The Maximizing Extubation outcomes Through Educational and Organizational Research Trial

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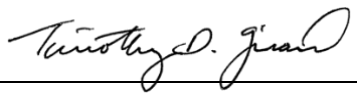
Signature Page
(signatures on file)

Trial title: The Maximizing Extubation outcomes Through Educational and Organizational Research Trial

The principal investigator approved this protocol (version 1.4) and confirms the trial will be conducted in compliance with the protocol or an approved amendment, the Declaration of Helsinki, Good Clinical Practices (ICH E6), and applicable regulatory requirements.

INVESTIGATOR		
Timothy Girard, MD, MSCI *Principal Investigator*	Signature: 	Date: March 7, 2025

METEOR TRIAL SUMMARY	
Objectives	• Test the effectiveness of interprofessional education (IPE), with or without a clinical protocol, on the implementation of two preventive, post-extubation respiratory support therapies: noninvasive ventilation (NIV) and high-flow nasal cannula oxygen (HFNC) • Compare the effectiveness of two preventive, post-extubation respiratory support therapies (NIV and HFNC), with that of conventional post-extubation oxygen on patient-centered clinical endpoints
Hypotheses	• IPE is superior to traditional online education as an implementation strategy in the ICU. • The benefits of IPE are increased when IPE is paired with a clinical protocol. • Preventive post-extubation NIV for high-risk patients and preventive post-extubation HFNC for low-risk patients are both superior to current clinical practice (i.e., conventional post-extubation oxygen therapy)
Inclusions	All adults treated with invasive mechanical ventilation >24 hrs in participating ICUs
Exclusions	None
Implementation interventions	• Traditional online education: 30-min, online, interactive, educational videos customized to provider type and offered with continuing education credits • IPE: (a) 60-min, in-person workshops consisting of a 30-min didactic session and a 30-min small group session during which learners work together to apply the content to cases, and (b) just-in-time training during which local champions meet with the ICU team each morning to identify eligible patients and review the evidence supporting proper use of the assigned preventive, post-extubation strategy • Clinical protocol: “adequately explicit” protocols for each preventive, post-extubation therapy provided to participating ICUs with instructions to work with key local stakeholders to revise the protocol, accounting for local needs and resources
Implementation content	• Post-extubation NIV for high-risk patients and HFNC for low-risk patients • Post-extubation HFNC for all patients
Trial design	Batched stepped wedge cluster randomized type 2 hybrid implementation-effectiveness trial
Randomization	• Each batch will include two to six clusters that will be randomly assigned to one of four different sequences for crossing over from usual care (a passive baseline control) to online education (an active control) to interprofessional education or protocol individually, then finally to both interprofessional education and protocol.

	• Each ICU will also be randomly assigned to one of two implementation contents at trial initiation. The assigned content will be the focus of the implementation interventions.
Implementation endpoints	• Primary: Rate of use of post-extubation NIV or HFNC among eligible patients • Secondary: Number of providers who completed an implementation intervention, number of eligible patients receiving care from providers who completed an implementation intervention, use of post-extubation NIV or HFNC among eligible patients 6 months after the implementation intervention (IPE plus protocol) is fully deployed
Clinical endpoints	• Primary: In-hospital mortality truncated at 60 days from intubation • Secondary: 90-day survival, ICU and hospital length of stay, post-extubation respiratory failure, duration of mechanical ventilation, 28-day ventilator-free days, ventilator-associated events, and organ failure (daily SOFA)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
CFIR	Consolidated Framework for Implementation Research
CRISMA	Clinical Research, Investigation, and Systems Modeling of Acute Illness Center
DSMB	Data and safety monitoring board
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
GLMM	Generalized linear mixed effect model
HFNC	High-flow nasal cannula oxygen
HRPO	Human Research Protection Office
ICC	Intraclass correlation
ICU	Intensive care unit
INR	International normalized ratio
IPAP	Inspiratory positive airway pressure
IPE	Interprofessional education
MD	Physician
NIV	Noninvasive ventilation
OE	Online education
P	Protocol
PT	Prothrombin time
PTT	Partial thromboplastin time
RCT	Randomized controlled trial
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance
RN	Nurse
RR	Relative risk
RT	Respiratory therapist
SAE	Serious adverse event
SAR	Suspected adverse reactions
SBT	Spontaneous breathing trial
SOFA	Sequential Organ Failure Assessment
SpO_2	Oxygen saturation
SUSAR	Serious unexpected suspected adverse reactions
UC	Usual care
UP	Unanticipated problem

1 BACKGROUND

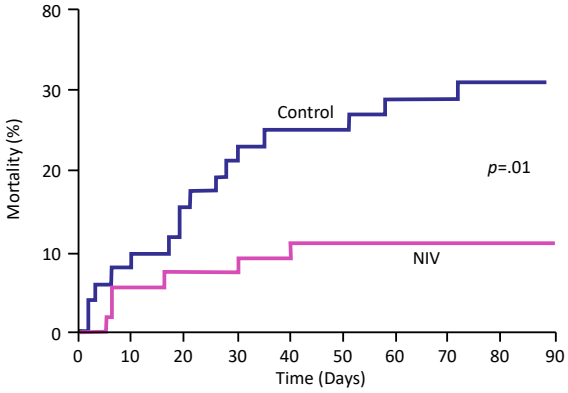
1.1 Acute respiratory failure

Acute respiratory failure requiring invasive mechanical ventilation affects nearly 800,000 patients in the United States each year.[1] Mortality for these patients is extremely high, with in-hospital mortality averaging 35% for all patients and approaching 50% for syndromes like ARDS.[1-3] Costs for these patients are also high, with an estimated $27 billion spent annually on their acute hospital care alone.[1] Recent improvements in the management of respiratory failure have led to better clinical outcomes, such that 70%-80% of mechanically ventilated ICU patients recover to the point of extubation.[2,4] Unfortunately, post-extubation outcomes remain unacceptably poor due to a high incidence of post-extubation respiratory failure. Multiple large cohort studies demonstrate that 10% to 20% of patients recovering from acute respiratory failure require reintubation after planned extubation.[2,4] In patients >65 years old who had chronic lung or heart disease (a group that comprises 24% of mechanically ventilated ICU patients), reintubation rates are 34%.[5] And in all patients, regardless of risk, reintubation is strongly associated with death,[5-8] increased costs,[9] prolonged hospital stays,[6,9] and long-term functional disability.[10]

1.2 Preventive post-extubation noninvasive ventilation (NIV)

Mechanically ventilated ICU patients should be extubated once they pass a spontaneous breathing trial (SBT) and are alert with adequate cough and minimal secretions.[12,13] Yet, for patients at high-risk for post-extubation respiratory failure, the decision to extubate is a difficult one, even after a successful SBT. Continuing invasive mechanical ventilation exposes the patient to risk and undue burden, but extubating without providing support is also undesirable. Preventive post-extubation non-invasive ventilation (NIV) offers clinicians a third option. In a landmark randomized controlled trial (RCT), Ferrer et al.[11] studied high-risk mechanically ventilated ICU patients and found that extubation to immediate NIV (rather than conventional oxygen treatment) reduced both post-extubation respiratory failure (RR = 0.31, 95%CI: 0.15 to 0.62) and 90-day mortality (RR = 0.36, 95%CI: 0.15 to 0.85) (Figure 1). A subsequent meta-analysis of five RCTs demonstrated that preventive post-extubation NIV improves multiple outcomes, including post-extubation respiratory failure, ICU length of stay, and mortality.[11,14-17] In light of these data, current American Thoracic Society/American College of Chest Physicians clinical practice guidelines on liberation from mechanical ventilation, made a strong recommendation that high-risk patients who pass an SBT should be extubated to preventive NIV.[18-20] A similar recommendation was made in guidelines published by the European Respiratory Society and American Thoracic Society.[21]

Figure 1. Effect of post-extubation NIV on mortality[11]



