multicenter recruitment is expected to generate a large and diverse dataset. Based on the experience of the previous international study by Ehrmann et al.,[2] the anticipated number of participating centers and patients should allow sufficiently precise estimates of contemporary aerosol therapy practices across a broad range of healthcare settings. The anticipated sample size and geographical diversity are therefore considered appropriate to generate reliable and clinically meaningful descriptive evidence while remaining proportionate to the observational nature of the study.

The observational design is ethically appropriate because the study aims to document existing clinical practices without influencing therapeutic decisions or exposing participants to experimental interventions. This methodology allows clinically relevant and externally meaningful knowledge to be generated while minimizing participant burden and respecting the principles of proportionality and non-maleficence. Overall, the minimal risks associated with participation are justified by the anticipated scientific, clinical, and societal benefits, resulting in a favorable benefit–risk balance.

References:

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