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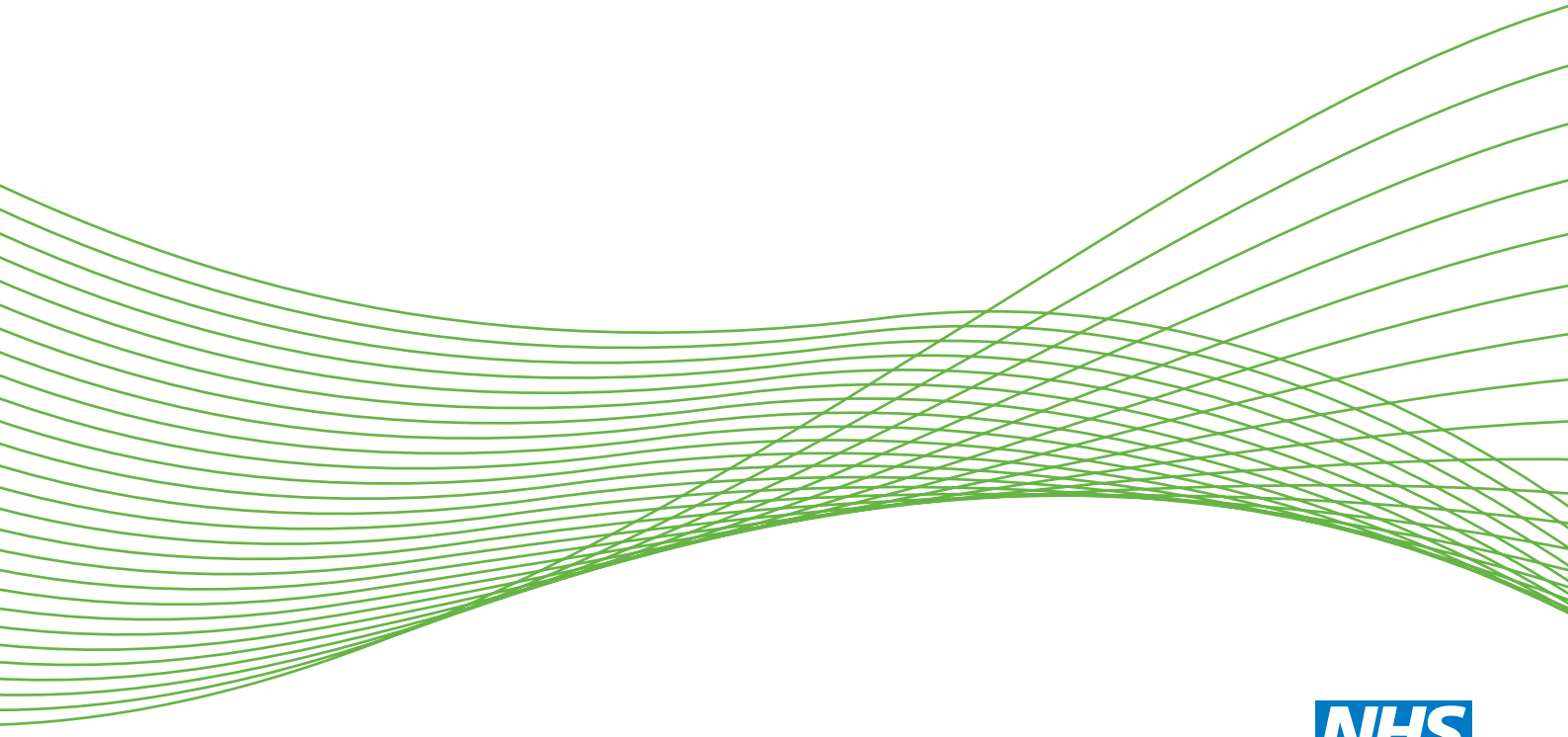

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Abstract

A randomised controlled trial and cost-effectiveness analysis of high-frequency oscillatory ventilation against conventional artificial ventilation for adults with acute respiratory distress syndrome. The OSCAR (OSCillation in ARDS) study

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Background: Patients with the acute respiratory distress syndrome (ARDS) require artificial ventilation but this treatment may produce secondary lung damage. High-frequency oscillatory ventilation (HFOV) may reduce this damage.

Objectives: To determine the clinical benefit and cost-effectiveness of HFOV in patients with ARDS compared with standard mechanical ventilation.

Design: A parallel, randomised, unblinded clinical trial.

Setting: UK intensive care units.

Participants: Mechanically ventilated patients with a partial pressure of oxygen in arterial blood/fractional concentration of inspired oxygen (P : F) ratio of 26.7 kPa (200 mmHg) or less and an expected duration of ventilation of at least 2 days at recruitment.

Interventions: *Treatment arm* HFOV using a Novalung R100® ventilator (Metran Co. Ltd, Saitama, Japan) ventilator until the start of weaning. *Control arm* Conventional mechanical ventilation using the devices available in the participating centres.

Main outcome measures: The primary clinical outcome was all-cause mortality at 30 days after randomisation. The primary health economic outcome was the cost per quality-adjusted life-year (QALY) gained.

Results: One hundred and sixty-six of 398 patients (41.7%) randomised to the HFOV group and 163 of 397 patients (41.1%) randomised to the conventional mechanical ventilation group died within 30 days of randomisation ($p = 0.85$), for an absolute difference of 0.6% [95% confidence interval (CI) −6.1% to 7.5%]. After adjustment for study centre, sex, Acute Physiology and Chronic Health Evaluation II score, and the initial P : F ratio, the odds ratio for survival in the conventional ventilation group was 1.03 (95% CI 0.75 to 1.40; $p = 0.87$ logistic regression). Survival analysis showed no difference in the probability of survival up to 12 months after randomisation. The average QALY at 1 year in the HFOV group was 0.302 compared to 0.246. This gives an incremental cost-effectiveness ratio (ICER) for the cost to society per QALY of £88,790 and an ICER for the cost to the NHS per QALY of £78,260.

Conclusions: The use of HFOV had no effect on 30-day mortality in adult patients undergoing mechanical ventilation for ARDS and no economic advantage. We suggest that further research into avoiding ventilator-induced lung injury should concentrate on ventilatory strategies other than HFOV.

Trial registration: Current Controlled Trials ISRCTN10416500.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 19, No. 23. See the NIHR Journals Library website for further project information.

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Glossary

Acute Physiology and Chronic Health Evaluation II A scoring system originally used to predict mortality in patients admitted to intensive care units but now widely used as a measure of severity of acute illness.

Centimetres of water (cmH_2O) A unit of pressure measurement used in respiratory measurement.

Consolidated Standards of Reporting Trials A standardised format for reporting clinical trials.

Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) A clinical trial of extracorporeal membrane oxygenation in patients with acute respiratory distress syndrome.

European Quality of Life-5 Dimensions A measure of health-related quality of life.

European Quality of Life Visual Analogue Scale A single dimension measure of recalled health-related quality of life.

Extracorporeal membrane oxygenation A technique to oxygenate blood outside the body in patients with severe respiratory failure.

Health Technology Assessment programme Part of the National Institute for Health Research.

Hertz (Hz) A unit of measurement of cycles per second.

HiFi trial An early randomised controlled trial of high-frequency ventilation in newborn children.

Kilopascal Unit of pressure measurement used in respiratory medicine to describe the partial pressure of (kPa) gases in the blood.

Millimetres of mercury (mmHg) A non-SI unit used in respiratory medicine to describe the partial pressure of gases in the blood and intravascular/intracavity pressures.

National Heart, Lung and Blood Institute Part of the US National Institutes of Health.

National Institutes of Health A US Government medical research funder.

Oxygenation index A measure of the effectiveness of oxygen exchange in the lung that takes account of pressures in the lung.

P : F ratio The ratio of the partial pressure of oxygen in the arterial blood to the fractional inspired oxygen concentration, a measure of the effectiveness of oxygen exchange in the lung.

Short Form questionnaire-12 items A measure of health-related quality of life.

Short Form questionnaire-36 items A more detailed measure of health-related quality of life.

List of abbreviations

ALI	acute lung injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	acute respiratory distress syndrome
BALTI-2	Beta Agonist Lung Injury TrIal-2
BNF	*British National Formulary*
CCCTG	Canadian Critical Care Trials Group
CE	Conformité Européenne
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CESAR	Conventional ventilation or ECMO for Severe Adult Respiratory failure
CI	confidence interval
cmH_2O	centimetres of water
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CRF	case report form
D_LCO	carbon monoxide diffusing capacity
DMEC	Data Monitoring and Ethics Committee
ECMO	extracorporeal membrane oxygenation
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	European Quality of Life Visual Analogue Scale
FDA	US Food and Drug Administration
FiO_2	fractional concentration of inspired oxygen
GCP	Good Clinical Practice
HFJV	high-frequency jet ventilation
HFOV	high-frequency oscillatory ventilation
HFPPV	high-frequency positive-pressure ventilation
HMRC	Her Majesty's Revenue and Customs
HTA	Health Technology Assessment
Hz	hertz
ICER	incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICON	Intensive Care Outcome Network study
ICS	Intensive Care Society
ICU	intensive care unit
I : E	inspiratory : expiratory
LY	life-year
MHRA	Medicines and Healthcare Regulatory Authority
mmHg	millimetres of mercury
MREC	Multicentre Research Ethics Committee
NCEPOD	National Confidential Enquiry into Peri-Operative Deaths
NHLBI	National Heart, Lung and Blood Institute
NHP	Nottingham Health Profile
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research

NRES	National Research Ethics Service
OI	oxygenation index
ONS	Office for National Statistics
OSCAR	OSCillation in ARDS
OSCILLATE	Oscillation for Acute Respiratory Distress Syndrome Treated Early
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PEEP	positive end expiratory pressure
P : F ratio	partial pressure of oxygen in arterial blood/fractional concentration of inspired oxygen ratio
PQOL	Perceived Quality of Life Scale
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
SGRQ	St. George's Respiratory Questionnaire
SICSAG	Scottish Intensive Care Society Audit Group
SIP/FLP	Sickness Impact Profile/Functional Limitations Profile
TNO	trial number
TSC	Trial Steering Committee
UTI	urinary tract infection

Plain English summary

The acute respiratory distress syndrome (ARDS) is a term covering most acute, severe, lung conditions that cause a reduction in the blood oxygen level. Most patients with ARDS need a period of treatment on an artificial ventilator (breathing machine) if they are to survive.

While initially life-saving, artificial ventilation using standard ventilator settings can further injure the patient's lungs and perpetuate, rather than cure, the lung inflammation that is the hallmark of ARDS. It is believed that 1 in 12 ventilated patients with ARDS may die as a result of the effects of artificial ventilation rather than the ARDS itself.

High-frequency oscillatory ventilation (HFOV) is a form of artificial ventilation where very small breaths are given very frequently (up to 10 times a second) while the patients' lungs are kept in a partly inflated state. This is believed to reduce the mechanical trauma to the lungs that causes the continued inflammation. The OSCAR (OSCillation in ARDS) study was set up to see if HFOV improved survival in patients with ARDS.

A total of 795 patients were randomised to either HFOV or conventional artificial ventilation. One hundred and sixty-six of 398 patients (41.7%) in the HFOV group and 163 of 397 patients (41.1%) in the conventional ventilation group died within 30 days. HFOV did not reduce the hospital stay of the survivors, but did increase the use of sedative and muscle-relaxant drugs during artificial ventilation.

The cost to the NHS of treating patients with ARDS for the time in hospital and the first year after their illness was higher in the HFOV patients, at £44,550, compared with £40,129 in those patients on conventional ventilation. Adding in the cost of patient and carers' expenses and the loss of earnings, the total cost to society was £50,583 in the HFOV group compared with £45,568 in the conventional ventilation patients.

In the first year after their illness, patients reported their quality of life at 30% of maximum in the HFOV group, compared with 25% in the conventional ventilation group. The computed cost to society of giving one patient a year of full-quality life was £88,790. Treatments at this price are not usually considered cost-effective.

In conclusion, we were unable to find any benefit or harm to the patients from the use of HFOV in adult patients with ARDS. We suggest that this mode of ventilation not be used for routine care. At the same time as this study was reported in the medical literature, a Canadian research team published the OSCILLATE study of HFOV [Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, *et al.* High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;**368**(9):795–805] which demonstrated an increased number of deaths in the HFOV group (47% vs. 35% in the control group). Overall we believe there may be better techniques to prevent lung damage during in patients with ARDS and suggest research funding is directed at these rather than at continued studies of HFOV.

