# Characteristics and Outcomes of Eligible Non-Enrolled Patients in a Mechanical Ventilation Trial of Acute Respiratory Distress Syndrome

Yaseen M. Arabi[1], Deborah J. Cook[2], Qi Zhou[3], Orla Smith[4], Lori Hand[3], Alexis F. Turgeon[5], Andrea Matte[6], Sangeeta Mehta[7], Russell Graham[8], Kristin Brierley[9], Neill K.J. Adhikari[10], Maureen O. Meade[2], Niall D. Ferguson[11], and the Canadian Critical Care Trials Group

[1] Intensive Care Department, King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, Saudi Arabia ,
[2] Departments of Medicine and Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada
[3] Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada
[4] Critical Care Department & Keenan Research Center, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada
[5] Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, and Population Health and Optimal Health Practices Research Unit, Research Center of the CHU de Québec, Université Laval, Québec City, Québec, Canada
[6] University Health Network, Toronto, Canada
[7] Interdepartmental Division of Critical Care Medicine, University of Toronto; Department of Medicine, Mount Sinai Hospital, Toronto, Canada
[8] Memorial Hermann, Texas Medical Center, Houston, Texas
[9] University of Michigan Health System, Ann Arbor, MI
[10] Interdepartmental Division of Critical Care Medicine, University of Toronto, Department of Critical Care Medicine, Sunnybrook Health Science Centre, Toronto, Canada
[11] Interdepartmental Division of Critical Care Medicine, Departments of Medicine and Physiology, and Institute for Health Policy, Management and Evaluation, University of Toronto; Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, Toronto, Canada

**Corresponding Author:**
Yaseen Arabi, MD, FCCP, FCCM
Chairman, Intensive Care Department
King Saud Bin Abdulaziz University for Health Sciences
King Abdullah International Medical Research Center
ICU 1425, PO Box 22490
Riyadh, 11426, Kingdom of Saudi Arabia
+966(11)801-1111 Ext 18855/18877
yaseenarabi@yahoo.com

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4.4

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**Scientific Knowledge on the Subject**
Enrollment in clinical trials may be associated with improved outcomes compared with standard care, but results are heterogeneous. The extent to which eligible-not-enrolled patients impact study generalizability is not well documented in the critical care setting.

**What This Study Adds to the Field**
Enrollment in trials of mechanical ventilation may be associated with improved outcomes compared with standard care outside of a trial. There is a need for prospective tracking and transparent reporting of eligible-not-enrolled patients as part of trial management

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

## ABSTRACT

**Rationale:** Patients eligible for randomized controlled trials (RCTs) may not be enrolled for various reasons. Non-enrollment may affect study generalizability and lengthen the time required for trial completion.

**Objectives:** We sought to describe characteristics and outcomes of eligible non-enrolled (ENE) patients in a multicenter trial of mechanical ventilation strategies.

**Methods:** Within the OSCILLATE trial of high-frequency oscillation (HFO) versus conventional ventilation (CV) in adults with ARDS, and with approval from research ethics boards, we collected a minimal dataset on patients who satisfied eligibility criteria but were not enrolled. We categorized ENE patients as ENE-HFO and ENE-CV based on receipt of HFO at any time. We used multivariable logistic regression to assess the association between ENE status and mortality.

**Measurements and Main Results:** 548 patients were randomized, and 546 were ENE. The most common reasons for ENE were no consent (42%), physician refusal (24%), missed randomization window (15%), and current HFO use (14%). Compared with randomized patients in respective arms of the trial, ENE-HFO patients were younger and had worse lung injury while ENE-CV patients had lower illness severity. ENE status was independently associated with mortality (adjusted OR 1.39, 95%CI 1.06-1.84; p=0.02); with no significant interaction with ventilation treatment group.

**Conclusions:** Non-enrollment was common, with approximately 1 ENE patient for every randomized patient. Our study suggests that enrollment in trials of mechanical ventilation may be associated with improved outcomes compared with standard care and highlights the need for prospective tracking and transparent reporting of ENE patients as part of trial management.

Keywords: randomized controlled trial, mechanical ventilation, high-frequency ventilation, patient recruitment, mortality

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## Introduction

Patients eligible for randomized controlled trials (RCTs) are often not enrolled for various reasons(1). Because non-enrolled patients may differ from enrolled patients(2), study generalizability may be limited if the non-enrollment rate is high and the treatment effect is influenced by factors related to non-enrollment (2, 3). In addition, non-enrollment prolongs the duration of study recruitment, thereby increasing study costs.

There are many reasons for non-enrollment of eligible patients into a trial, including lack of informed consent from patients or proxies, lack of available research personnel, competing trials, and logistical or procedural challenges (1). Non-enrollment may also result from physicians refusing to allow patients or proxies to be approached for consent. This may be due to a perception that one study arm is superior to the other, or that management of the patient based on physician judgment will be better for the patient than enrollment in the trial. However, such perceptions have not been validated. In fact, patients enrolled in a RCT may benefit from receiving protocolized care and more rigorous clinical monitoring. A Cochrane systematic review found that patients participating in RCTs have similar outcomes as patients receiving the same treatment in clinical practice outside the context of an RCT; however, results were heterogeneous in that some studies showed better outcomes among patients treated within RCTs, and others showed worse outcomes (4).