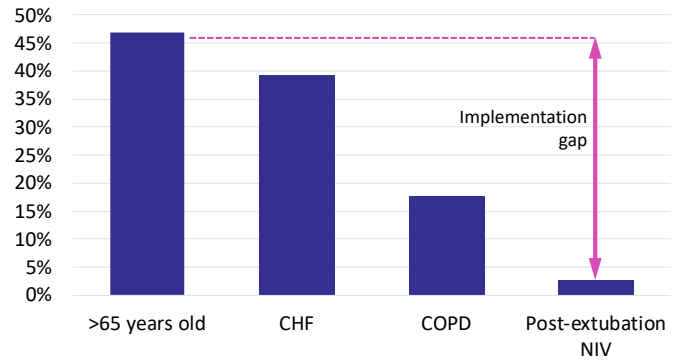
1.3 Post-extubation high-flow nasal cannula oxygen (HFNC)

Recent technological advances have enabled the delivery of high-flow oxygen therapy via nasal cannula (HFNC), a therapy that provides not only high and constant FiO_2 but a low level of continuous positive airway pressure via a simple, well-tolerated respiratory interface. Use of HFNC to treat hypoxemia is now commonplace, but its use as a preventive post-extubation therapy remains uncommon despite recent clinical trial evidence supporting its efficacy. Hernandez et al., for example, found that preventive post-extubation HFNC (compared with conventional oxygen therapy) reduced the reintubation rate by 7% (95% CI: 3% to 12%) among 527 low-risk mechanically ventilated ICU patients. Three recent meta-analyses examined the evidence and came to the same conclusions.[22-24] The most recent stated "both [NIV] and HFNC reduced reintubation in critically ill adults, compared to conventional [low-flow] oxygen therapy," and "NIV did not reduce incidence of reintubation when compared to HFNC."[24] At the same time, the systematic review graded the evidence regarding head-to-head comparisons of NIV and HFNC as "low" quality evidence, indicating that additional higher-quality evidence is needed.

1.4 Current use of preventive post-extubation respiratory therapies

Despite compelling evidence of the benefit of preventive post-extubation NIV (with or without HFNC), multiple cohort studies show that it is used infrequently in routine practice.[2,25] One of the largest studies found that even though nearly 50% of invasively ventilated patients had a risk factor for failed extubation, less than 3% received preventive post-extubation NIV (Figure 2).[25] Prior to our preparatory work (see Preliminary Studies), no studies specifically examined barriers to the use of preventive post-extubation NIV. Surveys about NIV in general[26-29] indicate that lack of familiarity with NIV, lack of awareness of the evidence, and concerns about the time required are key barriers to use. A large percentage of ICU patients are not receiving an important evidenced-based practice. Based on epidemiologic data, we estimate that at least 200,000 mechanically ventilated patients per year in the US are at high risk for extubation failure. If preventive post-extubation NIV leads to a 9% absolute reduction in mortality for this vulnerable population, as estimated in recent meta-analyses,[18-20] approximately 18,000 deaths per year in the US alone could be prevented by implementation of preventive post-extubation NIV.

Figure 2. Characteristics of 2,408 mechanically ventilated pts.[25]



1.5 Existing implementation strategies

Traditional strategies for knowledge transfer include education, guideline dissemination, audit and feedback of performance data, financial incentives, and automated reminders.[30] These strategies are extremely effort intensive yet often ineffective, typically resulting in either no

significant improvements in performance or small improvements that are not sustained over time.[31,32] One reason for the failure of traditional knowledge transfer in the ICU is that these strategies do not fully account for the team-based nature of critical care.[33] Most evidence-based practices in critical care are complex and multi-faceted, requiring ongoing coordination within a dynamic interprofessional care team.[34] Existing implementation strategies fail to account for the interdependent nature of critical care and instead target individual providers.[35,36] Yet targeting providers in isolation neglects the inherent role of collaboration in interprofessional teams.[37-39] When robust collaboration is absent, individual providers will find ways to circumvent even newer strategies like electronic prompts, making these interventions only modestly effective.[40] It is essential that the next generation of implementation strategies account for the complexity and interdependent nature of critical care to give interprofessional teams the skills they need to overcome challenges to the implementation of evidence-based practice as they dynamically arise.

1.6 Organizational learning

Over the last 30 years, a rich body of research has emerged regarding organizational learning, the process by which organizations create, retain, and transfer knowledge.[41] Though individual learning underlies basic knowledge acquisition, for new knowledge to be useful to an organization it must be embedded within a group repository so that it persists over time and can be accessed when needed. When performance requires coordination, like in the ICU, it is critical that knowledge be embedded in a supra-individual repository so all members can draw off the same knowledge repository for coordination to occur.[42] Such a repository is especially valuable when team membership is dynamic. Because ICU team members rotate in and out of the team, unembedded knowledge is easily lost. Current theory defines the system by which organizations acquire and apply specialized knowledge as a transactive memory system.[43] Colloquially, transactive memory systems are the knowledge of who knows what. When an organization has a robust transactive memory system, team members can rely on each other to recall and apply key knowledge about important tasks and to act in a way that is consistent with their shared understandings.[41] Extensive empirical evidence indicates that transactive memory systems underlie organizational learning and are linked to organizational performance in a variety of industries.[44] In this trial, we address limitations of past implementation work by adding an intervention specifically designed to strengthen transactive memory systems in ICUs: interprofessional education.

1.7 Interprofessional education

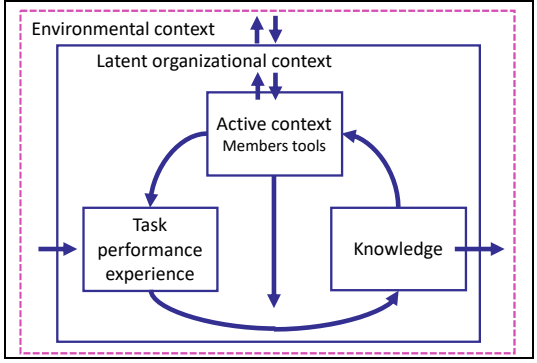
Education is a foundational element of nearly all implementation efforts. Yet traditional education focuses on individuals and occurs in professional silos—physicians learning from physicians, nurses learning from nurses, etc. As a result, the individual professions acquire different mental models and lack a shared understanding of the task at hand. Interprofessional education (IPE), in which members of different professions learn together, overcomes this problem by reinforcing not only shared mental models[45,46] but also the degree to which group members have accurate understandings of each other's' mental models.[47] IPE also fosters the development of a shared language and common set of terms, which enables effective

coordination and supports transactive memory.[48] An additional benefit of IPE is that it is highly amenable to delivery "just-in-time," i.e., directly at the point of care. Traditional education occurs separate from the "moment of need" and therefore divorced from the practical context. Just-in-time IPE overcomes this problem by tying knowledge acquisition directly to experience[49] and incorporating specific cases of immediate relevance,[50,51] thereby promoting coordination and reducing ambiguity in the learning process.[52]

1.8 Implementation research framework

We based our interventions on a foundational theory for organizational learning developed by Argote and Miron-Spektor.[49] This theory holds that organizational learning is a cycle by which shared experience leads to shared knowledge, which in turn feeds back on the context in which the task is performed, strengthening the underlying rationale and providing flexible tools for knowledge retention (Figure 3). This cycle is influenced by broader contextual factors specific to the organization (e.g., team backgrounds and team membership) and the environment (e.g., hospital policies and government regulations). The Argote-Miron-Spektor theory for organizational learning can be practically operationalized within the Consolidated Framework for Implementation Research (CFIR),[53] which holds that adoption of an intervention is influenced by the intervention, the environment, the organization, the individuals involved, and the process of implementation. We used both CFIR and the Argote-Miron-Spektor theory when developing and refining our implementation intervention. CFIR ensured that we didn't miss any key issues that would pose unexpected barriers to implementation, and the Argote-Miron-Spektor theory allowed us to more specifically place implementation within the context of organizational learning.

Figure 3. Theory for organizational learning[49]



1.9 Preliminary studies

To prepare for the METEOR Trial, we completed a number of preliminary studies. In these studies, we: (1) comprehensively assessed barriers and facilitators to adoption of preventive post-extubation respiratory therapies; (2) developed and pilot tested a novel IPE intervention as well as a control education intervention; and (3) refined our interventions based on lessons learned in the pilots.