Scientific summary

Background

The acute respiratory distress syndrome (ARDS) is a general term covering most causes of acute, severe type 1 (hypoxaemic) respiratory failure. Most patients with ARDS will require a period of artificial ventilation on an intensive care unit (ICU) if they are to survive. Although reasonably uncommon in population terms, the treatment of ARDS is very resource intensive and comprises a substantial proportion of the workload of most ICUs.

While initially life saving, artificial ventilation using conventional techniques can further injure the patient's lungs and perpetuate, rather than cure, the lung inflammation that is the hallmark of ARDS. The mortality attributed to artificial ventilation, over and above the underlying disease, may be 8% or more.

High-frequency oscillatory ventilation (HFOV) is a form of artificial ventilation first used on premature infants, where very small breaths are given very frequently (up to 10 times a second) while the patient's lungs are kept in a partly inflated state. This is believed to reduce the mechanical trauma to the lungs that causes the continued inflammation. A number of small studies in adults with ARDS, when combined in a meta-analysis, suggested that there might be a survival advantage if HFOV was used in place of conventional artificial ventilation. This, coupled with the increasing use of HFOV in the NHS, led the Health Technology Assessment programme to commission an effectiveness study comparing HFOV with conventional artificial ventilation in patients with ARDS, the OSCAR (OSCillation in ARDS) study, using mortality as the primary outcome.

Objectives

The primary research objective was to determine the effect of HFOV on all-cause mortality 30 days after randomisation in patients receiving artificial ventilation for acute, severe type 1 respiratory failure compared with conventional artificial ventilation.

Secondary research objectives included determining the effects of HFOV on survival at hospital discharge and later, on non-pulmonary organ failures while treated on an ICU, on health-related quality of life 6 months and 1 year after randomisation, on self-reported respiratory function, and on resource use in the ICU.

The economic analysis research objectives were to determine the health-care system benefit of HFOV measured as the cost per quality-adjusted life-year (QALY) gained 1 year after randomisation, and to determine the effect of HFOV on the utilisation of hospital and community care resources after acute hospital discharge 1 year after randomisation.

Methods

The study was an unblinded, randomised clinical trial of HFOV compared with usual ventilatory care in patients with severe type 1 respiratory failure. Patients were eligible for the study if they were ≥ 16 years of age, weighed 35 kg or more, were receiving artificial ventilation via an endotracheal or tracheostomy tube, and had acute hypoxaemic respiratory failure as defined by:

- lowest recorded partial pressure of oxygen in arterial blood/fractional concentration of inspired oxygen (P : F) ratio measured between onset of artificial ventilation and time of screening of ≤ 26.7 kPa with a positive end expiratory pressure ≥ 5 cmH_2O
- bilateral infiltrates on chest radiograph.

The patients had to be expected to require artificial ventilation until at least the evening of the day after enrolment (predicted by attending clinician) and had to have been artificially ventilated for < 7 consecutive days (≤ 168 hours) at the point of randomisation.

Patients ineligible for the study included those with respiratory failure attributable to left atrial hypertension from any cause, diagnosed clinically or with echocardiography or pulmonary artery catheterisation, and those in whom HFOV would be contraindicated, including patients with moderate or severe airway disease expected to cause expiratory airflow limitation. Patients enrolled in another therapeutic trial in the 30 days prior to randomisation were excluded. Patient consent, or, more commonly, consent/assent obtained from personal or nominated professional consultees in England and Wales, or welfare guardians/nearest relatives in Scotland, was required before enrolment.

The intervention was HFOV started after randomisation and continued until the patients had recovered sufficiently to be weaned from artificial ventilation, when their FiO_2 was 0.4 or less, and when the local clinician is satisfied that there are no non-pulmonary impediments to weaning. The study sites all used the Novalung R100® ventilator (Metran Co. Ltd, Saitama, Japan) for HFOV. The control group of patients received usual ventilator care for the study site.

The economic evaluation was carried out alongside the trial using recommended methods. An additional model-based analysis was used to extrapolate the results over the expected lifetime of the trial participants. The perspective of the NHS and personal social services was undertaken for the main analysis with an additional analysis from a societal perspective.

The primary health economic outcome was the cost per QALY gained 1 year after randomisation. The primary outcome for the clinical analysis was mortality at 30 days and the economic analysis therefore also used cost per life saved at 30 days and cost per life-year gained at 30 days. Cost analysis was undertaken to present costs at 30 days, costs at ICU discharge, costs at hospital discharge and costs over 1 year from randomisation.

Results

The study set-up and management were challenging. In common with many studies of patients in ICUs, a system to obtain consent/assent in unconscious patients had to be developed and approved in two jurisdictions with differing legal requirements (England and Scotland). As HFOV was a new technique in most study ICUs and was used on some of the highest risk patients, a comprehensive training and support package had to be developed. Recruitment proved difficult, and, as a result, both the study duration and the number of study sites had to be increased.

A total of 795 patients were randomised 1 : 1 to either HFOV or conventional artificial ventilation at 30 study sites. HFOV was used for a median of 3 days (interquartile range 2–5) in 388 patients. The longest initial period of HFOV was 24 days. The primary outcome was 30-day mortality. One hundred and sixty-six of 398 patients (41.7%) in the HFOV group and 163 of 397 patients (41.1%) in the conventional ventilation group died within 30 days of randomisation ($p = 0.85$), for an absolute difference of 0.6% (95% confidence interval −6.1% to 7.5%). The total duration of ICU stay was 16.1 ± 15.2 days in the conventional ventilation group and 17.6 ± 16.6 days in the HFOV group ($p = 0.18$); the total durations of hospital stay were 33.1 ± 44.3 days and 33.9 ± 41.6 days, respectively ($p = 0.79$). The HFOV group received more days of sedative (8.2 ± 6.4 days vs. 9.7 ± 7.4 days; $p = 0.004$) and muscle relaxant (2.0 ± 3.0 days vs. 2.5 ± 3.6 days; $p = 0.044$) medication than the control group. Antibiotic use was similar in both groups (control 12.2 ± 10.3 days, HFOV 13.3 ± 12.5 days; $p = 0.20$).

Data for inpatient resource use were collected on 792 patients (three died before study treatment was started); 397 in the conventional ventilation group and 398 in the HFOV group. Once discharged, 226 patients completed the 6-month questionnaires, 186 patients completed the 12-month questionnaires; 154 carers completed the 6-month questionnaires and at 12 months 108 carers completed the questionnaires. At 1 year following randomisation, the total cost to the NHS including inpatient stay and resources used following discharge was higher in the HFOV group at £44,550 compared with £40,129 in those patients on conventional ventilation to give an incremental cost of £4421. Taking into consideration the cost to the NHS, patient and carers' out-of-pocket expenses and the loss of earnings over 1 year post randomisation, the total cost to society was higher in the HFOV group at £50,583 compared with £45,568 with an incremental cost of £5015.

There was, however, a higher average QALY at 1 year in the HFOV group at 0.302 compared with those patients in the conventional ventilation group at 0.246 with an incremental QALY of 0.056. This gives an incremental cost-effectiveness ratio (ICER) for the cost to society per QALY of £88,790.57 and an ICER for the cost to the NHS per QALY of £78,260. The probability of being cost-effective at a threshold of £20,000 per QALY was 0.18, so the chance of HFOV ever being cost-effective must be considered low.

Conclusions

In conclusion, in a large multicentre effectiveness study, we were unable to find any clinical benefit or harm from the use of HFOV in adult patients with severe type 1 respiratory failure requiring artificial ventilation. A number of uncertainties in the evidence for cost-effectiveness remain but at present there is also no economic justification for the use of HFOV over conventional ventilation in these patients.

We therefore suggest that this mode of ventilation not be used for routine care of patients with severe type 1 respiratory failure requiring artificial ventilation.

However, taking this study's results together with those from the simultaneously reported Canadian OSCILLATE study of HFOV (Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, *et al.* High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;**368**:795–805) which demonstrated an increased mortality in the HFOV group (47% vs. 35% in the control group, number needed to harm = 8), we would also suggest that further research into avoiding ventilator-induced lung injury should concentrate on ventilatory strategies other than HFOV.

Trial registration

This trial is registered as ISRCTN10416500.

Funding

Funding for this study was provided by the *Health Technology Assessment* programme of the National Institute for Health Research.

Chapter 1 Introduction to the acute respiratory distress syndrome and the need for a trial of high-frequency oscillatory ventilation

The acute respiratory distress syndrome (ARDS) is a severe inflammatory lung condition that accompanies many critical illnesses. Though ARDS is reasonably uncommon, with an incidence estimated at 78–280 cases per million population per year, it is associated with a very high mortality (40% or greater).[1–9] Many of the deaths occur in young or middle-aged patients. In survivors, ARDS causes derangement of lung function for 2 years or more after hospital discharge,[10,11] as well as marked reductions in quality of life (QoL). Although patients with ARDS only account for 8% of intensive care unit (ICU) admissions, because they have a long average stay in ICU they use up to a quarter of ICU bed-days.[5]

To date, only two treatments, pressure- and volume-limited artificial ventilation and extracorporeal membrane oxygenation (ECMO), have been shown to decrease mortality in patients with ARDS.[12,13] These techniques reduce pressure swings and volume changes within the lung, and so reduce the secondary lung damage caused by artificial ventilation itself rather than influencing the disease process per se.

The benefits of tidal volume-limited artificial ventilation may increase as the tidal volume (volume of each breath delivered by an artificial ventilator) decreases. High-frequency oscillatory ventilation (HFOV) is a technique where tidal volumes can be reduced to the absolute minimum and so should provide the maximum protection against secondary lung damage. Yet, in spite of years of largely positive experimental studies, case series and small clinical trials, there were no adequate, large-scale randomised controlled trials (RCTs) to determine whether or not HFOV confers any advantage to patients requiring artificial ventilation for acute hypoxaemic respiratory failure when compared with conventional artificial ventilation. A Cochrane systematic review, also published as a journal paper,[14,15] located only two methodologically sound RCTs in this area, one in children[16] and one in adults.[17] A more recent systematic review of all of the eight clinical trials in children and adults[18] published to date concluded that, in patients with acute lung injury (ALI) or ARDS, HFOV initially improved oxygenation {as measured by the ratio of the arterial oxygen partial pressure to the fractional inspired oxygen concentration [$PaO_2 : FiO_2$ ratio (P : F ratio); 7 trials, $n = 323$, ratio of means and 95% confidence interval (CI) 1.24 to 1.10–1.40]} but did not alter the duration of mechanical ventilation. Hospital or 30-day mortality was reduced (six trials, $n = 365$, risk ratio and 95% CI 0.77 to 0.61–0.98) and there was no increase in adverse events. The small size and poor quality of the trials reviewed, along with the heterogeneity of the populations studied, contrasted with the increasing use of HFOV in UK adult ICUs. This increasing use was occurring without any clear evidence of efficacy, in a patient population and setting where a trial to obtain this information was probably feasible.

In 2007, in part in response to the Cochrane review and associated review,[14,15] the National Institute for Health Research (NIHR) [Health Technology Assessment (HTA) programme] in the UK commissioned the OSCAR (OSCillation in ARDS) study to determine if adult patients with ARDS who are treated with HFOV have a decreased mortality at 30 days compared with patients treated with conventional positive-pressure ventilation.

Overview of acute respiratory distress syndrome and acute lung injury

Acute hypoxaemic ('type 1') respiratory failure, where the patient is unable to maintain an adequate arterial oxygen partial pressure (PaO_2) without high inspired oxygen concentrations, is a common reason for admission to an ICU. This type of respiratory failure is either due to a primary pulmonary condition or is secondary to the systemic inflammatory process caused by extrapulmonary pathology. The term 'acute

(or adult) respiratory distress syndrome' was coined nearly 40 years ago[19] to describe the acute respiratory failure that accompanies severe systemic disease, but over the years has expanded to cover virtually all causes of hypoxaemic respiratory failure other than those caused by cardiac failure.

To aid epidemiological and interventional studies of patients with acute hypoxaemic respiratory failure, a standard set of definitions were agreed at a consensus conference in 1994.[20] Two degrees of severity were recognised: ALI and the more severe ARDS. Features common to both were:

- acute onset of impaired oxygenation
- bilateral infiltrates on chest radiograph
- pulmonary artery wedge pressure (an indirect measure of left atrial pressure) < 18 mmHg or exclusion of cardiogenic pulmonary oedema by other means
- a known precipitant of acute respiratory failure.

The degree of severity was determined from the P : F ratio. If this was 26.7–40.0 kPa (200–300 mmHg), the patient had ALI. If it was < 26.7 kPa (200 mmHg), the patient had ARDS.