The incidence and consequences of non-enrollment of eligible patients in mechanical ventilation RCTs are unclear. We recently reported the results of the OSCILLation for ARDS Treated Early (OSCILLATE) trial, which randomly assigned adults with early moderate-to-severe ARDS to a mechanical ventilation strategy using High Frequency Oscillation (HFO) versus conventional ventilation (CV) (5). In this secondary analysis, we sought to describe the prevalence and reasons of non-enrollment, examine the organizational and patient-level factors associated with non-enrollment, and determine whether an association exists

between non-enrollment and patient outcomes. Some of the results of this study have been previously reported in the form of an abstract.(6)

## Methods

Of the 41 ICUs that randomized patients into OSCILLATE, 36 (88%) had Research Ethics Board approval to collect a minimal dataset for eligible-not-enrolled patients with a waiver of consent. In 7 (17%) of these 36 ICUs, the research ethics boards stipulated that if the reason for non-enrollment was refusal of consent to participate in the trial, only the reason for non-enrollment could be recorded, and not the additional clinical data.

### Definitions

Patients meeting the OSCILLATE inclusion criteria were documented as *screened*. Screened patients who met no exclusion criteria were deemed *eligible*, after which the treating physician's agreement and the substitute decision maker's (SDM) consent to enroll were sought. If eligible patients could not be enrolled for any reason, they were considered *eligible-not-enrolled (ENE)*.

Local research coordinators prospectively documented the reasons for non-enrollment: no SDM consent (with a further list of reasons), physician refusal (with a further list of reasons, including 'definite plan to use HFO'), already on HFO at the time of screening, missed the randomization window of 72 hours, participation in a confounding trial, and lack of availability of an oscillator. We categorized ENE patients as ENE-HFO if they received HFO at any time during the course of their ICU stay; otherwise they were classified as ENE-CV. We categorized randomized patients as randomized-HFO or randomized-CV based on their group assignment.

### Data Collection

We recorded baseline demographics, severity of illness and ventilator and blood gas parameters. We also collected vital status at ICU and hospital discharge, duration of ventilation and lengths of stay in ICU and hospital.

To supplement this analysis, we surveyed participating centers about organizational factors that may be associated with non-enrollment, including the years of multicenter trial experience and the number of research staff. As a surrogate for research activity we recorded the number of observational and randomized studies ongoing at each site in 2010. We documented affiliation with research consortia, number of ICU beds, and duration of OSCILLATE participation. We also surveyed 31 research coordinators by telephone regarding their perceptions of the completeness of OSCILLATE ENE documentation and any impediments to recording ENE patients at their centers.

**Statistical Analysis**

We examined reasons for non-enrollment and trends of non-enrollment over the four quartiles of the study period using Cochran-Armitage Trend Test. We compared reasons for non-enrollment between ENE-HFO and ENE-CV patients using Chi-square or Fisher Exact tests. We classified centers into those with a low or high ENE:randomized ratio using the median ratio of 1.0 as a threshold, and compared organizational factors between these 2 groups. We constructed a linear regression model to assess predictors of the ENE:randomized ratio with the following independent variables: ratio of screened but ineligible:randomized patients, number of other ongoing studies, and number of research staff.

We compared baseline characteristics and outcomes of ENE-CV and ENE-HFO patients with their randomized counterparts and with each other. Normally distributed variables were reported as means and SDs and were compared using the t-test; non-normally distributed variables were reported as medians and interquartile range and were compared using the Wilcoxon rank test if the number of observations was below 30. We constructed a multivariable logistic

regression analysis to assess the association of the following *a priori* independent variables on hospital mortality: ENE status (vs. randomized), treatment group (HFO vs. CV), APACHE II score, sepsis, and $PaO_2/FiO_2$ ratio, and the interaction term between ENE and ventilator group. We conducted a post hoc sensitivity analysis restricting the population to patients from centers with Research Ethics Board approval to collect ENE data. Because of clinical differences between ENE-CV and ENE-HFO patients, we calculated separate odds ratios for mortality for these subgroups even though the interaction was not statistically significant. We considered a multilevel model with patients clustered in centers, but rejected this approach because of the large number of centers and relatively small number of patients per center. We set our significance level at alpha of 0.05 and did not adjust for multiple comparisons.

## Results

During the study period, 548 patients were randomized while 546 were ENE, with a considerable variability among centers (median ratio of ENE:randomized of 1.00, IQR: 0.35 – 1.80) (Figure 1 and E1). This ratio did not change over the study period quartiles (1.00, 0.97, 0.96, 1.08, p=0.90). The most common reasons for non-enrollment were no informed consent in 229 (41.9%), physician refusal in 129 (23.6%) and trial eligibility exceeding 72 hours in 81 (14.8 %) patients (Table 1).