1.9.1 Barriers to implementation of preventive post-extubation NIV and HFNC

We performed a web-based survey of 287 nurses (RNs), 125 respiratory therapists (RTs), and 84 physicians (MDs) who care for mechanically ventilated patients in 15 UPMC hospitals.[54] Members of the ICU team disagreed about risks of extubation failure and benefits of post-extubation NIV and HFNC. Whereas 75% of MDs agreed that "extubation failure causes harm," only 59% of RNs and 56% of RTs agreed with the statement (p=0.01). Similarly, 79% of MDs agreed that preventive post-extubation NIV is beneficial to high-risk patients, but only 42% of

RNs and 59% of RTs agreed (p<0.001). ICU team members also lacked a shared understanding of the major barriers to the use of preventive post-extubation NIV (Table 1). We explored these issues in more depth through 32 interviews and three focus groups during which we assessed ICU team members' knowledge, attitudes, and practices about preventive post-extubation NIV. Many respondents described an important disconnect between the straightforward act of a physician placing the order for NIV and the act of actually carrying out the order. Respondents further noted the challenges created by implementing complex therapies when there is not agreement among all team members that the therapies will help. When asked specifically about IPE, members of all three provider groups thought that it was an acceptable (and beneficial) way to learn and recommended that IPE include profession-specific content and be convenient, interactive, and to the point. These results underscore the potential value of IPE in the ICU. A single well-intentioned care provider is not enough: shared mental models and a robust transactive memory system are necessary to consistently deliver evidence-based complex interventions in team-based settings like the ICU.

Table 1. Provider perspectives regarding barriers to preventive postextubation NIV[54]

Barrier	% rating barrier important			
	RN	RT	MD	*P*
It's often contraindicated.	63%	70%	43%	<0.001
It's too difficult to identify high-risk patients.	55%	57%	23%	<0.001
Other team members don't suggest it.	50%	27%	15%	<0.001
Other team members are opposed to using it.	45%	27%	23%	<0.001
It may make patients uncomfortable.	39%	38%	22%	0.02

1.9.2 Feasibility and acceptability of interprofessional education

We developed and pilot tested three novel interventions informed both by our underlying theory and our qualitative work: Two were IPE interventions (classroom-based IPE and a just-in-time IPE), which we intentionally separated in order to learn the most from each pilot. The third was online education, which we developed to serve as an active control. Each pilot was held in a different UPMC hospital. Descriptions of each pilot are as follows:

- **Classroom-based interprofessional education (IPE)**. During a one-month period, RNs, RTs, and MDs from a medical/surgical ICU at one UPMC hospital were invited to attend one of three 90-minute, in-person workshops. The workshops were held in the same building that housed the ICU and were scheduled to coincide with ICU shift changes. During workshops, a trained facilitator explained the rationale and evidence supporting preventive post-extubation NIV and profession-specific implementation content in a 45-minute didactic session, which was followed by a 45-minute group discussion during which participants applied what they learned while reviewing cases. A total of 31 learners participated; 30 completed post-education surveys or interviews.
- **Just-in-time interprofessional education (IPE)**. During a one-month period, trained educators with medical backgrounds (e.g., nurse practitioners) screened patients in a medical ICU at a second UPMC hospital each weekday morning to identify high-risk patients who qualified for preventive post-extubation NIV. When the interprofessional ICU team rounded at the bedside of an eligible patient, the educator briefly reviewed the rationale and evidence supporting preventive post-extubation NIV in a manner designed

to make minimal disruptions to workflow.[55] A total of 7 learners participated; 6 of these completed post-education surveys or interviews.

- **Traditional online education (active control)**. During a one-month period, RNs, RTs, and MDs from a medical/surgical ICU at a third UPMC hospital were invited to complete a 30-minute, online, interactive, educational module that included a video describing all aspects of preventive post-extubation NIV and pre- and post-video quizzes. Videos were customized to each provider type, and learners were offered provider-specific continuing education credits. A total of 22 learners participated; 14 of these completed post-education surveys or interviews.

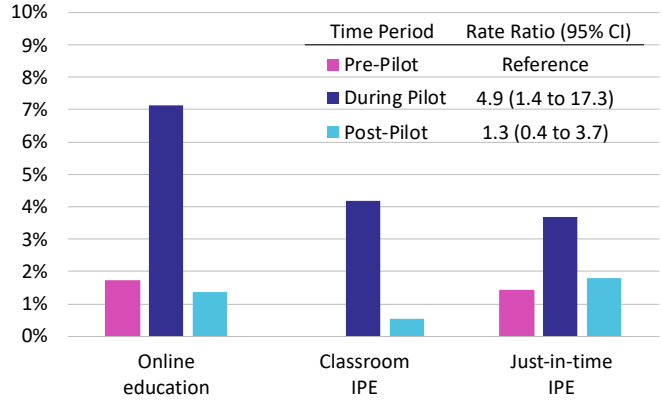
When analyzing interviews and surveys of learners, we focused on RN and RTs because we received the most data from them (Table 2). These providers reported that they enjoyed the classroom IPE and found the content valuable. They specifically reported that they valued learning together but indicated that MD participation and buy-in is key to adoption. In contrast, RNs and RTs had mixed opinions about just-in-time IPE. Though viewed as unobtrusive, the brief presentation of content was not convincing to some learners. Despite extraordinary efforts, no MDs attended the classroom IPE. The attending MD, however, was present at each just-in-time IPE intervention and reported "it wasn't burdensome at all." Thus, an intervention that combines classroom-based and just-in-time IPE will reach more providers.

Table 2. Perceptions regarding interprofessional education (IPE) interventions

Statement	Classroom IPE		Just-in-time IPE	
	RN	RT	RN	RT
I liked the way the information was presented.	90%	100%	73%	50%
The IPE was easy to fit into my schedule.	86%	100%	83%	25%
The content was relevant to my patients.	95%	100%	71%	75%
I feel more knowledgeable after the education.	100%	100%	71%	50%
My ICU will be more likely to use post-ext NIV.	90%	100%	86%	0%

We also analyzed implementation outcomes before, during, and after our pilots. Specifically, we measured use of preventive post-extubation NIV among eligible patients during the 1-month pilot period and the 6 months pre- and post-pilot. We interpret these results with caution, since the pilots were designed to refine our interventions and provide data for power calculations, not to identify clinically significant effects. Nonetheless, interrupted time series analysis found that use of preventive post-extubation NIV increased significantly during the pooled pilot periods (RR 4.9, 95% CI 1.4 to 17.3; Figure 4). This effect was blunted and no longer significant during the post-pilot period (RR 1.3, 95% CI 0.4 to 3.7).

Figure 4. Frequency of preventive post-extubation NIV



1.9.3 Interprofessional education and a clinical protocol

When interviewing the pilot participants, we specifically asked them how we could make the interventions more effective. Providers repeatedly discussed the importance of the intersection between clinical protocols and IPE. Protocols, defined as a set of standardized procedures for implementing and changing therapy, are widely used in critical care but are inconsistently associated with improved outcomes.[12,20,56-59] Providers frequently described the "top-down" nature of new protocols and noted that protocols do not preclude disagreements about care plans. Providers posited that IPE might create shared understanding around a protocol, and that protocols might be useful frameworks around which to base IPE. Together, these analyses strongly suggested that IPE can be paired with a clinical protocol to create a "virtuous circle" which reinforces local buy-in, standardizes implementation procedures, and provides ready access to knowledge.[32]

1.9.4 Preventive post-extubation HFNC

In interviews and during IPE sessions, learners also wanted to talk about HFNC. Our preliminary work focused on preventive post-extubation NIV because it is supported by the most robust clinical trial data and is strongly recommended by trustworthy clinical practice guidelines. The last two years, however, have seen the emergence of new data suggesting a complementary role for post-extubation HFNC. Participants in our pilot study were keenly aware of this evidence. One RT, for example, reported that using post-extubation NIV instead of post-extubation HFNC would be like "going backward." These data prompted a realization salient to both the METEOR Trial and the implementation science community writ large—any meaningful implementation work must grapple with the emergence of new evidence during the course of implementation efforts. Based on these data, we opted to design the METEOR Trial so that we could compare the effectiveness of post-extubation NIV and HFNC, making it a true type-2 hybrid effectiveness-implementation trial.[60,61]

1.9.5 Current use of preventive post-extubation NIV and HFNC in UPMC ICUs

To validate an EHR-based flag for preventive post-extubation NIV, two critical care physicians (the PI and one other) reviewed 40 medical records of mechanically ventilated ICU patients who underwent planned extubation. Based on our findings, we defined preventive NIV as any NIV initiated during the first 30 minutes after planned extubation. In 12 UPMC hospitals from 2017-2019, only 2.3% of high-risk patients received preventive post-extubation NIV (range across hospitals: 0.1% to 12.1%). This finding is similar to those of earlier cohort studies,[2,25] confirming a large implementation gap for this evidence-based practice. As expected, we found that post-extubation HFNC therapy was used even less often than NIV in UPMC hospitals.