This common classification has allowed comparisons of the incidence of, and mortality from, ARDS, and, to a lesser extent, ALI, to be made over time within single populations,[9] and between large national and subnational epidemiological studies.[1,3,4,7,8] There is now a large literature on the incidence and short-term outcome from ARDS.

While the OSCAR study was running, a different set of definitions for ALI and ARDS were developed at a consensus conference. The 'Berlin Definition'[21] defined three mutually exclusive categories of ARDS based on degree of hypoxaemia: mild [26.7 kPa (200 mmHg) < P : F ratio ≤ 40 kPa (300 mmHg)], moderate [13.3 kPa (100 mmHg) < P : F ratio ≤ 26.7 kPa (200 mmHg)], and severe [P : F ratio ≤ 13.3 kPa (100 mmHg)]. The 'mild' category is the group of patients previously categorised as ALI, otherwise the definitions are largely unchanged from those first proposed in 1994.

As ARDS almost never occurs in isolation and is secondary to another acute disease, the mortality attributable to the ARDS per se has been difficult to unpick from the mortality from the primary condition. For many years it was unclear if a treatment directed solely at ARDS, even if effective at improving gas exchange, would alter mortality. Treatments that clearly did improve arterial oxygenation, such as inhaled nitric oxide, prone positioning and high levels of positive end expiratory pressure (PEEP), proved ineffective when tested for an effect on mortality. However, in 2000, a large trial of limited tidal volume, pressure-controlled artificial ventilation compared with conventional artificial ventilation[12] showed an 8.8% absolute reduction in mortality, confirming simultaneously that there was an attributable mortality to ARDS and that this could be reduced with treatments directed solely at the lungs. This study also confirmed the long-held view that artificial ventilation, while immediately life-saving, could in the longer term cause lung damage in addition to that caused by the primary disease. While the OSCAR study was running, the Conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) study of ECMO, which allows respiratory failure to be treated with minimal ventilation of the lungs, reported a 12% absolute 6-month survival without disability benefit (relative risk 0.69, 95% CI 0.05 to 0.97; $p = 0.03$) for patients treated with ECMO. After recruitment had closed in OSCAR, a multicentre study reported a 16.8% absolute reduction in 28-day mortality by using prone positioning, which improves oxygenation by recruitment of collapsed lung [hazard ratio for death with prone positioning 0.39 (95% CI 0.25 to 0.63)].[22] For these reasons, attention has again focused on artificial ventilation techniques like HFOV which, at least in experimental studies,[23,24] minimise secondary lung injury.

Background to high-frequency ventilation

History of artificial ventilation

An artificial ventilator is essentially a device that replaces or augments the function of the inspiratory muscles, providing energy to ensure a flow of gas into the alveoli during inspiration. Exhalation during artificial ventilation is usually a passive process, so when this inspiratory assistance is removed the inspired gas is expelled as the lung and chest wall recoil to their original volume. In the earliest reports of artificial ventilation, the respiratory muscles of another person, as expired air resuscitation, provided this energy. Baker[25] has traced references to expired air resuscitation in the newborn as far back as 1472, and in adults there is a report of an asphyxiated miner being revived with mouth-to-mouth resuscitation in 1744. In the eighteenth century, artificial ventilation became the accepted first-line treatment for drowning victims, although bellows replaced mouth-to-mouth resuscitation.[26] Automatic artificial ventilators which did not require a human as a power source were proposed by Fell 150 years later[27] and made commercially available by Dräger in 1907.[28] These were still resuscitation devices as the Dräger company at that time made mine rescue apparatus not medical devices.

The introduction of artificial ventilators into anaesthetic practice proceeded slowly until surgical advances required surgeons to undertake thoracotomies. Without artificial ventilation during a thoracotomy, lung collapse and mediastinal movement made surgery difficult and anaesthesia hazardous. Mortality was markedly reduced with artificial ventilation. A further boost to the development of artificial ventilators occurred in 1952 when a catastrophic poliomyelitis epidemic struck Denmark. Although the combined use of tracheostomy and artificial ventilation reduced the mortality, especially in the patients with bulbar palsy, the artificial ventilation had to be provided entirely by hand and required 1400 university students working shifts. The fear of another epidemic expedited research into powered mechanical ventilators, leading to the development of the first modern ventilator, the Engström, in 1952.[29] Since the advent of microprocessors and computer-controlled gas valves, artificial ventilators have become increasingly sophisticated, though evidence of the effectiveness of any single ventilation mode or ventilator is often lacking.

During both spontaneous breathing and during artificial ventilation, tidal volumes (breaths) have to be greater than the volume of the trachea and conducting airways (the anatomical dead space). Tidal volumes less than the anatomical dead space move gas in and out of these airways but do not ventilate the alveoli, and so no gas exchange with blood in the pulmonary capillaries takes place. Anatomical dead space is usually about 2 ml/kg in adults, tidal volumes are usually set at about 10 ml/kg in anaesthetic practice and 6–8 ml/kg ideal body weight in adults artificially ventilated for acute lung conditions.

However, it has been known for many years that this 'convective' model of ventilation does not apply in all circumstances. As early as 1915, Henderson *et al.*[30] noted that panting dogs were able to eliminate carbon dioxide, even though the volume of each breath was less than their anatomical dead space. In 1954, Briscoe *et al.*[31] reported that in humans the anatomical dead space appears to be reduced at low tidal volumes, allowing more gas exchange than would be predicted using a convective model of ventilation. However, the absolute amount of carbon dioxide eliminated per breath is very small, so high respiratory frequencies are needed to clear metabolic carbon dioxide production.

The first description of high-frequency ventilation in a clinical setting is attributed to either Lunkenheimer *et al.* in 1972[32] or Jonzon *et al.* in 1971,[33] both of whom used the technique to minimise the cyclical effects of intermittent positive-pressure ventilation on the cardiovascular system. Subsequent research into high-frequency ventilation initially concentrated on three techniques to deliver the breaths, HFOV, high-frequency positive-pressure ventilation (HFPPV) and high-frequency jet ventilation (HFJV). External HFOV (EHFOV) using either a cuirass ventilator[34] or a pneumatic vest[35] was also introduced but was mostly used as an adjunct to physiotherapy and as a research tool rather than a mode of ventilation for critically ill patients.

It became apparent that both HFJV and HFPPV probably had no special properties and conformed to the conventional, convective model of gas exchange.[36] However, it also became clear that carbon dioxide clearance could be achieved with HFOV in animals[37] and humans[38] with tidal volumes that were half the anatomical dead space or less. There are many theories to explain this phenomenon. All of them reject the simple anatomical (series) dead space concept, and assume there is no sharp cut-off between dead space and alveolar gas, and some form of mixing takes place. The most likely mechanism, termed 'convective streaming', is that the interaction of the gas-airway wall friction and the asymmetrical inspiratory-expiratory flow profiles lead to an inward movement of gas in the core of the large airways and an outward movement near the wall.[39] These theories have been extensively reviewed.[40,41]

As tidal volumes during HFOV are very small, the peak pressures generated in the alveoli during artificial ventilation are correspondingly modest. Thus HFOV would seem an ideal technique to ventilate patients at risk from pressure-induced lung damage ('barotrauma') such as infants with the (infant) respiratory distress syndrome (RDS). This was the rationale behind the early trials of HFOV in infants.

Trials of high-frequency oscillatory ventilation in infants

In pre-term infants with immature lungs, (infant) RDS is a major cause of immediate mortality. In survivors there is also considerable long-term morbidity from bronchopulmonary dysplasia, a condition caused by the combination of high intrapulmonary pressures generated by artificial ventilators, and high concentrations of inspired oxygen. As case reports began to appear in the literature suggesting HFOV might benefit these patients, the National Institutes of Health (NIH) in the USA first convened a conference[42] and then commissioned a randomised controlled study. The HiFi study, published in 1989,[43] recruited 673 pre-term infants who were randomly assigned to either HFOV using a piston-driven ventilator or to conventional mechanical ventilation. This study showed no survival benefit or difference in the incidence of bronchopulmonary dysplasia in the HFOV group.

Since the HiFi study there have been have been a further 17 RCTs of HFOV in infants. These are described in a series of Cochrane reviews[44–47] and independent[48] reviews last updated in 2013. In general, though many studies showed more deaths in the conventional ventilation groups, either as individual studies or combined in a meta-analysis, no statistically significant difference could be detected. However, a repeated theme in both the commentaries in the meta-analyses, and in opinion pieces published alongside the trials,[49] is that the negative results may be partially due to errors in trial design.

Trials of high-frequency oscillatory ventilation in adults

As part of the preparation for the OSCAR study, we undertook a systematic review of HFOV in patients with ARDS and ALI in July 2006 to update the 2004 Cochrane review.[14] Among the 319 papers identified, there were only two adequate-quality RCTs of HFOV in adults.

The first and largest RCT was published in 2002.[17] Recruitment took place between October 1997 and December 2000 in 13 university-affiliated medical centres in the USA and Canada. A total of 148 patients were recruited. The entry criteria were the ARDS consensus criteria,[50] a PEEP of ≥ 10 cmH_2O, and a predicted 6-month survival of 50% or greater. The investigators initially set the HFOV ventilator to a frequency of 5 Hz (breaths per second) and a mean pressure 5 cmH_2O above the mean airway pressure on conventional ventilation, and the amplitude to 'visible chest wall movement'. The conventional ventilation group were treated with pressure-controlled ventilation to a maximum tidal volume of 10 ml/kg. The HFOV group had better oxygen exchange as measured by P : F ratios, most notably in the first 24 hours of HFOV, though when corrected for the difference in mean airway pressure (which increases oxygen exchange) using the oxygenation index (OI) this difference disappeared. Although more deaths were seen in the control group, this was not statistically significant (see *Figure 1, below*).

The second study was published in 2005.[51] Recruitment took place in four university-affiliated hospitals in London, Cardiff, Mainz and Paris between October 1997 and March 2001. The entry criteria and HFOV management were virtually identical to the 2002 study. A total of 61 patients were recruited. This study showed a beneficial effect of HFOV on oxygenation, even when airway pressures were taken into account. There was an excess of deaths in the HFOV group which was not statistically significant.

The results for 30-day mortality from both studies have been combined in the forest plot in *Figure 1*. There is no statistically significant benefit for HFOV seen.

The report from Bollen *et al.*[51] contained a post-hoc analysis showing how the treatment effect on mortality varied with the severity of the initial lung damage as determined by the OI. As the OI (and hence the severity of the lung injury) worsened the odd ratios for survival increasingly favoured HFOV. The numbers in each OI band were very small, and there were corrections added to remove other known causes of mortality. There was a clear stepwise increase in treatment effect with increasing OI and hence disease severity, suggesting that HFOV might be more effective in patients with worse ARDS, either because these patients are more prone to secondary lung damage or simply because they have a higher mortality.

The original systematic reviews of HFOV by Wunsch *et al.*[14,15] reviewed as part of planning the OSCAR study predated the publication of the Bollen *et al.*[51] study, though the subsequent 2008 revision made no mention of the study. The systematic review published in 2010 while the OSCAR study was under way[18] contained eight studies including the Bollen *et al.*[51] and Derdak *et al.*[17] studies, one study involving prone positioning which had been excluded from our original planning review, two studies undertaken in children and two studies published only as abstracts. The only fully reported study of 49 patients published since OSCAR started had no mortality data.[52]

Current practice of high-frequency oscillatory ventilation

Patients on HFOV are all intubated or have a tracheostomy, this is not a ventilatory mode that can be used non-invasively with a face mask. Both of the adult HFOV ventilators available in the UK have no facility for the patient to take breaths (interbreathe) during HFOV and so the patients are usually sedated, and, in some cases, are treated with neuromuscular blocking agents (muscle relaxants) to prevent respiratory effort.