### Organizational Factors and ENE rates

Univariable analyses demonstrated that centers with low versus high ENE:randomized ratios were similar in their organizational characteristics, with only the ratio of screened-ineligible:randomized patients trending towards higher in the centers with a higher ENE:randomized ratio (Table 2). This finding was confirmed in the multivariable analysis in which the only variable associated with the ENE:randomized ratio was the screened-ineligible:randomized ratio ($p<0.001$). The number of other ongoing trials (p=0.96) or number of research staff (p=0.96) were not associated with the ENE:randomized ratio (see Table E1 in the online data supplement).

## Comparison of ENE and Randomized Patients

Compared to randomized-CV patients, ENE-CV patients had better prognosis at baseline as demonstrated by lower APACHE II scores and less severe lung injury. Compared with randomized-CV patients, ENE-CV patients were mechanically ventilated with a higher tidal volume, lower respiratory rate, lower PEEP, and lower plateau pressure (Tables 3 and E2). In contrast, compared to both randomized-HFO and ENE-CV patients, ENE-HFO patients were younger but had worse lung injury as evidenced by higher airway pressures, and higher oxygenation index (Table 3). Unadjusted outcomes of ENE and randomized patients by ventilator group are also shown in Table 3.

The results of the multivariable logistic regression for hospital mortality are shown in Table 4. ENE status was independently associated with higher in-hospital mortality regardless of mode of ventilation (p=0.55 for interaction). The exclusion of the 21 randomized patients from the 7 centers that did not contribute ENE data did not alter these results (Table E3).

## Discussion

Non-enrollment of eligible patients was common in the OSCILLATE trial, and the ratio of ENE to randomized patients varied across centers. The only factor predicting a high ENE rate was a high ratio of screened-ineligible:randomized patients, suggesting that variable documentation practices may drive the ENE rate. Non-enrollment did not occur randomly: ENE patients ventilated with HFO outside the trial had more severe ARDS than study patients, while ENE patients ventilated with conventional ventilation had less severe ARDS than study patients. Non-enrollment was associated with increased risk of mortality.

The differences between ENE patients and randomized patients may be explained by physicians not wanting to enroll sick patients into the trial because they believed that HFO would be helpful, while also not wanting to enroll less sick

patients into the trial because they believed that patients were not ill enough for HFO and were concerned about exposure to additional sedation and neuromuscular blocking agents. Baseline differences between ENE and randomized patients in mode of ventilation, tidal volume and other ventilator parameters may also be related to pre-enrollment modifications made by the treating team in patients who were anticipated to be enrolled in the trial.

The most common reasons for not enrolling patients were SDM and physician refusal. In our study, we did not document the reasons for refusals by either SDMs or physicians. Decision making psychology suggests that humans tend to be risk-averse when the potential for regret associated with the decision is high. This is likely the case for SDMs, as studies have shown that anxiety and fear of risk are common reasons for declining consent.(7-9) Physician refusals are consistent with cognitive psychology research that suggests that people place too much confidence in human decision-making process, particularly when based on system 1 thinking which is rapid and subconscious, and influenced by biases, opinions, and misinformation.(10) Our findings do not support the assumption that physicians were accurate at judging when their specific approach to patient management would be superior to that of the research protocol. However, in a prior thromboprophylaxis trial, we found that tracking and analyzing why physicians decline to have their patients be considered for the trial helped trialists to understand and respond to bedside concerns, informing physician educational priorities bearing on enrollment, and enhancing recruitment efficiency (11)

One key message from this secondary analysis is that enrollment in an ARDS ventilation trial may be associated with better patient outcomes. We found higher survival rates for randomized patients who were ventilated using CV compared to ENE patients who were ventilated using CV, despite prognostic imbalances favoring the ENE group. The control ventilation strategy in the OSCILLATE trial was evidence-based, protocolized, and monitored for protocol adherence. It was a low tidal volume, high PEEP ventilation strategy, consistent with recent systematic reviews (12, 13). Protocol adherence was assessed in real time at the

Methods Centre and feedback was provided every two weeks to sites. In addition, a 24-hour help line was available for clinicians facing difficulties in keeping patients on protocol. It is likely that this approach achieved a higher level of lung protective ventilation than conventional ventilation strategies outside of the trial. In the OSCILLATE trial other aspects of care (e.g., fluid therapy, antibiotic management, sedatives and paralytics) were at the discretion of the treating team; we did not collect any data about these co-interventions in ENE patients and their contribution to outcomes is unknown.

ENE patients who received HFO had more severe ARDS than their randomized counterparts. This finding likely reflects clinician use of HFO to rescue deteriorating patients. However, after correcting for baseline imbalances, ENE-HFO patients did not fare better than randomized HFO patients. These are important findings in that they address a key hypothesis generated by the OSCILLATE Trial. The results of OSCILLATE, which showed increased mortality with HFO, conflicted with those of the OSCAR (High Frequency OSCillation in ARDS) RCT, which showed no difference in mortality between HFO and CV (14). One plausible explanation is that the OSCILLATE HFO strategy was more harmful than other HFO strategies. However, this possibility is less likely as 'usual care' HFO prescribed outside of the trial yielded similar results to HFO prescribed within the trial. In contrast, our findings suggest that variations in the degree of lung protection in CV strategies are more relevant to the disparate findings of OSCILLATE and OSCAR, since CV was protocolized in OSCILLATE but not in OSCAR.