2 OBJECTIVES AND HYPOTHESES

2.1 Objectives

- **Implementation objective:** Test the effectiveness of IPE, with or without a clinical protocol, on the implementation of two preventive, post-extubation respiratory support therapies (NIV and HFNC)

- **Clinical objective:** Compare the effectiveness of two preventive, post-extubation respiratory support therapies (NIV and HFNC) with that of conventional post-extubation oxygen on patient-centered clinical endpoints

2.2 Hypotheses

This type 2 hybrid implementation-effectiveness trial will test multiple interrelated hypotheses:

- **Implementation hypothesis 1:** IPE is superior to both traditional online education and to usual care (no structured education) as an implementation strategy in the ICU.
- **Implementation hypothesis 2:** The benefits of IPE are increased when IPE is paired with a clinical protocol.
- **Clinical hypothesis:** Preventive post-extubation NIV for high-risk patients and preventive post-extubation HFNC for low-risk patients are both superior to current clinical practice (i.e., conventional post-extubation oxygen therapy).

3 STUDY DESIGN

The METEOR Trial is a batched stepped wedge cluster randomized type 2 hybrid implementation-effectiveness trial. Clusters (ICUs or groups of ICUs) are randomized rather than individuals, and each cluster will cross over from control to intervention at a randomized timepoint. This design is ideal for the METEOR Trial for three reasons. First, patient-level randomization is scientifically problematic due to a high risk of contamination of the control group by a systems-level intervention.[62] Second, a parallel cluster RCT is infeasible because ICUs will be unwilling to serve as controls during the entire trial period.[63] Third, recruitment of all ICUs at the same time may significantly burden a health system that is severely constrained.[64]

We will employ three variations on the traditional stepped wedge design:

1. A factorial design will allow us to estimate the effects of two implementation strategies (IPE and a clinical protocol) separately as well as together.[65]
2. A concurrent design will allow us to compare two post-extubation strategies (HFNC for all patients vs. NIV for high-risk patients and HFNC for low-risk patients) with conventional post-extubation oxygen therapy and with each other.[65]
3. A batched design allows for the recruitment of clusters (i.e., ICUs) throughout the duration of the trial rather than requiring that all clusters commence participation in the trial at the same time.[64]

4 SETTING AND PARTICIPANTS

4.1 Study sites

Within participating UPMC hospitals, the METEOR Trial will include 24 clusters (ICUs or groups of ICUs) that admit at least 100 mechanically ventilated adults annually. Implementation

strategies will target all physicians, nurses, and respiratory therapists who work in participating ICUs. All patients who meet the following eligibility criteria will be included in analyses examining endpoints.

4.2 Inclusion criteria

All adults treated with invasive mechanical ventilation >24 hours in participating ICUs will be included.

4.3 Exclusion criteria

This pragmatic trial has no exclusion criteria. Having no restrictions on age, comorbidities, or expectations regarding outcomes reflects the realities of real-world decision-making.

5 RANDOMIZATION

The unit of randomization (the cluster) is the cluster (ICU or group of ICUs).[64] At baseline, participating ICUs are receiving usual care, i.e., no structured education regarding post-extubation respiratory support therapies. As shown in Table 3, a batch will include between two and six clusters, which will be randomly assigned using a computer-generated randomization scheme to one of six different sequences for crossing over from usual care (UC, a passive baseline control) to online education (OE, an active control) to interprofessional education (IPE) or protocol (P) individually, then finally to both IPE and P. In batch 1, the ICU randomly assigned to sequence 1 will continue UC during the first step of the trial (S1), with a step lasting one month, then will deploy OE for three steps, then IPE alone for two steps before finally deploying both IPE and P together. Alternatively, the ICU assigned to sequence 2 will continue UC for one step, then deploy OE for four steps, then deploy P alone for two steps, before finally deploying both IPE and P together. Sequences 3 and 4 are the same as sequences 1 and 2, respectively, but crossover to OE from UC occurs later, as shown. Batch 2 will include the same six sequences but will begin crossover six steps after Batch 1. Ultimately, all participating ICUs (not all of which are shown in Table 3) will deploy IPE plus P intervention by the end of the trial.

Table 3. Stepped-wedge deployment schedule

Batch	Sequence	ICU	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S…
1	1	1	UC	OE	OE	OE	IPE	IPE	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P
1	2	2	UC	OE	OE	OE	OE	P	P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P
1	3	3	UC	UC	UC	OE	OE	OE	IPE	IPE	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P
1	4	4	UC	UC	UC	OE	OE	OE	OE	P	P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P
1	5	5	UC	UC	UC	UC	UC	OE	OE	OE	IPE	IPE	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P
1	6	6	UC	UC	UC	UC	UC	OE	OE	OE	OE	P	P	IPE+P	IPE+P	IPE+P	IPE+P	IPE+P
2	1	7							UC	OE	OE	OE	IPE	IPE	IPE+P	IPE+P	IPE+P	IPE+P
2	2	8							UC	OE	OE	OE	OE	P	P	IPE+P	IPE+P	IPE+P
2	3	9							UC	UC	UC	OE	OE	OE	IPE	IPE	IPE+P	IPE+P
2	4	10							UC	UC	UC	OE	OE	OE	OE	P	P	IPE+P
2	5	11							UC	UC	UC	UC	UC	OE	OE	OE	IPE	IPE
2	6	12							UC	UC	UC	UC	UC	OE	OE	OE	OE	P
3	1	13													UC	OE	OE	OE
3	2	14													UC	OE	OE	OE
…	…	…													UC	UC	UC	OE

In addition to being randomly assigned to a specific deployment sequence, each cluster will also be randomly assigned to one evidence-based strategy promoted by the IPE and P—a strategy emphasizing post-extubation HFNC for all patients vs. a strategy emphasizing post-extubation NIV for high-risk patients and HFNC for low-risk patients.

6 STUDY PROCEDURES

6.1 Implementation interventions

The METEOR Trial will examine three implementation strategies: traditional online education (an active control), IPE, and an evidence-based clinical protocol. The latter two will be examined both alone and in combination. In each participating ICU, the specific preventive, post-extubation respiratory therapy supported by these implementation strategies will be determined by randomization (as described above).

6.1.1 Traditional online education

To closely replicate standard implementation efforts, we will use an active control consisting of best existing practices for continuing education.[66] Providers working in all ICUs will be asked to complete a 30-minute, online, interactive, educational video at the beginning of the trial. The video will be customized to each provider type and offered with provider-specific continuing education credits. ICUs will also receive printed guidelines and flyers encouraging use of the assigned evidence-based strategy.[67]

6.1.2 Interprofessional education (IPE)

Providers working in ICUs that have crossed over to this strategy will participate in two forms of IPE. In classroom-based IPE, a trained physician educator with content expertise who works in the ICU will lead 60-minute, in-person, IPE workshops consisting of a 30-minute didactic session and a 30-minute small group session, during which participants will work together to apply the content to authentic cases. The workshops, which are designed according to modern principles of adult learning and IPE, will present the rationale and evidence supporting the preventive, post-extubation therapies. They are specifically designed to foster authenticity, reinforce role identity, and relate the content to life experience.[68,69] In just-in-time IPE,[55] trained local champions (RN and/or RT educators) will meet with the interprofessional ICU team each morning to identify eligible patients and, as needed, briefly review the evidence supporting proper use of the assigned preventive, post-extubation strategy.

6.1.3 Clinical protocol

Two “adequately explicit” protocols,[56] one for each preventive, post-extubation therapy, provide specific rules for use of the therapies based on patient data. ICUs that have crossed over to a clinical protocol will be provided “ready-to-customize” versions of the protocol with instructions to work with key local stakeholders to revise the protocol, accounting for local needs and resources. A local champion will then disseminate the protocol based on local practices.