High-frequency oscillatory ventilation, much as conventional artificial ventilation, can be divided into components which maintain or improve oxygenation, and components that assist with carbon dioxide elimination. Patients on HFOV have their lungs maintained in an expanded (inflated) state by a standing pressure, usually termed the mean airway pressure. This pressure is maintained by passing a stream of warmed, humidified air and oxygen (the bias flow) across the top of the artificial airway to a valve that

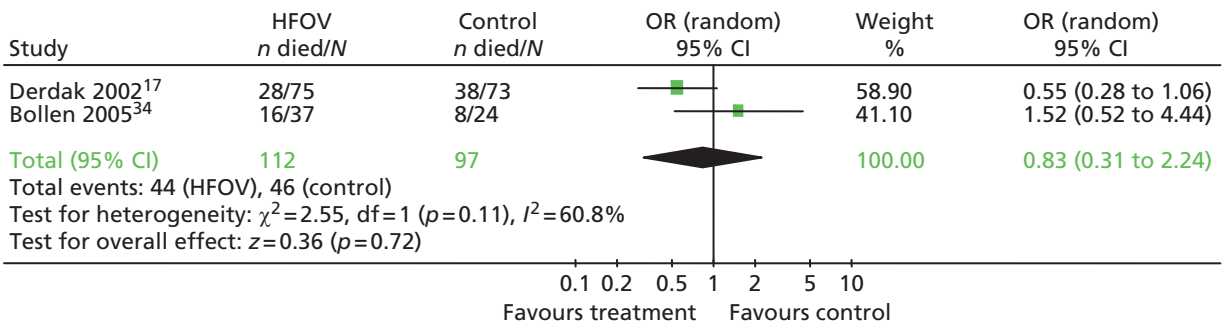


FIGURE 1 Forest plot showing 30-day mortality in the two methodologically sound trials of HFOV in adult patients with ARDS identified at the start of the OSCAR study. OR, odds ratio.

allows the mean airway pressure to be adjusted. The pressures used are typically about 5 cmH_2O above the pressure used to inflate the lungs in conventional ventilation (the plateau pressure). The bias flow is typically 20 l/minute. The patients' arterial oxygenation can be increased by increasing the mean airway pressure or by increasing the fractional concentration of oxygen in the bias flow gas.

To eliminate carbon dioxide, pressure fluctuations are superimposed around the mean airway pressure using an oscillating diaphragm. These pressure fluctuations cause small volumes of gas to move in and out of the lungs, removing carbon dioxide which is swept away in the bias flow. The superimposed pressure fluctuations are very rapid, typically 5–10 Hz (cycles/second). Although the fluctuations around the mean airway pressure, measured at the ventilator, can be large, these pressure oscillations are almost totally dissipated by a combination of gas inertia, gas compression and tubing expansion, such that the pressure changes at alveolar level are probably 5 cmH_2O or less.[53] The relationship between carbon dioxide elimination and oscillatory frequency is the reverse of that seen in conventional ventilation. More carbon dioxide is eliminated at lower frequencies, because for a given superimposed pressure the volumes of gas moved in and out of the lungs are greater at lower frequencies.

High-frequency oscillatory ventilation cannot be used in patients with expiratory airflow limitation, as the short expiratory time does not allow the tidal volume to leave the lungs and so air-trapping occurs. The high intrathoracic pressures used in HFOV also impair venous return causing a reduction in stroke volume and hypotension.

Identification of data to inform the study design

Types of high-frequency oscillatory ventilators available

Although there is a wide range of high-frequency oscillatory ventilators available for neonatal use [e.g. SensorMedics 3100A® (SensorMedics Corporation, Yorba Linda, CA), Stefan SHF3000 (Fritz Stephan GmbH, Gackenbach, Germany), Hummingbird V (Metran Co. Ltd, Saitama, Japan), Dufour OHF1 (Dufour, Villeneuve d'Ascq, France)], there are only two commercially available positive-pressure HFOVs suitable for adults. The ventilator used in all of the studies in adults up to the start of the OSCAR study was the 'SensorMedics Model 3100B® high-frequency oscillatory ventilator' (SensorMedics Corporation, Yorba Linda, CA), manufactured by SensorMedics Corporation in California and distributed in the UK by Viasys Healthcare. This ventilator was approved by the US Food and Drug Administration (FDA) in 2001 for ventilation of selected patients over 35 kg in weight with acute respiratory failure. The second adult HFOV ventilator available is the 'Novalung' Metran R100® high-frequency ventilator (Metran Co. Ltd, Saitama, Japan) (also called the 'Vision Alpha') manufactured in Saitama, Japan by Metran Co. Ltd and distributed in the UK by Inspiration Healthcare, which has a long history of use in Japan but, at the time the OSCAR study was being planned, had only recently been CE (Conformité Européenne) marked for European use. A negative pressure external (cuirass) HFOV for adults ['Hayek Oscillator', United Hayek Industries (Medical) Ltd, London, UK] is also marketed in the UK and elsewhere.

Current users of high-frequency oscillatory ventilation in the UK

Viasys Healthcare provided us with details of all 3100B ventilators ever sold in the UK at the planning stage of the OSCAR study. A total of 38 ventilators have been sold by 2007 to 25 adult ICUs in England, Wales and the Isle of Man. Eighteen units had one ventilator; the remainder had two or three devices. No further data were obtained during the OSCAR study.

'Substantial uncertainty' within units already using high-frequency oscillatory ventilation

To run a RCT of HFOV in ICUs that already own one or more HFOV ventilators would require all clinicians caring for the patients to be substantially uncertain about which ventilation was best for their patients. As patients in the trial would be randomised in a 1 : 1 ratio to conventional positive-pressure ventilation or HFOV, up to 50% of the patients who the clinicians would treat with HFOV under their current protocols

or guidelines would be randomised to conventional positive-pressure ventilation. In essence, the clinicians would have to withhold their standard treatment from half of the patients in the trial. The nature of medical care for patients in ICUs, where each consultant works for a block of time before handing onto a colleague, means that 'substantial uncertainty' would have to be present in the whole team to ensure the allotted trial treatment was continued throughout a patient's ICU stay.

Lack of 'substantial uncertainty' would expose the study to a considerable risk of bias. Clinicians might elect not to enter the more severely ill patients in the study and treat them with HFOV outside of the trial. This would mean the trial population would not be representative of the UK patients with ARDS and would reduce the generalisability of the results. Crossover from the control to the treatment group might also occur, limiting the ability of the study to show an effect.

We tried to find evidence in the literature to determine whether or not these problems had occurred in previous trials. In the clinical trial of HFOV reported by Bollen *et al.* in 2005,[51] 61 patients were recruited from four major European ICUs in 41 months, or about one patient per centre per 3 months. This would be about 0.4% of total admissions. All of these ICUs had prior experience with HFOV. The inclusion criteria for the study were the standard consensus criteria for ARDS[50] which include patients with a P : F ratio of < 26.7 kPa (200 mmHg). The mean P : F ratio in the treatment group was 12.6 kPa and in the control group was 16.0 kPa. No Consolidated Standards of Reporting Trials (CONSORT) diagram was published. From published data, we know that about 8% of admissions to general ICUs meet the consensus criteria for ARDS during their ICU stay. Therefore, both the low recruitment rate and the severity of the respiratory failure would suggest there was considerable case selection taking place, though whether or not patients received HFOV outside the study is not known. The trial was stopped prematurely because of 'poor recruitment' attributed, in the paper, to lack of local trial-dedicated staff. Crossovers (18%) occurred by protocol in this study.

The other clinical trial reported by Derdak *et al.* in 2002[17] took place in 13 university-affiliated medical centres in the USA and Canada over 38 months, a recruitment rate of one patient per centre per 3.6 months. There are no data on whether or not these centres had prior experience with HFOV but seven of the sites' clinical leads had published on HFOV prior to the study. The inclusion criteria for the study were the standard consensus criteria for ARDS. The mean P : F ratio in the treatment group at enrolment was 15.0 kPa and in the control group 14.6 kPa. Again, no CONSORT diagram was published. Crossovers were 4/75 (5.3%) from HFOV to control, and 9/73 (12.3%) from control to HFOV. Again, these data suggest marked case selection was taking place, though again it is not known if HFOV was used outside of the trial.

We discussed the OSCAR trial with the clinical leads or senior clinicians in five UK ICUs where HFOV was used. Although all initially expressed interest in the study, when we explained that the study would require withholding HFOV in some patients, four of the clinicians suggested they could not take part in a trial under these circumstances.

Finally, we reviewed the experience gained by the Chief Investigator (DY) as a member of the management group for the PAC-Man study.[54,55] The clinicians in ICUs were asked to withhold a pulmonary artery catheter in half of the patients they would normally have used one in. Although the study was successful, a considerable effort was required in the early stages of the trial to generate equipoise. The trial probably only succeeded because it was a trial of a monitoring device, not a treatment, and nearly two-thirds of the ICUs used another monitoring method to generate at least some of the information a pulmonary artery catheter would have given them.

We concluded there are considerable risks to running the trial in centres which already used HFOVs. We believed the major risk was that HFOV would continue outside the trial as a rescue therapy and so the patients in the study would be an unrepresentative sample. The final trial design was a compromise;

most ICUs were HFOV-naïve at study commencement, but two centres with HFOV experience did initially join the study and provided a pool of experienced health-care staff.

Identification of other trials of high-frequency oscillatory ventilation and trials competing for the same patient population

When the OSCAR trial was starting we were aware that Professor Meade and Dr Ferguson from the Canadian Critical Care Trials Group (CCCTG) had received funding for a national pilot study of HFOV [the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) study]. The OSCAR team contacted Professor Meade and agreed a common core data set to facilitate future meta-analyses should the pilot study progress to a full study. The OSCILLATE study did proceed to a full study and ceased recruitment just after the OSCAR study closed to recruitment. The OSCILLATE results[56] are covered in *Chapter 6*.

The National Heart, Lung, and Blood Institute (NHLBI) in the USA funded a phase II study of HFOV using surrogate outcome measures (inflammatory cytokine concentrations in plasma) as a prelude to a full clinical trial (ClinicalTrials.gov identifier NCT00399581). This started in 2006 and was completed in 2009. The Chief Investigator was Dr Roy Brower. The results have not yet been published at the time of writing.

Identification of other trials in the UK competing for the same population

None of the ICUs we contacted as potential trial sites identified any studies of patients with ARDS that would compete for patients.

Three of the OSCAR investigators were on the management group of the Beta Agonist Lung Injury TrIal-2 (BALTI-2) study, a trial of intravenous salbutamol in ARDS. As the OSCAR study commenced, this was in a pilot phase in the West Midlands. It subsequently went to a full study[57] and required the OSCAR study team and the BALTI-2 study team to communicate to prevent competition for patients as the entry criteria for the two studies were near identical.

There was a single-centre RCT of the effects of simvastatin in patients with ARDS under way in the Royal Victoria Hospital, Belfast as OSCAR started. This study became multicentre (HARP-2 study,[58] ISRCTN88244364) but used different study centres.

Identification of data to inform estimates of the recruitment rate

A systematic review of all epidemiological studies of ALI and ARDS undertaken after the consensus criteria were formulated in 1994 was recently published.[7] The European and Australasian studies using consensus criteria to define ARDS cited in this review, along with additional studies identified from a systematic literature search undertaken in August 2006 by ourselves, are summarised in *Table 1*.

TABLE 1 Epidemiological studies of the incidence of ARDS in Europe and Australasia since 1994

Study	Population	Population incidence of ARDS (per 100,000 population per year)	Percentage of ICU admissions with ARDS	Mortality (%) for patients with ARDS
Brun-Buisson *et al.*, 2004[3]	78 ICUs across Europe	Not calculated	6.1	49.4 (hospital)
Bersten *et al.*, 2002[2]	21 ICUs in Australia	28.0	Not calculated	34.0 (time point not given)
Luhr *et al.*, 1999[6]	132 ICUs in Scandinavia	13.5	Not calculated	41.2 (90 day)
Roupie *et al.*, 1999[59]	36 ICUs in France	Not calculated	6.9	60.0 (28 day)
Monchi *et al.*, 1998[60]	Single French ICU	Not calculated	7.4	65.0 (28 day)
Sigvaldason *et al.*, 2006[9]	All Icelandic ICUs	7.8	Not calculated	40.0 (hospital)
Hughes *et al.*, 2003[5]	23 Scottish ICUs	16.0	8.1	60.9 (hospital)

From these studies, it would appear the incidence of ARDS in ICUs was about 6–8% of all admissions when OSCAR started.

Three estimates of the incidence of ARDS in UK ICUs were available. The Scottish Intensive Care Society Audit Group (SICSAG) published data from 23 of the 26 ICUs in Scotland for an audit run between May and December 1999.[5] They recorded patients meeting the diagnostic criteria for ARDS (including chest radiographs) on a daily basis. The results are in *Table 1* (Hughes *et al.*[5]).

Two other (unpublished) estimates of the number of cases of ARDS in UK ICUs were available. In both data sets, the diagnosis of ARDS is based on the P : F ratio only and did not include chest radiograph information or any clinician 'filtering'.

The Intensive Care National Audit & Research Centre (ICNARC) reviewed 261,193 admissions to UK ICUs over a 10-year period to 2005 and found an incidence of ARDS, defined solely on the P : F ratio in the first 24 hours of ICU admission, of 49.3%. These data are unpublished.