Non-enrollment of otherwise eligible patients has several potential implications. Non-enrollment, driven to large extent by human decision-making, does not occur at random, and as illustrated in our trial, ENE patients had different baseline characteristics and outcomes, despite meeting the same inclusion criteria. This point is important because clinicians attempting to implement evidence in practice can only apply the written inclusion criteria; the ENE criteria

remain opaque. In addition, there are operational consequences. Many RCTs are terminated because of slow recruitment (15) and in many others, enrollment is prolonged beyond the planned recruitment period, especially in RCTs of standard-of-care interventions based on lower levels of evidence (16). High rates of non-enrollment reduce the efficiency and increase the cost of conducting RCTs. In addition, the delay in obtaining a timely answer to the research question may deprive patients from receiving more appropriate therapy or, conversely, expose patients to harm. For example, delays in recruitment to the ISIS-2 trial of streptokinase and aspirin for the treatment of acute myocardial infarction may have resulted in up to 10,000 unnecessary deaths of patients treated in routine practice before the trial results were available (17).

Our study showed considerable variability across centers in their ENE: randomized ratios as reflected by the wide IQR. Because this ratio is greatly influenced by the extent of faithful reporting of ENE patients, a low ratio may be obtained if the process of randomization is highly efficient (ensuring almost all eligible patients are randomized) or if the ENE patients are simply not documented and reported. Differences in patient populations among centers may also contribute to this variability. Our data showed that the number of reported ENE is strongly associated with the number of reported screened but ineligible patients, suggesting that differences in documentation and reporting may be the major driver of this variability. This may reflect that screening and documentation of ENE patients is not typically subjected to the same rigor of trial oversight (e.g., in the form of site-specific audit and feedback) compared with oversight focused on randomized patients. In our study, organizational factors including staff experience were not independent predictors of ENE reporting. In addition, the lack of difference in perception of completeness of ENE reporting between high and low ENE centers suggests that complete reporting ENE may not be a primary focus of attention of research staff. It is possible that the trial's financial compensation structure was a factor in the variable reporting, because (like many other trials) remuneration was based on payment per randomized patient, not per eligible patient; we are unable to examine this further. Other consequences of

under-reporting ENE patients remain unclear, but we cannot exclude the possibility that ENE patients, including those not enrolled because of SDM or physician refusal, may in general be under-estimated. Given our findings, we suggest the need for standardized reporting of ENE and screened patients and budgeting for this data collection from study outset to ensure reliable and complete information.

In our study, 12% of ICUs did not receive Research Ethics Board approval to collect a minimal dataset for any ENE patients with a waiver of consent, and an additional 17% of ICUs were not allowed to collect these data for patients whose SDMs refused consent to participate in the trial. The inability to collect these data represents a barrier to monitoring the characteristics and outcomes of patients not enrolled in randomized trials. By extension, this precludes one important method to understand the generalizability of trial results. Research practices vary by jurisdiction, ranging from disinclination or prohibition of such data collection to endorsement or protocolization of data collection under a waived consent model. Thus, the interpretation of trial results in light of the characteristics of eligible non-enrolled patients is only possible for some trials in some jurisdictions.

Our analysis should be interpreted in light of both its strengths and weaknesses. This is the largest trial in mechanical ventilation that has examined non-enrollment of otherwise eligible patients. In our survey, we aimed to learn about trial enrollment and non-enrollment of eligible patients in multiple centers participating in OSCILLATE; however, more complex factors such as research culture, health care delivery models, and decision-making models for research were not addressed and would be worthy of future work using different study designs. The OSCILLATE trial was open-label and thus our findings may not apply to patient- and clinician-blinded trials. Clinical decisions to use HFO in the ENE setting are inherently complex, and our multivariable analysis may not have accounted for all confounders. The limited dataset in ENE patients did not allow the examination of factors such as the ventilation strategy and other therapies

beyond the time of eligibility. Finally, our analysis of trends of non-enrollment over time may be confounded by some new centers starting sequentially as the trial unfolded, each being at different points in their learning curve with respect to screening and enrollment.

In summary, we found that non-enrollment of eligible patients in a mechanical ventilation randomized trial was common and that characteristics of non-enrolled patients differ from randomized patients. Randomized patients managed within the clinical trial had better outcomes than ENE patients managed outside the trial. Therefore, enrollment in trials of mechanical ventilation may be associated with improved outcomes compared with standard care, which supports the notion that a protocolized lung protective strategy is associated with lower mortality. Our study suggests the need for prospective tracking and transparent reporting of ENE patients as part of trial management in interventional studies.

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Figure 1. Patient Flow. REBs for 5 ICUs prohibited any data on ENE patients from being collected. In 7 of the remaining 36 ICUs, the REB stipulated that if the reason for non-enrollment was refusal of consent to participate in the trial, only the reason for non-enrollment could be recorded, and not the additional clinical data.