6.2 Implementation content

The two implementation interventions involving education (online education and IPE) will:

1. Demonstrate the evidence supporting use of preventive post-extubation respiratory support (NIV or HFNC) over conventional post-extubation oxygen
2. Acknowledge equipoise regarding the relative effectiveness of preventive post-extubation NIV vs. HFNC
3. Indicate that the learner's ICU will be provided with implementation support (including additional IPE and an evidence-based protocol) for a specific preventive post-extubation respiratory therapy to facilitate comparison of the two
4. Describe the role of the ICU team in determining the specific post-extubation therapy that is most appropriate for an individual patient

The implementation interventions will support the deployment of one of two evidence-based approaches to preventive post-extubation respiratory care, with the specific approach determined by randomization.

6.2.1 Post-extubation NIV for high-risk patients and HFNC for low-risk patients

ICUs randomized to this approach will receive education, protocols, and materials designed to promote the following two steps, which are supported by multiple RCTs and meta-analyses.[18-21]

- **Step 1 – Risk stratification**: Patients will be classified as either high risk (age >65 years[4-6] and/or chronic cardiac and/or respiratory disease[5,6]) or low risk (all others). Though other risk factors, such as hypercapnia during an SBT, also have predictive value, the selected risk factors are readily available at the bedside without additional testing. This step will also identify patients with contraindications to NIV, such as facial fractures.
- **Step 2 – Therapy**: High-risk patients who have passed an SBT (per the participating ICU's standard definition) and meet other criteria for extubation (per the ICU team's judgment) will be extubated to preventive NIV, whereas low-risk patients who have passed an SBT and meet other criteria for extubation (per the ICU team's judgment) will be extubated to HFNC (see Table 4 for details).

Table 4. Preventive post-extubation respiratory therapies

Risk	Rx	Duration	Settings
High	NIV	≥4 consecutive hours immediately after extubation and ≥12 cumulative hours during the 24 hours after extubation	**Interface**: Mask **Ventilator**: Non-invasive **IPAP**: 12-20 cm H_2O initially and titrated to target RR<25 **EPAP**: 5-10 cm H_2O **FiO_2**: 100% initially and titrated to target SpO_2≥92%
Low	HFNC	24 consecutive hours immediately after extubation	**Flow**: 10 L/min initially and titrated up to 50 L/min or until discomfort **Temp**: 37°C **FiO_2**: 100% initially and titrated to target SpO_2≥92%

6.2.2 Post-extubation HFNC for all patients

ICUs randomized to this approach will receive education, protocols, and materials designed to advance a strategy by which all patients who were mechanically ventilated >24 hours, have passed an SBT, and meet other criteria for extubation (per the ICU team's judgment) will be

extubated to HFNC as described in Table 4. This post-extubation therapy is also supported by multiple RCTs and meta-analyses.[22-24]

6.3 Intervention fidelity

The METEOR Trial's strategy to achieve intervention fidelity is grounded in best practice recommendations from the NIH Behavior Change Consortium[70] and involves establishing and maintaining intervention fidelity with a standardized training program.

6.3.1 Establishing intervention fidelity

Physician educators and respiratory therapist/nurse champions will undergo standardized training that was built on principles of adult learning theory[71] and established best practices for "training the trainer"[72,73] and was refined based on results of our pilot study. Led by the PI and a trained implementation specialist, the training will include brief didactic sessions, which provide an overview of the IPE and basic communication skills followed by focused training on the conduct of each component of IPE, including modeling of IPE by the PI. The bulk of the training will focus on skills practice, using simulated learners and personalized feedback. Training will be followed by simulation testing using a key-skills checklist to ensure that the educators and champions can deliver all elements of the IPE. Educators and champions will receive a detailed IPE manual for reference.

6.3.2 Monitoring and maintaining intervention fidelity

We will ensure successful intervention delivery by 1) conducting quarterly booster sessions with physician educator and respiratory therapist/nurse champions during which key skills are reviewed and 2) evaluating IPE deployment throughout the trial. Using the key skills checklist, the implementation specialist will directly observe 25% of classroom IPE workshops and will evaluate just-in-time IPE via brief, semi-structured interviews with local champions once a week (for a total of 4 weeks) during each ICU's first month of IPE deployment and then once a quarter after their first month. If problems with IPE fidelity are detected, the PI and the implementation specialist will provide tailored education and skills practice.

6.4 Evaluation framework and endpoints

6.4.1 RE-AIM evaluation framework

The METEOR Trial will measure the effects of each implementation intervention using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) evaluation framework (Table 5).[74] We chose the RE-AIM framework because it (1) effectively links both implementation endpoints and clinical endpoints, (2) explicitly addresses sustainability of the implementation, and (3) is amenable to complex interventions for which there may be multiple mechanisms of effect.

Table 5. Endpoints according to the RE-AIM evaluation framework

Element	Endpoints	Measurement
Reach	Providers (N) completing each intervention	Participation logs
	Eligible patients (N) receiving care from those providers	EHR

Effectiveness	**Primary clinical endpoint**: In-hospital mortality truncated at 60 days from intubation	EHR
	Secondary clinical endpoints: 90-day mortality, ICU and hospital length of stay, post-extubation respiratory failure, duration of mechanical ventilation, 28-day ventilator-free days, ventilator-associated events, and organ failure (daily SOFA)	EHR and National Death Index
Adoption	Fidelity of the implementation strategies	Direct observation
	Provider and educator perceptions of the implementation strategies (online education, IPE, clinical protocol, and IPE + protocol)	Ancillary study[a]
Implementation	**Primary implementation endpoint**: Rate of use of post-extubation NIV or HFNC among eligible patients	EHR
	Secondary implementation endpoints: Providers' knowledge and attitudes toward post-extubation respiratory failure; specialization, coordination and cross-understanding; role clarity; psychological safety; and intra-team conflict	Ancillary study[a]
Maintenance	Continued use of post-extubation NIV or HFNC among eligible patients	EHR
	Provider and educator perceptions of the implementation strategies	Ancillary study[a]

[a]Assessments that require interaction with providers will be evaluated during an ancillary mixed-methods study described in the Appendix.

6.4.2 Endpoints

This type 2 hybrid effectiveness-implementation trial will measure endpoints that reflect the effectiveness of the interventions on both implementation and clinical endpoints.

Implementation endpoint:

- **Primary implementation endpoint**: Rate of use of post-extubation NIV or HFNC among eligible patients throughout the trial
- **Secondary implementation endpoints**:
    a. Number of providers who completed an implementation intervention
    b. Number of eligible patients receiving care from providers who completed an implementation intervention
    c. Use of post-extubation NIV or HFNC among eligible patients 6 months after the implementation intervention (IPE plus protocol) is fully deployed

Clinical endpoints:

- **Primary clinical endpoint**: In-hospital mortality truncated at 60 days from intubation
- **Secondary clinical endpoints**:
    a. 90-day survival
    b. ICU length of stay
    c. Hospital length of stay
    d. Rate of post-extubation respiratory failure (defined as reintubation within 48 hours of planned extubation)

e. Time to successful liberation from mechanical ventilation (defined as breathing without assistance for at least 48 hours)
f. 28-day ventilator-free days (defined as the number of days alive and breathing without assistance during the 28 days after index intubation with death equated to 0 ventilator-free days)
g. Rate of ventilator-associated events
h. Organ failure (measured using daily Sequential Organ Failure Assessment score)

6.5 Data collection

Nearly all quantitative data will be obtained directly from the UPMC EHR (Cerner PowerChart). Data collected from the Cerner EHR will include demographic data, laboratory values, vital signs, ventilator settings, medication use, and other key variables. These data will be augmented with data on death dates obtained from the National Death Index.

7 STATISTICAL ANALYSIS

7.1 Sample size and power calculations

To inform sample size and power calculations and demonstrate the feasibility of using the EHR to capture our relevant endpoints, we queried the UPMC ICU registry for data from the ICUs expected to participate. The rate of post-extubation NIV or HFNC among eligible patients was 2.3% with an ICC of 0.418. The in-hospital mortality rate was 21.7% with an ICC of 0.064. The number of eligible patients averaged 30 per month per ICU. In power calculations, we conservatively assumed an average of 23.3 patients with complete assessments per cluster per one-month time period. Based on our batched cluster-randomized, stepped-wedge design (see Table 3) and a 5% type I error rate, we estimate the METEOR Trial will have 90% power to detect a 1.44% increase in the primary implementation endpoint and a 4.56% decrease in in-hospital mortality for key comparisons (e.g., IPE+E vs OE). Importantly, we anticipate that this sample size will also provide us with adequate power to analyze interactions between the implementation interventions, providing granular insight about our results that we can link to Aim 3.