We undertook a similar study using data on admissions to the adult ICU at the John Radcliffe Hospital, Oxford, for calendar year 2005. Of 973 admissions, 850 had simultaneous arterial blood gas analyses and FiO_2 records which allowed P : F ratios to be calculated. The incidence of ARDS, defined on P : F ratio only at any point in the patient's stay, was 78.9%. As the incidence was so high, we also searched the discharge summaries for any mention of ARDS. Only 2.5% of the patients had both a P : F ratio of < 26.7 kPa and any mention of ARDS in the discharge summary.

The true incidence of ARDS in ICU patients was almost certainly greater than the 2.5% we identified by retrospectively searching the Oxford database of discharge summaries because of errors of omission. However, it is also very clear that estimates of the incidence of ARDS based on the incidence of P : F ratios of < 26.7 kPa grossly overestimate the true incidence of ARDS.

As a result, the ICNARC and Oxford data on the incidence of ARDS were not used to inform recruitment rates or sample size calculations. The erroneously high incidence of ARDS identified in these databases presumably results from the loose definitions of ARDS used by ICNARC and at Oxford which did not include chest radiograph data, and because at least 50% of patients who meet the ARDS oxygenation criteria (P : F ratio of < 26.7 kPa) only have a very transient reduction in the P : F ratio which rapidly improves.[61]

Selection of entry criteria, acute lung injury and acute respiratory distress syndrome or just acute respiratory distress syndrome?

As discussed above, acute hypoxaemic respiratory failure was divided into two severity bands by the consensus conference held in 1994. The less severe band was termed Acute Lung Injury or ALI, and includes patients with a P : F ratio of between 26.7 and 40.0 kPa. The more severe band, where the P : F ratio was < 26.7 kPa, was termed acute respiratory distress syndrome or ARDS.

There is often confusion over the terms ALI and ARDS. In some literature, the term ALI is incorrectly used to encompass all patients with a P : F ratio < 40 kPa, and the term ARDS is used to describe a subset of these with a P : F ratio of < 26.7 kPa. We did not use this convention and kept to the definitions published after the consensus conference in which ALI and ARDS are two discrete bands of severity of acute hypoxaemic respiratory failure with no overlap.

The commissioning brief from the HTA requested a study of HFOV in patients with ALI or ARDS. We elected to use ARDS only as an entry criterion for the trial. The reasons for this are as follows.

ALI represents a group of patients who will require between 30% and 45% inspired oxygen to maintain a normal PaO_2 of 12 kPa. This degree of hypoxaemic respiratory failure would normally be managed with simple face mask oxygen as the patients do not require artificial ventilation. It follows from this that patients with ALI who are on artificial ventilators are probably ventilated as a result of non-pulmonary pathology which would not be improved by HFOV, and so would reduce the chance of seeing an effect of any ventilatory strategy if included in a clinical trial. Examples of such patients would be those with neurological conditions such as head injury, meningitis or similar. In a large study of 5183 mechanically ventilated patients in Europe and North America, patients with ALI had the same mortality as patients with no ALI at all.[62]

The two RCTs of HFOV[17,51] reviewed at the planning stage of OSCAR only recruited patients with ARDS. In the Bollen *et al.* study,[51] a post-hoc analysis revealed that there might have been a treatment effect seen at the more severe end of the spectrum of ARDS. There was no treatment effect seen at the milder end of the ARDS severity spectrum. This suggests any benefit of HFOV would not be seen in patients with ALI.

As ALI is a relatively mild pulmonary insult and does not require artificial ventilation, most patients with this condition are managed on the general wards. In the Europe-wide epidemiological study of ALI and ARDS,[3] only 62 out of 6522 ICU admissions (0.9%) had ALI against 6.1% with ARDS. More than half of the patients with ALI rapidly progressed to ARDS, leaving only 0.4% of admissions who had ALI alone. Only two-thirds of these patients with ALI alone were ventilated. By not including ALI patients, we are probably only excluding 0.1–0.2% of all admissions, many of whom will be ventilated for non-pulmonary reasons and could probably not benefit from HFOV. For all of these reasons, we believed it was inappropriate to undertake a study of HFOV that included patients with ALI.

As noted earlier, while the OSCAR study was running, a different set of definitions for ALI and ARDS were developed at a consensus conference. The 'Berlin Definition'[21] will have no effect on the interpretation of the results. The 'mild' category is the group of patients previously categorised as ALI, otherwise the definitions are largely unchanged from those first proposed in 1994.

Identification of data to inform the choice of measures used for long-term follow-up

The primary outcome for OSCAR was mortality, as specified in the commissioning brief. The brief also requested longer-term outcome measures. These were included in the OSCAR study, and are reported in this monograph for most, but not all, patients as data collection was still continuing at the monograph submission date.

The HTA commissioned a systematic review into outcome measures for adult critical care in 1998. The results were reported in 2000 both as a monograph and a paper.[63,64] At that time, the three measures of health-related QoL that had been most commonly used in follow-up studies of critically ill patients were the Sickness Impact Profile/Functional Limitations Profile (SIP/FLP), the Perceived Quality of Life (PQOL) and the Nottingham Health Profile (NHP). In addition, the Short Form questionnaire-36 items (SF-36) was increasingly being used.

At the time the review was undertaken, the European Quality of Life-5 Dimensions (EQ-5D) measure was not used in to any extent in critical care research and so did not feature in the reports, even though it was first developed in 1990.[65] However, it has since rapidly gained popularity in critical care research, to the extent that in 2004 a European consensus conference suggested that EQ-5D or SF-36 were the two preferred measures for health-related QoL in survivors of critical illness.[66]

The SF-36 is a feasible and reliable instrument with sufficient discriminatory power to detect changes in the health-related QoL of ICU patients with different levels of chronic health and varied severity of their acute illness.[67] SF-36 contains 36 items to measure eight QoL domains: physical functioning, role

limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health.[68]

European Quality of Life-5 Dimensions is also a general health-related QoL measure that has also proven to be a useful tool in a mixed critical care population.[69] The EQ-5D comprises two parts: the EQ-5D self-classifier, a self-reported description of health problems according to a 5-dimensional classification (i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression); and the European Quality of Life Visual Analogue Scale (EQ-VAS), a self-rated health status using a visual analogue scale, similar to a thermometer, to record perceptions of participants own current overall health. The scale is graduated from 0 (the worst imaginable health state) to 100 (the best imaginable state).[65]

As part of the background work for the Intensive Care Outcome Network (ICON) studies (studies of long-term ICU survival and QoL being run by the OSCAR Chief Investigator), a systematic review of all of the ICU outcome studies that have used either EQ-5D, SF-36 or both was undertaken. Numerically there are more studies that use the SF-36, though there are eight high-quality studies using the EQ-5D. A similar systematic review was published in 2005 but this only identified five of the eight studies using EQ-5D.[70]

A direct comparison of the EQ-5D and SF-36 as measures of health-related QoL in ICU survivors was undertaken in Sheffield in 2004.[71] The report came out strongly in favour of the EQ-5D, because it was simpler, had less floor and ceiling effects and so greater discrimination, and, if response rates were poor, follow-up using face-to-face or telephone interviews was easier.

There is only one published cost-effectiveness study of a treatment for ARDS.[72] This was a retrospective study using data from a large, long-term ICU outcome study undertaken in the USA (project SUPPORT). The treatment studied was artificial ventilation. Utilities were estimated using time-trade off questions and costs were from a hospital perspective.

The decision to use EQ-5D in the OSCAR study was made on a number of grounds. The EQ-5D serves both as a measure of health-related QoL and as a utility measure for calculating quality-adjusted life-years (QALYs). There is a large (3400) reference population database available, and the ICON study generated data on a population of mixed UK ICU survivors at the same time as the OSCAR trial was running, giving two appropriate reference populations. There is a large 11-centre study of survivors of ARDS planned in Baltimore, USA[73] which will use EQ-5D as an outcome measure, allowing transatlantic comparisons.

We had originally planned to use formal, laboratory pulmonary function tests to determine residual respiratory dysfunction in survivors. However, two high-quality studies[10,11] suggest this might not be cost-effective. The studies followed survivors of ARDS for up to 2 years.[10,11] At both 1 and 2 years, spirometry and lung volumes were normal. There was a reduction in carbon monoxide diffusing capacity (D_LCO) compared with normal values, but, from the HTA review of outcome measures, this test is known to have poor measurement properties.[64] The 6-minute walking distance was also reduced compared with predicted values at both 1 and 2 years, but the patients attributed this to muscle weakness rather than cardio-pulmonary problems. The best measure of respiratory dysfunction was the physical problem domain of the SF-36. Thus if formal pulmonary function testing were to be used as an outcome measure, unless one of the treatments caused additional harm, spirometry and lung volumes would show no difference between groups (a ceiling effect). D_LCO is probably not a valid measure of lung function after ARDS, and the 6-minute walk acts as a surrogate measure for muscle wasting. Thus the probability of distinguishing between treatment groups is very small, and, given both the burden to patients and the cost of transporting patients to pulmonary function laboratories, using laboratory pulmonary function tests as an outcome measure was abandoned.

Public and patient involvement

We used 'CritPal' (now the Patients and Relatives Committee of the UK Intensive Care Society) to provide advice and guidance on study documentation, consent procedures and publicity.

Health economics

The background to the health economic analysis is in *Chapter 5*.

Chapter 2 Methods (interventions)

Descriptions of interventions

The OSCAR study sought to answer the question 'What effect would the introduction of high-frequency oscillation into the NHS have on the short-term mortality of patients artificially ventilated for ARDS?'. The study was a randomised controlled effectiveness study. The study groups which were compared in this trial were (a) HFOV versus (b) conventional positive-pressure ventilation (usual care). The detailed methodology for the study follows in *Chapter 3*, but as the experimental intervention is complex, the interventions are described separately in this chapter.

High-frequency oscillatory ventilation (experimental group)

In the original protocol, we had stipulated that the intervention would be HFOV, delivered using a SensorMedics 3100B ventilator ventilating at a rate of 5–15 Hz (breaths/second). When the study was designed this was the only commercially available high-frequency oscillatory ventilator for adult patients with CE marking marketed in the UK. Prior to the start of the study (early 2007), we became aware that a second CE-marked HFOV ventilator was due to come onto the UK market in May 2007. This ventilator is manufactured in Japan by Metran Co. Ltd (Kawaguchi, Saitama Prefecture, Japan) and marketed as the 'R-100' in the Asia-Pacific region. It is imported into Europe and rebadged as the 'Novalung Vision Alpha' by Novalung GmbH (Heilbronn, Germany) and distributed in the UK by Inspiration Healthcare Ltd (Leicester, UK). The SensorMedics 3100B was first released in 1993 and has a long history of use worldwide, but it uses analogue electronics, does not incorporate a conventional ventilator, and is noisier than the Vision Alpha device. The Vision Alpha is a digital device, which incorporates a conventional ventilator, but at the start of the study was little used outside Japan. The SensorMedics 3100B uses an electromechanical actuator to generate the oscillation, and, by modifying the driving signal, the ratio of inspiratory to expiratory time (I : E ratio) can be varied. The Vision Alpha uses a rotating mechanical valve and compressed gas to generate the oscillation and has a fixed 1 : 1 I : E ratio. Both ventilators have a frequency range of 5–15 Hz. After careful discussion, the investigators agreed that the study should proceed using the Vision Alpha ventilator, primarily because the transition from conventional ventilation to oscillatory ventilation and back was far simpler and the control interface was more intuitive which was felt to be important as many of the study sites would not have used HFOV prior to the study. The HTA was informed of the decision in June 2007.

The management of artificial ventilation with HFOV was based on two simple algorithms illustrated graphically in *Figure 2*, designed to allow arterial oxygen and carbon dioxide tensions (PaO_2 and $PaCO_2$) to be managed separately. The algorithms were derived from guidelines which had been used successfully at Addenbrooke's Hospital ICU (Cambridge) and the University Hospitals Birmingham ICU for 5 years. The algorithms are virtually identical to the protocols used in the two published RCTs.[17,51]

The algorithm for maintaining arterial oxygenation specified starting at a fractional concentration of inspired oxygen (FiO_2) of 1.0, a frequency of 10 Hz, a mean airway pressure 5 cmH_2O above the plateau or equivalent pressure on conventional ventilation, and a cycle volume of 100 ml (the cycle volume is the volume of gas displaced by the diaphragm, the volume reaching the alveoli is far less due to tubing expansion, gas compression and gas inertia). The starting bias flow was 20 l/minute. The target PaO_2 was 8 kPa or greater. As the patient improved, the inspired oxygen was gradually reduced to 0.4 and then the mean airway pressure to 24 cmH_2O. A 'recruitment' strategy was used for patients who did not demonstrate the expected improvement in P : F ratio after starting HFOV. When the patient had been stable on a FiO_2 of 0.4 or less with a PaO_2 in excess of 8 kPa, the patient was converted to conventional ventilation and weaned in the usual way. It is not possible to wean patients from artificial ventilation while on HFOV as the ventilator has no facility for spontaneous or patient-triggered breaths.