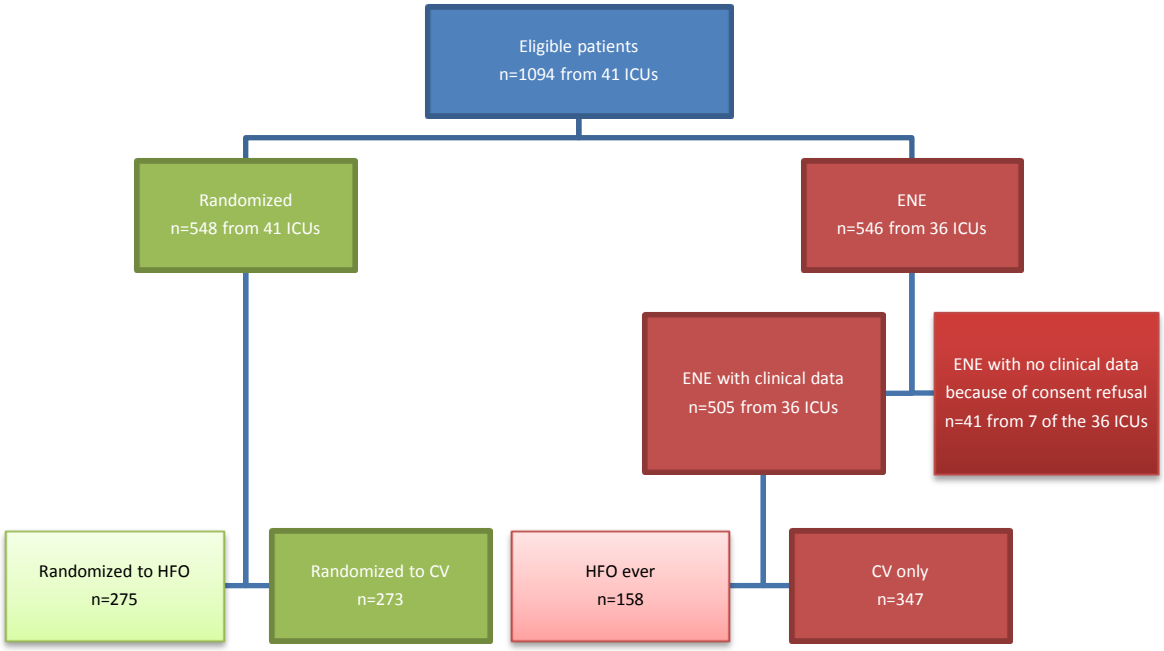

**Table 1.** Reasons for non-enrollment among eligible patients

| Reason for non-enrollment | All ENE patients n=546 | HFO-ENE n=158 | CV-ENE n=388 | P-value |
|---|---|---|---|---|
| **No patient/SDM consent obtained, n (%)** | **229 (42.0)** | **26 (16.5)** | **203 (52.3)** | **<0.0001** |
| No SDM | 47 (20.5) | 8 (30.8) | 39 (19.2) | 0.49 |
| Unable to locate SDM | 35 (15.3) | 5 (19.2) | 30 (14.8) | |
| SDM unable to decide in time | 23 (10.0) | 2 (7.7) | 21 (10.3) | |
| SDM declined | 109 (47.6) | 9 (34.6) | 100 (49.3) | |
| Other | 15 (6.6) | 2 (7.7) | 13 (6.4) | |
| **Physician refusal, n (%)** | **129 (23.7)** | **46 (29.1)** | **83 (21.4)** | **0.05** |
| Definite plan to use HFO | 38 (29.5) | 33 (71.7) | 5 (6.0) | < 0.0001 |
| Refuse HFO | 17 (13.2) | 4 (8.7) | 13 (15.7) | |
| Concern about paralysis | 7 (5.4) | 0 | 7 (8.4) | |
| Concern about HFO protocol | 13 (10.1) | 3 (6.5) | 10 (12.1) | |
| Concern about CV protocol | 5 (3.9) | 0 (0) | 5 (6.0) | |
| Reluctant to follow protocols in general | 24 (18.5) | 2 (4.4) | 22 (26.5) | |
| Other concern with study | 4 (3.1) | 0 (0) | 4 (4.8) | |
| Other | 21 (16.3) | 4 (8.7) | 17 (20.5) | |
| **Eligible > 72 hours, n (%)** | **81 (14.8 )** | **10 (6.3)** | **71 (18.3)** | **0.0004** |
| **Current HFO use, n (%)** | **76 (13.9)** | **76 (48.1)** | **/** | **/** |
| **Participation in another trial, n (%)** | **22 (4.0)** | **0** | **22 (5.7)** | **0.0006** |
| **Oscillator unavailable, n (%)** | **9 (1.6)** | **0** | **9 (2.3)** | **0.07** |

ENE: eligible-not-enrolled, HFO: high-frequency oscillation, CV: conventional ventilation, SDM: substitute decision maker
Reasons for non-enrollment are mutually exclusive. P-value reflects comparison between HFO-ENE and CV-ENE.