7.2 Statistical analysis plan

All analyses will be conducted by modified intention to treat and will consider online education (active control) the primary comparator, and usual care (passive control) will be treated as a secondary comparator. We will use several approaches to account for the stepped-wedge design. First, the analysis will incorporate time specifications to model secular trends and allow these trends to be different between the control and intervention conditions. Second, our model will include cluster-specific random effects to account for within-cluster correlations as well as random cluster by time interactions to assess for heterogeneity of secular trend across clusters. Third, we will assess whether and how the intervention effects change over time. Fourth, we will include random interactions between intervention status and cluster to assess for heterogeneity of treatment effects across clusters.

The exact specifications for our implementation endpoints and clinical endpoints are shown above in Table 5. For each endpoint, the primary estimate of the treatment effect will be a time- and cluster-adjusted rate ratio (aRR) along with 95% confidence intervals. For endpoints that are binary, the basic model will be a generalized linear mixed effect model (GLMM) with random clustering effect to estimate aRR. The above-mentioned terms to test secular trend and account for heterogeneous features will be included and tested. The final parsimonious model will only retain terms that are significant at 0.05 level. The primary clinical endpoint will be estimated via a frailty model. For endpoints that are continuous, linear mixed models will be used. We will appropriately transform endpoints for which the distribution is not normal. Components in these models will be similar to the GLMMs described above, but instead, we will estimate adjusted hazard ratios (aHRs). Based on the final models, we will compare the intervention to the control conditions and test the equality of effects between the two intervention regimens (UC → OE → IPE → IPE+P vs. UC → OE → P → IPE+P). This approach allows us to examine for important interactions (e.g., test whether the implementation strategies led to improved outcomes and test whether implementation success varied by clinical strategy).

In the case of non-convergence of the GLMM, a smaller number of points or a Laplace approximation will be used. To correct the potential inflation of the type I error rate due to a small number of clusters, the Kenward and Roger small sample correction will be used. We will also estimate and account for loss to follow-up. To increase estimation efficiency in the setting of missing data, if necessary we will perform multiple imputation before model fitting, using Rubin's rule to combine the results. We will also perform a path analysis linking our implementation outcomes to our clinical outcomes with a goal of determining the degree to which process change mediates our observed clinical effects.[75] The trial will be registered at ClinicalTrials.gov and detailed analysis plans will be published a priori in the peer-reviewed literature.

7.3 Interim analysis

To monitor for evidence that one of the two implementation contents resulted in greater effectiveness than the other, we will conduct an interim analysis after 18 months of recruitment, approximately halfway through the trial. At the end of month 18, the expected status of the participating clusters (ICUs or groups of ICUs) is shown in Table 6.

Table 6. Status of participating ICUs at month 18

		Implementation group[a]		
		UC±OE[c]	**UC → OE → IPE → IPE+P**	**UC → OE → P → IPE+P**
Content[b]	**Risk-stratified post-extubation NIV or HFNC**	7 ICUs	3-4 ICUs	3-4 ICUs
	Post-extubation HFNC for all patients	7 ICUs	3-4 ICUs	3-4 ICUs

Abbreviations: OE, online education; P, protocol; IPE, interprofessional education; UC, usual care

[a]The timing of crossover and the order (IPE first or P first) will be determined by randomization (section 5).

[b]The implementation content will be determined by randomization and will be fixed throughout the trial (section 5).

[c]Two ICUs will have crossed over from UC to OE at the end of month 18; 12 ICUs will still be under UC.

We anticipate that both implementation contents will reduce mortality compared with conventional post-extubation oxygen therapy. Because one implementation content group may experience greater benefit than the other, we will conduct an interim analysis using a two-sided significance test. The hypotheses to be tested in the interim analyses are:

- **H_0**: The difference in in-hospital mortality for those randomized to preventive post-extubation NIV for high-risk patients and preventive post-extubation HFNC for low-risk patients vs those randomized to preventive post-extubation HFNC is ≤5%.
- **H_1**: The difference in in-hospital mortality for those randomized to preventive post-extubation NIV for high-risk patients and preventive post-extubation HFNC for low-risk patients vs those randomized to preventive post-extubation HFNC is >5%.

Using the O'Brien-Fleming method to control for an overall type I error rate of 0.05 and accounting for one interim analysis after approximately 50% recruitment, the METEOR trial should be modified if p<0.0055746 at the interim analysis (Table 7). If this *a priori* rule is triggered, the trial will continue to evaluate the effectiveness of IPE (with or without a clinical protocol) but all participating ICUs will be assigned from that time on to the implementation content that results in superior survival. E.g., if the interim analysis finds that in-hospital mortality is lower in ICUs randomized to risk-stratified post-extubation NIV/HFNC, then ICUs that were originally randomized to post-extubation HFNC for all patients will immediately receive the online education for risk-stratified post-extubation NIV/HFNC. Then, at the time determined by randomization, these ICUs will deploy either IPE or a clinical protocol promoting risk-stratified post-extubation NIV/HFNC (rather than post-extubation HFNC for all patients). Two months later, the same ICU will deploy the remainder of the implementation intervention (IPE or protocol).

Table 7. Interim analysis stopping boundaries

Analysis	Boundary[a]	P value
Interim	≥ 2.7718 or ≤ -2.7718	0.0055746
Final	≥ 1.96 or ≤ -1.96	0.05

[a]Wald z test statistic value comparing in-hospital mortality between the risk-stratified post-extubation NIV/HFNC and post-extubation HFNC

8 ETHICAL CONSIDERATIONS

8.1 Justification for usual care

Clinical trial evidence supports the use of preventive, post-extubation respiratory support therapies (NIV or HFNC), but these therapies are currently used infrequently in routine practice, including in the ICUs that will participate in the METEOR Trial. The infrequent use of preventive, post-extubation respiratory support therapies in these ICUs is likely attributable to barriers to implementation (as described in section 1.9.1). Though the efficacy of preventive, post-extubation respiratory support therapies is not in question, equipoise exists regarding how best to address implementation barriers. The inclusion of usual care periods in the trial, during which ICUs will receive no structured education about preventive, post-extubation respiratory support therapies, is justified because the implementation interventions being studied during the trial remain unproven. Additionally, the simultaneous rollout of online education (active

control) in all participating ICUs is not feasible due to limitations in health system staff and research staff, both of which are required to effectively deploy online education.

8.2 Informed consent

Because the research interventions are education directed solely at ICU clinicians, the only research activity directed specifically at individual patients will be collection of protected health information. We will request that the IRB waive the requirement for informed consent for patients based on the premise that the trial meets the OHRP regulations regarding waiver of consent (45 CFR 46.116(f)(3)). Specifically, (1) the research involves no more than minimal risk to the subjects (patients are the subjects of data collection procedures, which pose minimal risk to them), (2) the research could not practicably be carried out without the requested waiver (trial activities are designed to be completed before individual patients are admitted to participating ICUs), and (3) the waiver will not adversely affect the rights and welfare of the subjects (collected data will be securely protected and maintained per institutional policies).

We could practicably document informed consent from the ICU clinicians who are the subjects of the education interventions but doing so will increase the burden on the clinicians without enhancing their research protections given the nature of the research. We will therefore request that the IRB waive the requirement to document informed consent from the ICU clinicians on the premises that the trial meets the OHRP regulations regarding waiver of the requirement to document consent (45 CFR 46.117(c)). Specifically, (1) the research (in this context, the education) presents no more than minimal risk of harm to subjects (the ICU clinicians) and involves no procedures for which written consent is normally required outside of the research context.