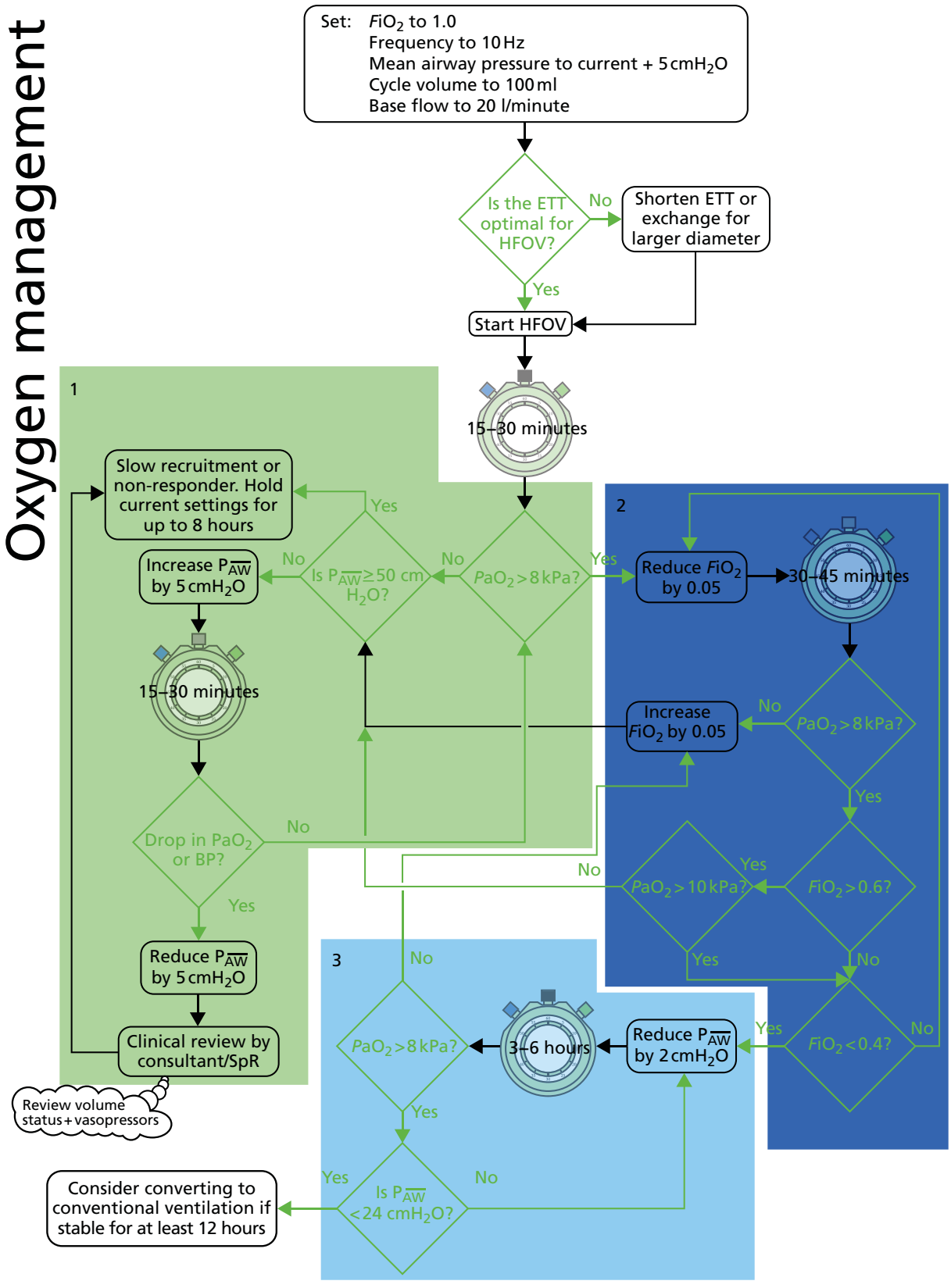


FIGURE 2 The algorithms for managing HFOV. ABG, arterial blood gas analysis; BP, blood pressure; ETT, endotracheal tube; $P_{\overline{AW}}$, mean airway pressure; SpR, specialist registrar. (*continued*)

OSCAR

Carbon dioxide management

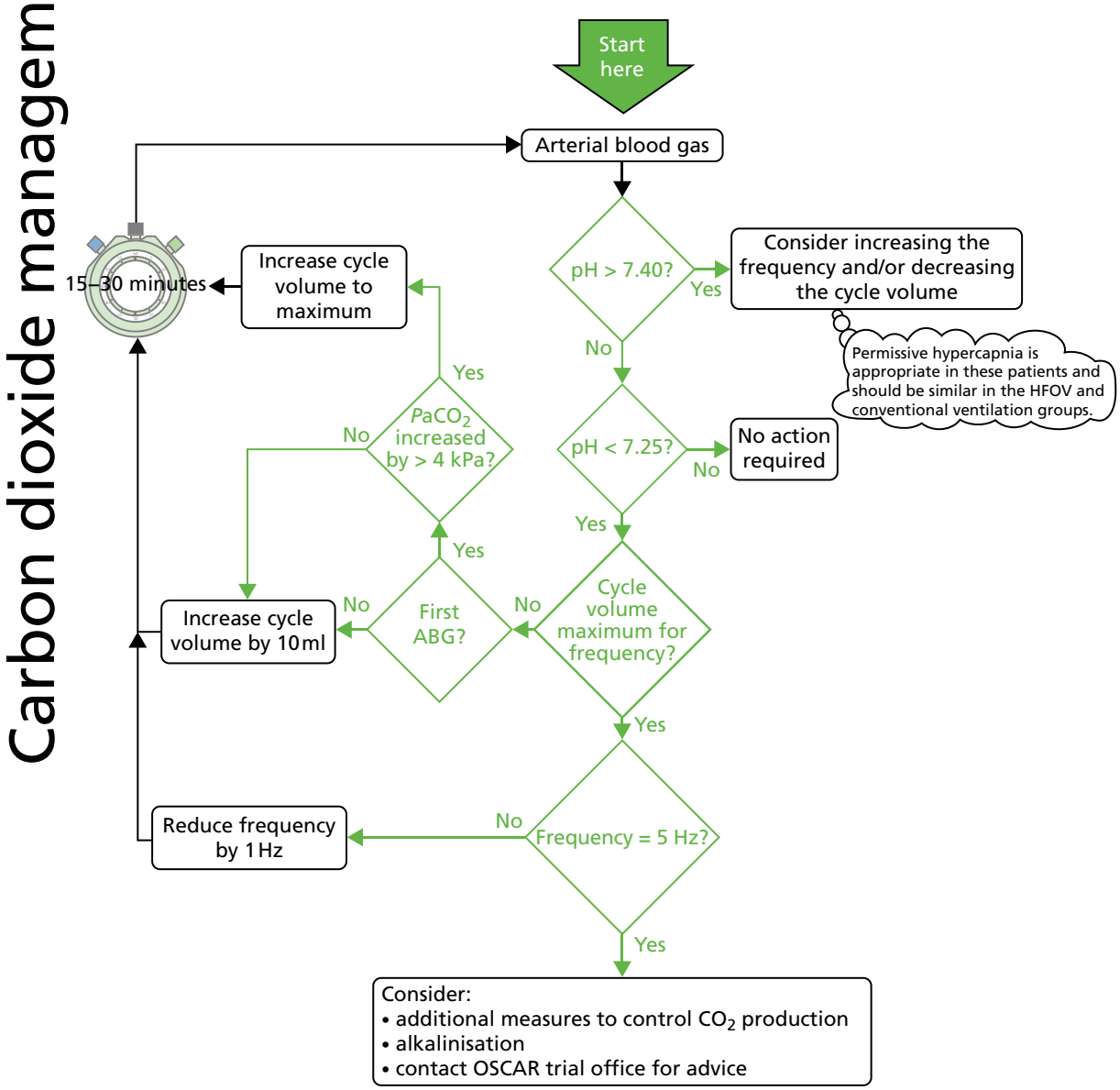


FIGURE 2 The algorithms for managing HFOV. ABG, arterial blood gas analysis; BP, blood pressure; ETT, endotracheal tube; $P_{\overline{AW}}$, mean airway pressure; SpR, specialist registrar.

The algorithm for controlling arterial carbon dioxide tension ($PaCO_2$) on HFOV involved a target arterial pH of 7.25–7.40, corresponding to a modest respiratory acidosis (mild permissive hypercapnia) in patients with normal metabolic acid-base status. To reduce $PaCO_2$, the cycle volume was increased up to the maximum for the frequency (on the Vision Alpha ventilator cycle volume increases with decreasing frequency) and if that was insufficient the frequency was reduced. If the frequency was 5 Hz and the cycle volume maximised but the $PaCO_2$ was still out of range, the on-call clinician was contacted for advice. Early experience with the ventilator identified a small number of patients in whom the $PaCO_2$ increased rapidly (> 4 kPa rise) after starting on HFOV, and so the algorithm was modified to include a series of faster settings changes in these patients.

Training using the high-frequency oscillatory ventilation

In the original protocol it was anticipated that training would be carried out in the Netherlands and Germany. Before the study started it became clear this would not be practical. An amendment to the protocol was submitted (see *Appendix 1, List 2: Substantial amendment 1, No. 5*) which allowed training to be carried out in the UK (see *Training in use of the ventilator and algorithms*).

Troubleshooting with the high-frequency oscillatory ventilation ventilator

Troubleshooting notes prepared specifically for the study were supplied with the abbreviated operating manual. Clinical assistance was available from one of the principal investigators and technical assistance was available from Inspiration Healthcare by telephone at any time.

Supplying the Vision Alpha ventilators and associated disposables to collaborating centres

Collaborating ICUs were supplied with one Vision Alpha high-frequency oscillatory ventilator and humidifier. Inspiration Healthcare supplied service replacements within 48 hours if a ventilator or humidifier failed.

Centres were specifically told that the ventilator:

- was not to be used until the trial office notified them that the appropriate national and local approvals were in place
- was not to be used for treating patients outside of the OSCAR trial
- would be removed from their ICU if there was evidence of violation of its use.

The Vision Alpha ventilators require a disposable 'tubing set' for each patient consisting of heated inspiratory and expiratory hoses, oscillator diaphragm assembly, the 'wet' assembly for the humidifier, pressure monitoring tubes and expiratory filter. Each patient also required a non-disposable sterile inspiratory valve, used to isolate the oscillator diaphragm from the breathing circuit during conventional ventilation. Each centre kept a stock of disposable tubing sets and sterile inspiratory valves. Used valves were returned to the study office and then sent to Novalung for cleaning and ethylene oxide sterilising. In 2009, the ventilators were retro-fitted with a 'vent-protect' heated filter assembly which prevented contact between the patient's expiratory gases and the inspiratory valve and removed the requirement to sterilise the valves.

Training in use of the ventilator and algorithms

As HFOV had not been used previously in most of the ICUs in the study, a robust training/mentoring system was needed. Experience in neonatal trials where HFOV was introduced into special care baby units that had not previously used the technique suggested a major investment in training was required.[43,49]

Before the study started, the clinicians in these units were trained to operate the HFOV ventilator and follow the treatment algorithms. Training was offered in various forms to suit the collaborating unit. During the first year of the study, a 2-day workshop-based course on the HFOV ventilator and how to manage ventilated patients was organised at each centre. In addition, follow-up 'drop-in' sessions were

offered, usually on the ICU. These shorter sessions were to suit busy units and allow staff to dip in when possible during clinical shifts to top up their skills.

This training was to be backed up with centralised training programs run in Birmingham and Oxford for staff from each study site, targeting the ICU consultant medical staff, senior nursing staff and the local research nurses co-ordinating the OSCAR trial. These used the teaching suites equipped with patient simulators [Laerdal 'SimMan®' (Laerdal Medical Limited, Orpington, UK)] available at Birmingham and Oxford. The trial had a full-time, clinically trained research fellow in the team for the first year to lead and organise the training both centrally and locally, and two half-time senior nurse trainers for the next 3 years of the study. In addition, a member of the team regularly travelled to collaborating centres to support the use of the HFOV. Inspiration Healthcare also offered local training based on the need at individual centres.