**Table 2.** Comparison of organizational factors between centers with low vs. high ENE: randomized ratio categorized using the median (1) as cutoff point.

| | **Centers with low ENE: randomized ratio n=21** | **Centers with high ENE: randomized ratio n=20** | **P-value** |
|---|---|---|---|
| **Site investigator years of multicenter trial experience, n (%)** | n=19 | n=20 | |
| 0 -11 years | 8 (42.1) | 13 (65.0) | 0.15 |
| > 11 years | 11 (57.9) | 7 (35.0) | |
| **Research coordinator years of multicenter trial experience, n (%)** | n=19 | n=20 | |
| 0 - 8 years | 10 (52.6) | 10 (50.0) | 0.87 |
| > 8 years | 9 (47.4) | 10 (50.0) | |
| **Full time ICU research staff, n (%)** | n=19 | n=20 | |
| <=1 FTE | 9 (47.4) | 11 (55.0) | 0.63 |
| >1 FTE | 10 (52.6) | 9 (45.0) | |
| **Number of ongoing observational studies in 2010**, median (IQR) | n=19<br>2 (1-4) | n=20<br>2 (1-2) | 0.66 |
| **Number of other ongoing randomized trials in 2010**, median (IQR) | n=19<br>3 (2-5) | n=20<br>4 (3.5-6) | 0.08 |
| **Affiliation with research consortium** | n=19 | n=20 | 0.23 |
| Research Coordinator - RT | 7 (36.9) | 5 (25.0) | |
| Research Coordinator - RN | 1 (5.3) | 6 (30.0) | |
| Research Coordinator - Other | 3 (15.8) | 4 (20.0) | |
| MD - Attending | 4 (21.05) | 3 (15.0) | |
| MD - Fellow/resident | 0 (0) | 1 (5.0) | |
| Other | 4 (21.05) | 1 (5.0) | |
| **Number of ICU beds, n (%)** | n=19 | n=20 | |
| <= 26 beds | 8 (42.1) | 12 (60.0) | 0.26 |
| > 26 beds | 11 (57.9) | 8 (40.0) | |
| **Duration of OSCILLATE participation, years,** median (IQR) | n=21<br>2.1 (1.2-4.7) | n=20<br>2.4(1.6-4.8) | 0.63 |
| **Participation in the Pilot phase, n (%), median (IQR)** | n=21<br>7 (46.7) | n=20<br>8 (40.0) | 0.66 |
| | | | |
| **Ratio of screened-ineligible: randomized,** median (IQR) | N=21<br>3.0 (2.3-4.0) | N=20<br>4.2 (2.6-6.7) | 0.06 |
| **Research Coordinator retrospective rating of the completeness of documenting ENE**<br>Complete or near complete (81-100%)<br>High (61-80%)<br>Intermediate (41-60%),<br>Low (21-40%)<br>Very low (0-20%) | n=14<br><br>11 (78.7%)<br>1 (7.1%)<br>1 (7.1%)<br>1 (7.1)<br>0 | n=17<br><br>9 (52.9%)<br>4 (23.5%)<br>3 (17.7%)<br>0<br>1 (5.9%) | 0.33 |

| | | | |
|---|---|---|---|
| **Research Coordinator perception of the <u>biggest</u> impediment to recording all ENE** | n=14 | n=17 | 0.24 |
| Workload related to ENE forms | 3 (21.4%) | 1 (5.9%) | |
| Workload in general | 4 (28.6%) | 7 (41.2%) | |
| Patient approached for other study | 0 | 0 | |
| Patients screened Monday to Friday only | 1 (7.1%) | 5 (29.4%) | |
| Other: | 6 (42.9%) | 4 (23.5%) | |