8.3 Risks of trial interventions

Though many of the endpoints to be studied point to the frail medical condition of the patient participants in the trial, the research interventions themselves pose minimal incremental risk to participants. The research interventions being tested during the trial will educate clinicians about two preventive post-extubation respiratory therapies that were found to be efficacious in previous randomized trials. We have no reason to suspect that these educational interventions directed at clinicians will lead to increased risk for patients because the content of the education is not experimental but rather consists of evidence-based practices that improve outcomes relative to commonly used care practices (e.g., post-extubation low-flow oxygen). Based on this evidence, a hospital could reasonably encourage either therapy with the expectation that patients will benefit. Thus, patients admitted to participating ICUs during the trial will be reasonably expected to benefit from the implementation interventions; there is no reason to anticipate harm to patients as a result of the implementation interventions.

Additionally, we hypothesize that the implementation interventions will improve clinical outcomes relative to current practice, but the clinical impact will depend on the implementation impact. Our plan to compare the two evidence-based respiratory therapies promoted by the implementation interventions reflects the notion that the overall clinical

impact of the practices cannot be meaningfully separated from the implementation effort, making it imperative to study both in context. This is the rationale for type 2 hybrid effectiveness-implementation trials.[76]

We could conduct a pure implementation trial that compares IPE with online education promoting post-extubation NIV, which the evidence shows is better than current practice (low-flow oxygen). We could also separately conduct an implementation trial comparing IPE vs. online education promoting post-extubation HFNC, which is also justified by the evidence. Both of these trials would be considered "minimal risk" trials per the OHRP criteria. During a type 2 hybrid trial, we are doing conducting both of these trials simultaneously and randomizing to strengthen causal inference about the combined effectiveness-implementation effects. Given the nature of the interventions (education promoting effective practices), the act of randomization does not increase risk for the patients.

9 DATA AND SAFETY MONITORING PLAN

9.1 Confidentiality

9.1.1 Protection of participant privacy

We will take extensive precautions to guard against disclosure of protected health information and maintain participant confidentially. All data management and analysis activities will take place on the University of Pittsburgh Health Services Research Data Center (HSRDC)'s secure, HIPAA-compliant servers. No data containing any protected health information will ever leave the secure server. All investigators, programmers, and analysts working with the files will sign a confidentially agreement committing them to full privacy.

9.1.2 Confidentiality during adverse event (AE) reporting

Adverse event reports and annual summaries to regulatory bodies will not include participant- or group-identifiable material. Each report will only include the identification code.

9.2 Adverse event information

The primary purpose of METEOR Trial interventions (including traditional online education, interprofessional education, and provision of a clinical protocol) is to change the behavior of providers (physicians, nurses, and respiratory therapists) in UPMC ICUs such that they increase implementation of post-extubation therapies that are evidence-based and recommended in clinical practice guidelines. The direct targets of these interventions are ICU providers rather than patients. Thus, the only research activity that directly involves patients is the collection of identifiable data from the UPMC EHR (Cerner Powerchart).

9.2.1 Clinical outcomes (not considered adverse events)

In this trial involving critically ill patients who are at high risk for death or other adverse outcomes due to their underlying critical illness, we will systematically track clinical outcomes, including death and organ dysfunction, and include these outcomes as part of the safety and effectiveness analyses for this study. For the purposes of reporting, death and organ

dysfunction will not be recorded as AEs unless the investigator believes the event may have been related to study participation or is more severe or prolonged than expected given the underlying critical illness. We anticipate that this determination will be very rare given that the direct targets of the trial interventions are ICU providers rather than patients, and the purpose of trial interventions is increase implementation of evidence-based therapies. This approach—considering death and organ dysfunction as outcomes rather than AEs and systemically tracking expected safety outcomes for analysis rather than solely recording individual AEs—is common in critical care trials because these outcomes/events occur commonly in the ICU, and this system mandates that data regarding death, organ dysfunction, and expected outcomes be tracked systematically for all patients and analyzed appropriately. Listed below are events that will be tracked as clinical outcomes and will not therefore be reported as AEs during this study (unless believed to be study related and/or more severe or prolonged than expected given the underlying illness):

- Death
- Respiratory failure, including need for mechanical ventilation (invasive or noninvasive) or episodes of hypoxemia
- Circulatory failure, including shock (whether requiring vasopressors or not) and cardiac arrhythmias, and hypertension
- Hepatic failure or injury leading to increased bilirubin, AST, or ALT
- Renal failure or injury leading to an increased creatinine or acute hemodialysis
- Coagulation derangements leading to elevated PT/INR or PTT, thrombocytopenia, or thrombocytosis
- ICU readmissions

In addition to the clinical endpoints (section 6.4.2) and comprehensive organ dysfunction outcomes listed above, we will track the following adverse outcomes of special interest, which are rare but potential consequences of post-extubation respiratory support when implemented as part of usual care.

- Unplanned death (i.e., without a “comfort measures only” order) within 24 hours of planned extubation
- Reintubation within 24 hours of planned extubation

9.2.2 Adverse event (AE) monitoring and classifications

We define an Adverse Event (AE) as any untoward medical occurrence for a trial participant that is not tracked as a clinical outcome, regardless of whether the event is considered study related or not. Study personnel will communicate regularly with clinicians in participating ICUs to solicit information about any potential AEs. All identified AEs will be assessed as to whether they are (1) related to study participation, (2) serious, and/or (3) unexpected according to the following definitions:

Related. AEs that investigators suspect are related to study participation will be classified as Suspected Adverse Reactions (SARs). Certainty of relatedness is not required as long as a reasonable possibility exists that the AE is related to study participation.

Serious. AEs that result in any criteria below will be considered Serious Adverse Events (SAEs):

- Death
- A life-threatening episode requiring immediate intervention
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacitation or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An episode that requires intervention to prevent the above and/or permanent impairment or damage

Unexpected. AEs, including SARs, that are not listed in the protocol (see section 9.2.3) or are listed but are more severe or prolonged than expected will be considered Unexpected.

All events that are *related*, *unexpected*, and *serious* will be reported as Serious Unexpected Suspected Adverse Reactions (SUSARs). Given that the expected risks (as outlined below) are very unlikely to lead to events that will be classified as serious, we do not expect SUSARs to occur during the METEOR Trial, but we will monitor for and report any events that meet these criteria.

In keeping with ORHP guidance, events that are *unexpected*, *related* (or possibly related), and *suggest greater risk of harm* (including physical, psychological, social, economic, legal, or informational harm) than was previously known will be reported as Unanticipated Problems (UPs). We anticipate that all SUSARs will be classified as UPs and nearly all UPs will be classified as SUSARs but will make determinations about SUSARs and UPs separately.

9.2.3 Expected risks

Potential incremental risks of trial participation (i.e., relative to those incurred in the course of usual care) include risks from implementation interventions and the risk of the disclosure of protected health information.

Risks from implementation interventions. For the ICU providers exposed to implementation interventions (traditional online education, interprofessional education, and provision of a clinical protocol), the risk is limited to the possibility of psychological distress related to being observed in their place of employment and/or an educational setting. Psychological distress could occur if a participant feels uncomfortable being observed by researchers. We consider this work to be “minimal risk” under the Department of Health and Human Services Code of Federal Regulations because it involves social research methods (e.g., observation), and the probability and magnitude of physical and psychological harm is similar to that normally encountered in daily life.

Risk of the disclosure of protected health information. The trial will use only existing data originally collected for clinical purposes. Potential risk to research participants who are patients is limited to accidental disclosure of protected health information should there be a breach in our data security procedures.

9.2.4 Protections against risk

The protocol we propose has been through a multitude of refinement stages that have involved input of experts in critical care medicine, implementation science, educational theory, and biostatistics. To ensure strict adherence to the study protocol and high-quality data collection, all study personnel will be thoroughly trained on the study protocol and procedures. Prior to conducting any research procedures, an independent data and safety monitoring board (DSMB) and the University of Pittsburgh Human Research Protection Office (HRPO) will approve the trial protocol. Additionally, we will take the following steps:

ICU providers. All eligible ICU providers will be given the opportunity to opt out of implementation interventions, thereby reducing the risk of pressure from superiors to participate. We will obtain oral assent from all providers who participate in a classroom-based IPE session using an IRB-approved script. We will not obtain written consent for these activities because it is not feasible nor practical given the sheer number and rapidity of these interventions. We will request that the University of Pittsburgh HRPO waive the requirement for written informed consent under the rationale that the research involves no more than minimal risk, that the research could not be practically carried out without the waiver, and that the waiver does not adversely affect the rights and welfare of our participants.