Teaching material was prepared at the trial office and distributed to the ICUs taking part, both electronically and on paper. A newsletter was used to share any problems and solutions related to HFOV. We had planned to use a website to distribute information, but decided targeted e-mails with the information were more effective. The trial website held only contact details, details of regulatory approvals and the protocol.

Medical Devices Regulations 2002

As the trial employed a medical device (the Vision Alpha ventilator) for a purpose for which it was CE marked, approval from the competent authority [the Medicines and Healthcare Regulatory Authority (MHRA)] was not required.

Conventional ventilation (control group)

The control group received conventional positive-pressure ventilation using conventional pressure-controlled artificial ventilation.

Clinical management of patients in the control group (conventional ventilation)

When implementing the control intervention in the OSCAR trial, we suggested, but did not mandate, that the conventional ventilation strategy be based on limited tidal volume, pressure-controlled artificial ventilation using tidal volumes of 6–8 ml/kg, ideal body weight and fixed PEEP/FiO_2 combinations as used in the ARDSnet study,[74] the only ventilator mode for patients with ARDS with proven benefit. Most ICUs used pressure-controlled or pressure-supported ventilation modes. Two ICUs used airway pressure release ventilation (pressure-controlled ventilation with a very long inspiratory time and a very short expiratory time) on some of the control patients.

Other treatment

All patients were artificially ventilated at the point of randomisation, as this was one of the eligibility criteria. Both groups began the assigned treatment immediately following randomisation (or continued conventional ventilation if assigned to the control group). Patients in the experimental (HFOV) group remained on HFOV until the start of weaning from artificial ventilation. Weaning strategies were not specified by protocol, each unit followed its usual practice.

We recommended the following combinations of FiO_2 and PEEP (*Table 2*).

This ventilation strategy was reported as normal practice in most UK ICUs.

TABLE 2 The recommended PEEP/FiO_2 combinations

FiO_2	PEEP (cmH_2O)
0.3	5
0.4	5
0.4	8
0.5	8
0.5	10
0.6	10
0.7	10–14
0.8	12–14
0.9	12–16
1.0	12–18

Proposed duration of treatment and weaning

The patients continued on HFOV until they had recovered sufficiently to be weaned from artificial ventilation when their FiO_2 was 0.4 or less, their mean airway pressure was 24 cmH_2O or less, and the local clinician was satisfied that there were no non-pulmonary impediments to weaning. The HFOV ventilation mode does not allow any form of spontaneous (patient-triggered) ventilation which is normally required for weaning, so at this point the patients were placed back on conventional ventilation and weaned according to local protocols using inspiratory pressure support (*Figure 3*).

The point at which patients could be fully weaned from conventional artificial ventilation depended on a large number of factors that could not be protocolised.

Restarting high-frequency oscillatory ventilation

Patients who began weaning but then deteriorated could be restarted on HFOV for 48 hours after it was discontinued. If they deteriorated after 48 hours they were returned to conventional ventilation. This meant that for 48 hours after discontinuation of HFOV the HFOV ventilator was unavailable and so no recruitment of new patients could take place as each site only had one ventilator.

Health economics

The methods for health economic data collection are given in *Chapter 5*.

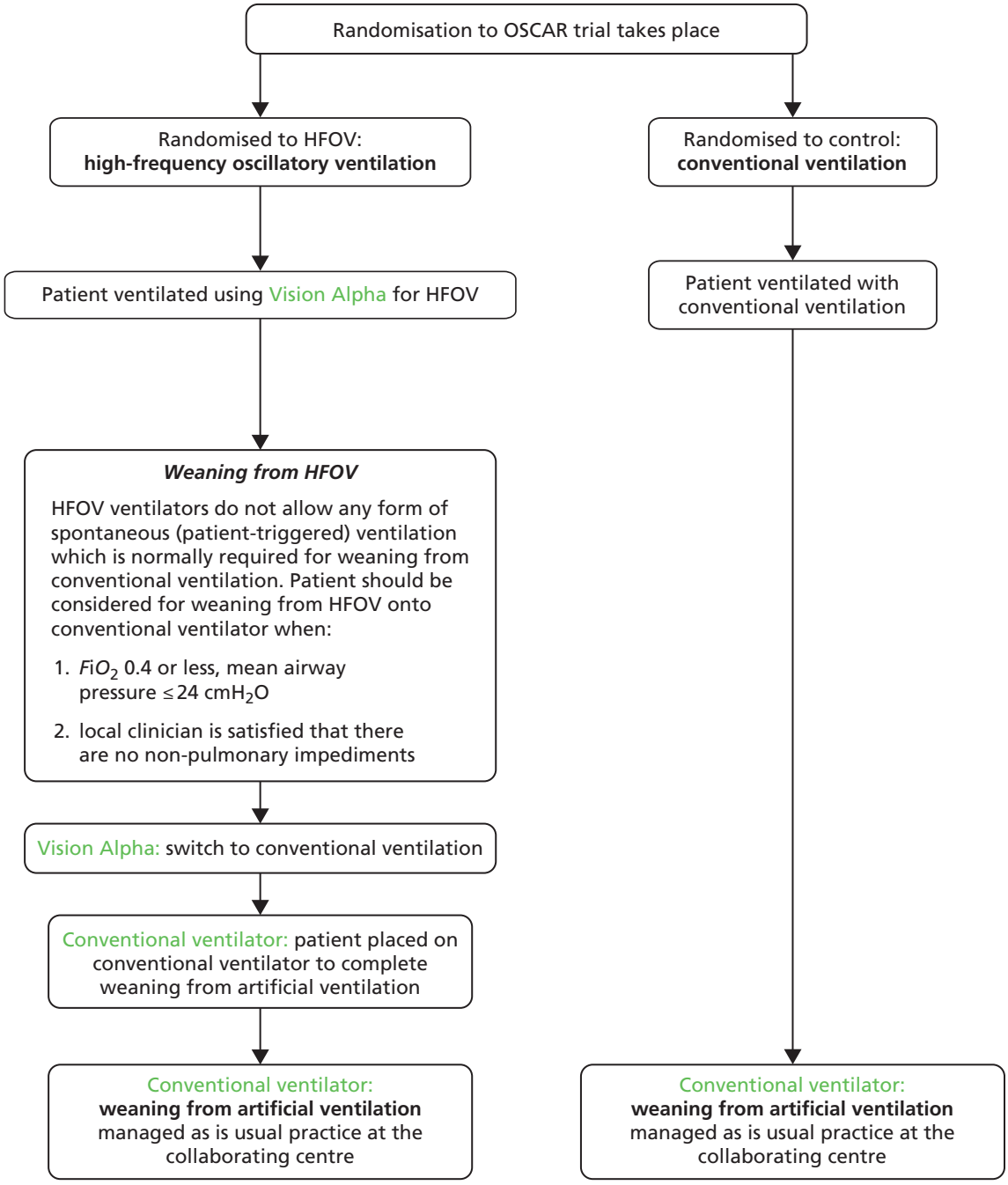


FIGURE 3 Patient treatment and weaning flow chart.

Chapter 3 Detailed methods

Hypothesis

The hypothesis for the OSCAR trial was that patients with ARDS who were treated with HFOV had a decreased mortality at 30 days following randomisation compared with patients treated with conventional positive-pressure ventilation (usual care).

Study design

OSCAR was a multicentre, open, randomised controlled effectiveness trial.

Setting

In the protocol, we planned to recruit patients in 12 ICUs in the NHS in the UK, which were able to care for Level 3 patients as defined by the Department of Health's *Comprehensive Critical Care: A Review of Adult Critical Care Services*.[75] To achieve adequate recruitment, additional centres were added so a total of 30 ICUs had taken part by the end of the OSCAR trial.

Intensive care units

In the protocol, the timeline for the project was approximately 57 months. The anticipated start date for the project was 1 June 2007 and the completion date was 29 February 2012. In this timeline, it was anticipated that the first 6 months of the study would be allocated to ethic approvals, design and production of trial material and on-site training for the staff using ventilators.

Initially, 12 centres were recruited to the study: 10 were allocated the Vision Alpha ventilators which had been leased and two sites had their own ventilators. The John Radcliffe Hospital was the first site to recruit in December 2007. The remaining 11 sites were due to start shortly after this date. However, there were delays as the final Multicentre Research Ethics Committee (MREC) (ethics) approval was not obtained until October 2007, despite submitting to ethics in July 2007. Also, there was a delay in the delivery of the ventilators from Japan and Germany and therefore the ventilators were not available for a December 2007 start.

Recruitment was lower than anticipated and it was recognised very early on in the trial (May 2008) that the required number of patients would not be achieved in the original timescale and that an extension would be required. An application for this was submitted to the HTA. The decision was to award the funding, conditional on a HTA recruitment review visit which was scheduled for 18 December 2008.

Following the visit, a 13-month extension approval was confirmed in June 2009, moving the completion date of the project to the end of March 2013. Ten additional ventilators were purchased and this allowed an additional 10 new sites to collaborate (see *Table 3*). Allowing for the lead in time for arrival of the ventilators (12 weeks), it was estimated that the start date for recruitment for these new sites would be 1 October 2009. However, owing to a delay in arrival of the ventilators, setting up of new sites was not possible until end/beginning of 2009/2010. There were a further five sites which had their own ventilators and were approached and agreed to recruit patients into OSCAR.

In 2009/2010, some reallocation of the ventilators occurred:

i. Aberdeen Royal Infirmary closed for recruitment when the local Principal Investigator left in May 2009 and the ventilator was relocated to Stirling Royal Infirmary.
ii. Royal United Hospital in Bath closed in June 2009 with the ventilator relocated firstly to the John Radcliffe Hospital to support HFOV training and then relocated to Queen Alexandra Hospital in Portsmouth once the new sites had all been set up.
iii. University Hospital of Wales closed for recruitment in July 2010 owing to lack of recruitment and the ventilator from this site was sent to the highest recruiting site at the time, Queen Elizabeth Hospital in Birmingham, for use as a second ventilator.

In December 2010, the leasing period for the first 10 ventilators was coming to an end. Negotiations with Novalung led to the lease being extended to 3 March 2011, at no additional cost to the study. Also, there were enough additional funds to extend the lease on seven of these ventilators up to end of recruitment (August 2011). Thus, in the beginning of 2011, it was planned that four of the lowest recruiting sites would be closed so the lease could be extended for the remaining sites.

By the end of August 2011, 637 of the target of 802 patients had been recruited into the trial. It was decided to approach 17 sites (as indicated in *Table 3*) to see if they were prepared to continue recruiting patients into OSCAR until the end of July 2012 (when the last 12-month follow-up was due for the 637 patients). The sites were seven with their own ventilators and 10 which had a purchased (study) ventilator. A substantial amendment to the protocol was submitted to the MREC, as some documentation needed updating because follow-up might not be complete for all patients and this was approved (see *Appendix 1, List 6: substantial amendment 5*).

Inclusion criteria for centres

An ICU was considered for collaboration in the trial if it met the following criteria:

i. The number of annual admissions to the ICU suggested patients with ARDS occurred sufficiently frequently (amended from the original protocol as stated in *Appendix 1, List 2: substantial amendment 1, No. 1*).
ii. The ICU had a history of collaborating in research and staff members were keen to be involved.
iii. All consultants in the ICU had 'substantial uncertainty' about the use of HFOV generally and were prepared to enter patients into a trial comparing HFOV with conventional treatment for patients with ARDS.
iv. Consultants were willing to attend HFOV training.
v. The PI was prepared to negotiate the release of all other appropriate staff for HFOV training.

Inclusion criteria for patients

Our aim was to recruit adults (age $\geq$ 16 years old) admitted to an ICU with ARDS who were predicted to require artificial ventilation for 48 hours or greater. ARDS was defined using the American-European Consensus Committee definition of a P : F ratio of $<$ 26.7 kPa[51] from two arterial blood gas analyses 12 hours apart. We exclude patients who weighed $<$ 35 kg as the ventilators were not CE approved for treatment of patients below this weight. Patients with obstructive lung pathologies and conditions in which HFOV might be hazardous were excluded.