**Table 3.** Characteristics and outcomes for ENE and randomized patients

| | HFO- ENE n=158 | HFO- Randomized n=275 | P-value | CV- ENE n=347 | CV- Randomized n=273 | P-value | P-value for HFO-ENE vs. CV- ENE |
|---|---|---|---|---|---|---|---|
| **Age, mean (SD), yr** | 48.9 (17.5) | 54.7 (16.2) | 0.001 | 53.8 (16.0) | 53.6 (15.7) | 0.92 | 0.002 |
| **Female sex, n (%)** | 59 (37.3) | 108 (39.3) | 0.69 | 141 (40.6) | 120 (44.0) | 0.41 | 0.48 |
| **APACHE II score, mean (SD)** | 28.7 (8.7) | 28.7 (8.8) | 0.83 | 25.1 (8.1) | 28.8 (7.2) | < 0.0001 | <0.0001 |
| **ARDS risk factors, n (%)** | | | | | | | |
| Sepsis | 73 (46.2) | 128 (46.5) | 0.96 | 145 (41.8) | 130 (47.6) | 0.15 | 0.35 |
| Pneumonia | 91 (57.6) | 155 (56.4) | 0.80 | 214 (61.7) | 164 (60.1) | 0.69 | 0.39 |
| Gastric aspiration | 16 (10.1) | 49 (17.8) | 0.03 | 41 (11.8) | 44 (16.1) | 0.12 | 0.58 |
| Trauma | 6 (3.8) | 10 (3.6) | 0.93 | 17 (4.9) | 5 (1.8) | 0.04 | 0.58 |
| Other | 46 (29.1) | 71 (25.8) | 0.46 | 104 (30.0) | 67 (24.5) | 0.13 | 0.85 |
| **Ventilator mode, n (%)*** | | | 0.02 | | | 0.002 | 0.01 |
| Pressure Assist Control | 88 (56.4) | 150 (54.5) | | 146 (42.5) | 136 (49.8) | | |
| Volume Assist Control | 28 (18.0) | 56 (20.4) | | 76 (22.1) | 65 (23.8) | | |
| Volume-targeted Pressure Control | 16 (10.3) | 20 (7.3) | | 76 (22.1) | 27 (9.9) | | |
| Pressure Support | 13 (8.3) | 43 (15.6) | | 28 (8.1) | 31 (11.4) | | |
| Other | 11 (7.0) | 6 (2.2) | | 18 (5.2) | 14 (5.1) | | |
| **Tidal volume, mean (SD), ml/kg PBW** | 448 (152) | 422 (119) | 0.08 | 474 (129) | 424 (113) | < 0.0001 | 0.07 |
| **Respiratory rate, mean (SD), $cmH_2O$** | 25.8 (7.4) | 26.2 (6.4) | 0.59 | 24.4 (6.9) | 26.8 (5.8) | < 0.0001 | 0.04 |
| **Plateau pressure, mean (SD), $cmH_2O$** | 31.0 (7.3) | 28.8 (6.6) | 0.003 | 26.3 (6.3) | 29 (6.4) | < 0.0001 | < 0.0001 |
| **Peak inspiratory pressure, mean (SD), $cmH_2O$** | 36.6 (6.5) | 31.9 (7.1) | 0.0003 | 31.2 (6.6) | 31.8 (7.1) | 0.53 | < 0.0001 |
| **Mean inspiratory pressure, mean (SD), $cmH_2O$** | 21.7 (6.0) | 19.4 (4.8) | 0.0001 | 17.0 (4.8) | 19.7 (4.4) | < 0.0001 | < 0.0001 |
| **Set PEEP, mean (SD), $cmH_2O$** | 13.8 (4.8) | 13.1 (3.2) | 0.12 | 11.1 (3.7) | 13.4 (3.3) | < 0.0001 | < 0.0001 |
| **$FiO_2$, mean (SD)** | 0.87 (0.16) | 0.73 (0.16) | < 0.0001 | 0.71 (0.18) | 0.75 (0.16) | 0.01 | < 0.0001 |
| **Oxygenation index, mean (SD)** | 30.6 (17.1) | 19.7 (10.4) | < 0.0001 | 16.3 (8.9) | 20 (9.8) | < 0.0001 | < 0.0001 |
| **$PaO_2/FiO_2$, mean (SD)** | 87.4 (40.9) | 115.8 (38.6) | < 0.0001 | 121.6 (44.2) | 113.1 (38.6) | 0.01 | < 0.0001 |
| **$PaCO_2$, mean (SD), mm Hg** | 51.0 (22.2) | 46.8 (13.1) | 0.04 | 43.9 (12.1) | 46.8 (13.5) | 0.01 | 0.0002 |
| **Arterial pH, mean (SD)** | 7.26 (0.15) | 7.31 (0.10) | 0.0003 | 7.33 (0.11) | 7.31 (0.09) | 0.01 | < 0.0001 |
| **Received HFO any time during the ICU stay, n** | 158 (100) | 275 (100) | NA | 0 | 34 (12.5) | < 0.0001 | NA |
| **Duration of HFO use, mean (SD)** | 4.5 (5.3) | 6.3 (5.9) | 0.001 | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Death in hospital, n (%)** | 78 (49.4) | 129 (46.9) | 0.62 | 123 (35.5) | 96 (35.2) | 0.94 | 0.003 |
| **Death in ICU, n (%)** | 77 (48.7) | 123 (44.7) | 0.42 | 111 (32.0) | 84 (30.8) | 0.76 | 0.0003 |
| **Days of mechanical ventilation, median (IQR)** | 11.5 (8–24) | 11 (7–19) | 0.26 | 9 (5–21) | 10 (6–18) | 0.60 | 0.13 |
| **Days of mechanical ventilation in survivors, median (IQR)** | 11 (8–24.5) | 11 (7–19) | 0.21 | 10 (6–21) | 10 (6–18) | 0.59 | 0.13 |
| **Days of intensive care, median (IQR)** | 13 (6–30) | 13 (7–22) | 0.20 | 13 (7–24) | 13 (8–22) | 0.32 | 0.37 |
| **Days of intensive care in survivors, median (IQR)** | 17 (10–34) | 15 (9.5–26) | 0.36 | 14 (8–25) | 14 (9–26) | 0.88 | 0.13 |
| **Days of hospitalization, median (IQR)** | 19 (7–37) | 19 (8–37) | 0.46 | 20.5 (10–44) | 20 (11–35) | 0.21 | 0.69 |
| **Days of hospitalization in survivors, median (IQR)** | 31 (17–53) | 30 (16–45) | 0.79 | 26 (14–54) | 25 (15–41) | 0.25 | 0.84 |

- Patients who were receiving HFO at the time of screening had last conventional settings prior to HFO recorded
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- **Table 4.** Predictors of hospital mortality using multivariate logistic regression analysis.