Patients. We will take extensive precautions to guard against disclosure of protected health information and to maintain participant confidentially. All data management and analysis activities will take place on the University of Pittsburgh Health Services Research Data Center (HSRDC)'s secure, HIPAA-compliant servers. Clinical data from the EHR will be uploaded directly to the server via secure FTP. No data will ever leave the secure server at any time. All investigators, programmers, and analysts working with the files will sign a confidentially agreement committing them to full privacy.

9.2.5 Communication and reporting of adverse events

All AEs will be reported to the University of Pittsburgh Human Research Protection Office and to the NHLBI per local and NHLBI policies. Our procedures for reporting the various adverse events will be as follows:

- AEs and SAEs will be recorded in the electronic database and reported to the PI within 5 days of identification. Annually, the PI and Project Manager will provide a batched report of all AEs that increase risk to the DSMB and to the NHLBI.
- SUSARs will be recorded in the electronic database and reported to the PI within 24 hours of identification. The PI will report the event within 24 hours to the DSMB Chair

and to the University of Pittsburgh Human Research Protection Office. The DSMB Chair will serve as a real-time "Clinical Monitor" over all SUSARs by systematically reviewing SUSARs, evaluating relatedness of each event. The DSMB Chair will work in concert with the rest of the DSMB to determine if any additional actions are warranted as result of the event in order to increase the safety of the protocol. After the DSMB's review, the PI will report the SUSAR to the University of Pittsburgh Human Research Protection Office and the NHLBI within 7 calendar days of initial receipt of information. Additionally, actions taken by the Human Research Protection Office in response to SUSARs or other AEs will be reported to the NHLBI.

- UPs that are also SUSARs will be reported as SUSARs. UPs that are not SAEs (and therefore not SUSARs) will be recorded in the electronic database and reported to the PI within 24 hours of identification. The PI will report the SUSAR to the University of Pittsburgh Human Research Protection Office and the NHLBI within 14 calendar days of the investigator becoming aware of the problem.

9.3 Data quality and safety review plan and monitoring

The PI or Project Manager will review all data collection forms on an ongoing basis for completeness and accuracy as well as protocol compliance. The frequency of review will vary according to the event (Table 8).

Table 8. Data review plan

Data type	Frequency	Reviewers
Participant (ICU provider) accrual	Weekly	PI, PM
eCRFs	Biannually	PI, PM
AEs	Annually	PI, DSMB, HRPO, NHLBI
SUSARs	Per occurrence	PI, DSMB, HRPO, NHLBI
UPs that are not SAEs	Per occurrence	PI, HRPO, NHLBI

Abbreviations: AEs, adverse events; eCRFs, electronic case report forms; HRPO, University of Pittsburgh Human Research Protection Office; NHLBI, National Heart, Lung, and Blood Institute; PI, principal investigator; PM, project manager; SAEs, serious adverse events; SUSARs, serious unexpected suspected adverse reactions; UPs, unanticipated problems

9.4 Reporting changes in study status

Any action resulting in a suspension of the trial will be reported to the NHLBI Program Official.

9.5 Data safety monitoring board (DSMB)

Additional details regarding the METEOR DSMB are provided in a separate charter.

9.5.1 Membership

The DSMB will include five independent voting members (three members will constitute a quorum) who are not study investigators and have no financial, scientific, or other conflict of interest with the trial; written documentation attesting to absence of conflict of interest will be required. These members will be recommended by the PI and approved by the NHLBI. A representative of the NHLBI will serve as an ex officio nonvoting member. Collectively, the DSMB will have expertise in the following fields: critical care medicine, implementation science,

clinical trial methodology, research ethics, and biostatistics. The Chair will be responsible for overseeing meetings, developing agendas in consultation with the NHLBI and PI, and being the contact person for the DSMB.

9.5.2 Charter

The DSMB's first order of business will be to work with the PI and the trial Steering Committee to develop and approve a DSMB Charter, which will specify DSMB responsibilities; procedures for disclosing conflict of interest, calling unplanned meetings and/or interim analyses, and conducting meetings; planned meeting schedule; meeting materials; and planned interim analyses. The following two sections represent suggestions by the PI, which may be approved, modified, or rejected by the DSMB.

9.5.3 Initial meeting

Prior to the initiation of the trial, the DSMB will meet and review the entire IRB-approved study protocol with regard to participant safety, recruitment, randomization, intervention, data management, quality control and analysis. Also, they will review the informed consent document with regard to applicability and readability. If the protocol and other study documents are deemed satisfactory by the DSMB, they will recommend to the PI and trial Steering Committee that the trial begin. If, alternatively, modifications to the protocol or other study documents are needed, the DSMB will recommend such modifications and postpone its recommendation to begin recruitment. This initial meeting may occur via conference call or in person and will begin with an introduction by the PI, then continue as an executive session, including only DSMB members and (if available) NHLBI program staff.

9.5.4 Additional meetings

Throughout the trial, the DSMB will meet in person or by teleconference at least once a year (with additional meetings as needed) to review blinded or unblinded data as needed and appropriate, including data on recruitment, randomization, retention, protocol adherence, operating procedures, form completion, intervention effects, gender and minority inclusion, and subject safety. The DSMB is responsible for identifying problems related to safety, requesting additional data relevant to safety, proposing analyses of safety endpoints as needed, and considering the rationale for continuation of the study in light of safety data, progress of randomization, retention, protocol adherence, and data management. Reports of AEs and SUSARs will initially be provided to the DSMB in a blinded fashion (i.e., treatment group assignment will not be revealed), but the DSMB will retain the right to request an unblinded report. Only DSMB members will have access to unblinded data in order to preserve the integrity of data and minimize potential for bias while maintaining appropriate safety monitoring. After each DSMB meeting, the DSMB Chair will provide a written report to the PI and trial Steering Committee and the NHLBI program official. In addition, the PI, in turn, will provide the reports to the University of Pittsburgh Human Research Protection Office.

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11 APPENDIX – ANCILLARY MIXED-METHODS STUDY

11.1 Objective

To inform our interpretation of the results of the METEOR Trial, we will perform an ancillary mixed-methods study designed to examine contextual factors that influence the effectiveness of interprofessional education and preventive, post-extubation respiratory therapies (NIV and HFNC).

11.2 Study design

During and after the parent METEOR Trial, we will perform in-person interviews and surveys of providers in ICUs that participate in the METEOR Trial and use thematic content analysis to understand the mechanisms of the observed effects and identify organizational factors that may modify the observed trial results.

11.3 Participants and procedures

We will invite all physicians, nurses, and respiratory therapists working in participating ICUs to complete surveys at four time points:

1. Before online education is deployed in the respondent's ICU
2. After online education is deployed in the respondent's ICU
3. After either interprofessional education or the clinical protocol are deployed in the respondent's ICU
4. After both interprofessional education and the clinical protocol are deployed in the respondent's ICU

We will also conduct in-person, semi-structured interviews in a one-on-one setting to explore important topics in greater depth and allow participants to frame issues in their own words. Trained qualitative research coordinators will perform all interviews, which will be audiotaped and transcribed. Based on our past work, we expect to reach thematic saturation after interviewing 15 participants per ICU in 16 ICUs, which we will stratify based on (1) the order they received the interventions and (2) which clinical strategy they received.

Lastly, to determine the organizational contexts that support sustained use of the interventions, we will conduct interviews after the trial has ended. Based on our past work, we anticipate that we will reach thematic saturation by interviewing 8 participants per ICU in 6 ICUs—3 high-performing ICUs (per the primary implementation outcome) and 3 low-performing ICUs.

11.4 Endpoints

As specified in Table 5, endpoints assessed during surveys and interviews will include:

- ICU provider and educator perceptions of the implementation strategies
- ICU providers' knowledge and attitudes toward:

a. Post-extubation respiratory failure
b. Specialization
c. Coordination and cross-understanding
d. Role clarity
e. Psychological safety
f. Intra-team conflict

11.5 Analysis

We will perform a constant comparative, iterative, thematic content analysis designed to uncover perceptions regarding the relative importance of the different components of the METEOR implementation strategy. The analysis will be based on our conceptual framework for organizational learning and will initially focus on the relationship between task performance experience, knowledge, and both the organizational and environmental contexts. As new themes emerge these will be incorporated into our framework and further specified.