| **Predictors of hospital mortality** | **OR (95%CI)** | **p-value*** |
|---|---|---|
| ENE status (vs. Randomized) | 1.39 (1.06, 1.84) | 0.02 |
| Ventilation Group (HFO vs. CV) | 1.68 (1.28, 2.22) | <0.001 |
| APACHE II | 1.08 (1.06, 1.10) | <0.001 |
| Sepsis | 1.24 (0.94, 1.63) | 0.11 |
| $PaO_2/FiO_2$ | 0.998 (0.994, 1.001) | 0.16 |

*p value for interaction of ENE status and assigned ventilation group was 0.55; OR (95%CI) ENE-HFO 1.23 (0.78-1.93), ENE-CV 1.47 (1.02-2.11)

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Table E1 – Multivariable linear regression for predictors of center ENE:Randomized ratio

| **R-square=0.36, n=39** | **Reg. coefficient (SE)** | **P-value** |
|---|---|---|
| Ratio of screened-ineligible patients: randomized | 0.12 (0.02) | 0.0001 |
| Number of other ongoing randomized trials in 2010 | 0.002 (0.05) | 0.96 |
| Full time ICU research staff (hour) | -0.01 (0.11) | 0.96 |

**Table E2.** Comparison of pre-enrollment patient-level factors between ENE and randomized patients.

| | **ENE patients n=505** | **Randomized patients n=548** | **P-value** |
|---|---|---|---|
| Age, mean (SD), yr | 52.2 (16.6) | 54.2 (15.9) | 0.05 |
| Female sex, n (%) | 200 (39.6) | 228 (41.6) | 0.51 |
| APACHE II score, mean (SD) | 26.2 (8.4) | 28.7 (7.4) | < 0.0001 |
| ARDS Risk Factors, n (%) | | | |
| Sepsis | 218 (43.2) | 258 (47.1) | 0.20 |
| Pneumonia | 305 (60.4) | 319 (58.2) | 0.47 |
| Gastric aspiration | 57 (11.3) | 93 (17) | 0.01 |
| Trauma | 23 (4.6) | 15 (2.7) | 0.11 |
| Other | 150 (29.7) | 138 (25.2) | 0.10 |
| **Mechanical ventilation data** | | | |
| Ventilator mode, n (%) | | | |
| Pressure Assist Control | 234 (46.8) | 286 (52.2) | <0.0001 |
| Volume Assist Control | 104 (20.8) | 121 (22.1) | |
| Volume-targeted Pressure Control | 92 (18.4) | 47 (8.6) | |
| Pressure Support | 414 (8.2) | 74 (13.5) | |
| Other | 29 (5.8) | 20 (3.6) | |
| Tidal Volume, mean (SD) | 466 (137) | 423 (116) | < 0.0001 |
| Respiratory rate, mean (SD), cm $H_2O$ | 24.8 (7.0) | 26.5 (6.1) | <0.0001 |
| Plateau Pressure, mean (SD), cm $H_2O$ | 27.7 (7.0) | 28.9 (6.5) | 0.01 |
| Peak inspiratory pressure, mean (SD), cm $H_2O$ | 32.5 (6.9) | 31.8 (7.1) | 0.33 |
| Mean inspiratory pressure, mean (SD), cm $H_2O$ | 18.4 (5.6) | 19.6 (4.6) | 0.001 |
| Set PEEP, mean (SD), cm $H_2O$ | 11.9 (4.3) | 13.2 (3.2) | < 0.0001 |
| $FiO_2$, mean (SD) | 0.76 (0.19) | 0.74 (0.16) | 0.03 |
| Oxygenation Index, mean (SD) | 20.5 (13.6) | 19.9 (10.1) | 0.43 |
| $PaO_2/FiO_2$, mean (SD) | 111.2 (46.0) | 114.5 (38.6) | 0.22 |
| $PaCO_2$, mean (SD), mm Hg | 46.1 (16.2) | 46.8 (13.3) | 0.41 |
| Arterial pH, mean (SD) | 7.31 (0.13) | 7.31 (0.10) | 0.99 |
| Received HFO any time during the ICU stay, n (%) | 158 (31.5) | 309 (56.4) | < 0.0001 |
| Duration of HFO use, median (q1–q3) | 4.5 (5.3) | 6.4 (6.0) | 0.001 |

**Table E3.** Predictors of hospital mortality using multivariate logistic regression analysis restricted to patients in the 36 sites that had Ethics Board approval to collect a limited dataset from ENE patients

| **Predictors of hospital mortality** | **OR (95%CI)** | **p-value** |
|---|---|---|
| ENE status (vs Randomized) | 1.33 (1.00, 1.77) | 0.047 |
| Ventilation group HFO vs CV | 1.69 (1.27, 2.23) | 0.0003 |
| APACHE II | 1.09 (1.07, 1.11) | <0.0001 |
| Sepsis | 1.26 (0.96, 1.66) | 0.10 |
| $PaO_2/FiO_2$ | 0.997 (0.994, 1.001) | 0.12 |

*p value for interaction of ENE status and assigned ventilation group was 0.49.

Figure E1: A scatterplot of the number of ENE patients from each center (per study year) vs. the number of screened-ineligible (per study year).