TABLE 3 Initiation of the sites for the OSCAR trial

Status of ventilator	Type of ventilator	Site code	Hospital name	Start date	End date	Number of recruits
Obtained from original funding	Leased	6201	John Radcliffe Hospital[a]	3 December 2007	31 July 2012	15
	Leased	6203	Aberdeen Royal Infirmary[b]	3 December 2007	28 May 2009	15
	Leased	6204	Medway Hospital	7 January 2008	31 January 2011	27
	Leased	6202	Derriford Hospital[a]	7 January 2008	31 July 2012	46
	Leased	6206	Royal Sussex County Hospital[a]	14 January 2008	31 July 2012	46
	Leased	6210	Manchester Royal Infirmary (General)	11 February 2008	31 January 2011	24
		6220	Manchester Royal Infirmary (Cardiac)	7 September 2009	31 January 2011	1
	Leased	6209	Royal United Hospital, Bath[b]	4 March 2008	26 June 2009	20
	Leased	6207	University College Hospital[a]	17 March 2008	31 July 2012	63
	Leased	6205	Queen Elizabeth Hospital Birmingham[a]	25 March 2008	31 July 2012	102
	Leased	6208	University Hospital of Wales	9 June 2008	2 July 2010	16
	Own	6211	Ysbyty Maelor[a]	21 April 2008	31 July 2012	32
	Own	6213	Queen Elizabeth Hospital, Gateshead[a]	1 December 2008	31 July 2012	14
Transferred	Leased	6214	Stirling Royal Infirmary (from Aberdeen)	17 June 2009	31 August 2011	19
	Leased	6222	Queen Alexandra Hospital (from Bath/Oxford)[a]	4 November 2009	31 July 2012	37

continued

TABLE 3 Initiation of the sites for the OSCAR trial (*continued*)

Status of ventilator	Type of ventilator	Site code	Hospital name	Start date	End date	Number of recruits
Funded: extension grant	Purchased	6215	Royal Cornwall Hospital[a]	15 December 2008	31 July 2012	56
	Purchased	6224	Royal Blackburn Hospital[a]	10 December 2009	31 July 2012	26
	Purchased	6216	Wythenshawe Hospital	4 January 2010	31 August 2011	15
	Purchased	6217	University Hospital of North Staffordshire	4 January 2010	31 August 2011	15
	Purchased	6218	Ipswich Hospital	4 January 2010	31 March 2011	5
	Purchased	6223	Queen Margaret Hospital	4 January 2010	31 January 2011	8
	Purchased	6227	St James's University Hospital[a]	4 January 2010	31 July 2012	68
	Purchased	6228	York Hospital	4 January 2010	31 August 2011	13
	Purchased	6226	Southampton General Hospital	8 February 2010	31 August 2011	14
	Purchased	6229	Victoria Hospital Blackpool[a]	15 February 2010	31 July 2012	28
	Own	6230	Southend Hospital[a]	20 September 2010	7 November 2011	3
	Own	6221	James Paget Hospital[a]	2 November 2009	31 July 2012	23
	Own	6225	Leeds General Infirmary[a]	26 October 2009	31 July 2012	30
	Own	6231	Royal Victoria Infirmary[a]	11 October 2010	31 July 2012	8
	Own	6232	James Cook University Hospital[a]	17 January 2011	31 July 2012	6

a Centres which recruited to July 2012, beyond the original August 2011 end date, with ventilators purchased by the study or their own locally funded ventilators.
b Ventilator transferred to another hospital.

Patients were therefore eligible for the trial if they met the following inclusion criteria:

i. age ≥ 16 years
ii. weight ≥ 35 kg
iii. was receiving artificial ventilation via an endotracheal or tracheostomy tube
iv. had acute hypoxaemic respiratory failure as defined by:

- lowest recorded P : F ratio measured between onset of artificial ventilation and time of screening of ≤ 26.7 kPa with a PEEP ≥ 5 cmH_2O
- bilateral infiltrates on chest radiograph

v. was not likely to be extubated by the following evening (predicted by attending clinician)
vi. had been mechanically ventilated for < 7 consecutive days (≤ 168 hours) at the point of randomisation.

Exclusion criteria for patients prior to trial entry

Patients who were likely not to benefit from HFOV included the following:

i. Patients with left atrial hypertension from any cause, diagnosed clinically or with echocardiography or pulmonary artery catheterisation.
ii. Patients who had been mechanically ventilated for more than 7 consecutive days at the point of enrolment.
iii. Patients with moderate or severe airway disease expected to cause expiratory airflow limitation.
iv. Patients who would have had a lung biopsy or resection during this hospital admission.
v. Patients with any other condition the clinician believed would make receiving HFOV hazardous.

Administrative, practical and ethical exclusions:

i. Patients who had previously enrolled in the OSCAR trial.
ii. Patients (or their representative) who refused consent.
iii. Patients (or their representative) who did not understand written or verbal information and for whom no interpreter was available.
iv. Patients who had been enrolled in another therapeutic trial in the 30 days prior to randomisation.
v. Patients in whom active treatment had been withdrawn or withdrawal was planned.

Where a patient met one of the exclusion criteria, screening was stopped. Most patients were expected to be unable to give informed consent when recruited so patient representatives were used to provide an opinion/assent.

Conventional positive-pressure ventilation (control group)

Patients randomised to the control group received conventional positive-pressure ventilation using conventional pressure-controlled artificial ventilation (as detailed in *Chapter 2*).

High-frequency oscillatory ventilation

Patients randomised to the experimental group received (artificial) HFOV delivered using a Vision Alpha ventilator (as detailed earlier).

Patient flow

Figure 4 illustrates the flow of patients (screened and randomised) in the OSCAR trial.

Patient consent

Patients were almost invariably unable to give informed consent owing to alterations in conscious level caused by their illness and therapeutic sedation. As a result, assent from personal or professional consultees (a relative or a nominated health-care professional) was obtained in line with the legal requirements in England and Wales (Mental Capacity Act 2005[76]), and in Scotland [Adults with Incapacity (Scotland) Act 2000[77]]. See *Appendix 2* for informed consent process, information and forms.

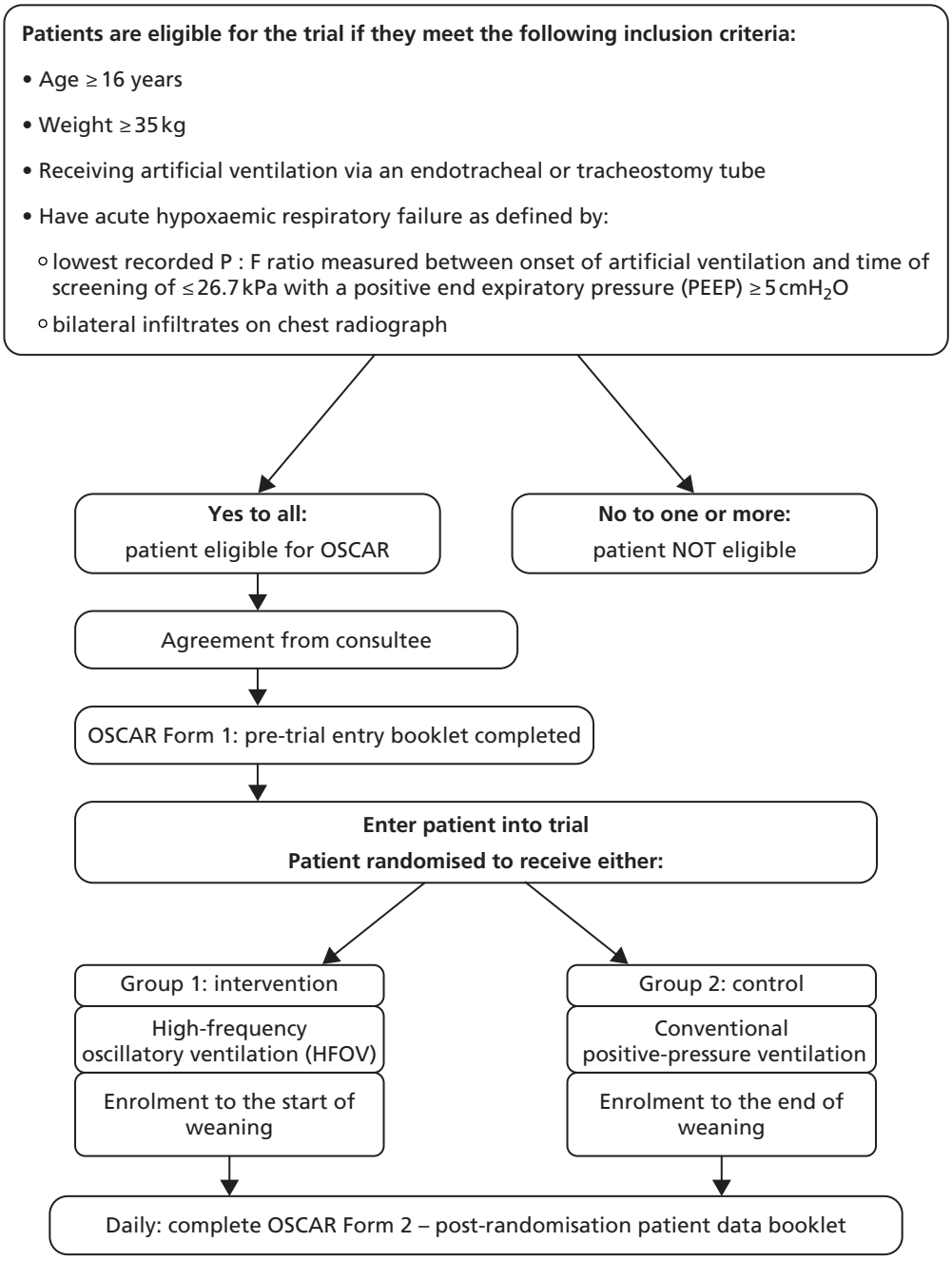


FIGURE 4 The flow of patients (screened and randomised) in the OSCAR trial.

If a patient or their representative ['Consultee' (personal or nominated professional), in England and Wales; 'Welfare Guardian/Nearest Relative' in Scotland] refused assent, the patient received usual treatment as defined by the clinician responsible for their care.

Checking eligibility and ventilator availability

Prior to entry, the appropriate items on the eligibility checklist were ticked and the patient was assessed for suitability for entry into the OSCAR study.

Prior to randomisation, it was necessary to check the availability of the HFOV ventilator, in case it was in use treating another trial patient.

Pre randomisation

Patients who satisfied the eligibility criteria had their baseline data collected prior to randomisation.

The procedures for the data collected prior to randomisation are listed in *Table 4*. The use of antimicrobial drugs and sedatives was recorded. As an aide-memoire and because antimicrobial drugs are sometimes used for purposes other than treating infections (e.g. erythromycin used as a prokinetic agent), a table of antimicrobials was included in the case report form (CRF). Similarly, some drugs are variously used for their sedative or analgesic properties (e.g. morphine) so an explanatory table was included. These are given in *Box 1* and *Table 5*.

The randomisation system

Randomisation was carried out by the Health Services Research Unit in Aberdeen. Randomisation was telephone based and was continuously available. Random allocation was generated by an independent programmer in an equal number assigned to each intervention.

Method of randomisation

We used stratified block randomisation. The randomisation was stratified by site, age of the patient ($\leq$ 55 years and > 55 years) and P : F ratio ($\leq$ 15 kPa and > 15 kPa). The block lengths were random so that prediction of intervention allocation could not be made.

Patients not in the trial

Brief details of patients initially eligible for the trial but not entered into the trial was recorded on a 'Why not in trial' log at each collaborating unit to monitor for bias in case selection and provide full reporting in accordance to the CONSORT statement.[78]

Immediately post randomisation

Hospital admission date and time and reason for admission were recorded following randomisation. Data on the initial ventilation and the patient's height (to allow calculation of ideal body weight) were also recorded.

For patients randomised to receive HFOV, the date and time the patient was connected onto the HFOV ventilator was recorded. In addition, the date/time the first FiO_2 was reduced and the cause of the acute hypoxaemic respiratory failure were recorded.

TABLE 4 Hospital assessments and the procedures used to collect the data

Time points	Measurement category	Measurements collected	Procedures and notes for data collection
Pre-randomisation/daily data in ICU/weaning off HFOV	**Ventilation measurements:** (these measurements had to relate to the arterial blood sample of ≤ 26.7 kPa with a PEEP ≥ 5 cmH_2O)	Exhaled minute volume	This was the total volume of gas exhaled in 1 minute, as measured by the ventilator. It included both mandatory and spontaneous breaths
		Total respiratory rate	This was the total respiratory rate per minute as measured by the ventilator. It included both mandatory and spontaneous breaths
		PEEP	This was the set PEEP. No measured auto-PEEP was included. The measurements related to the required repeat arterial blood sample to confirm ARDS (taken at least 12 hours after the initial arterial blood sample)
		Plateau pressure (cmH_2O)	This was the plateau pressure on mandatory breaths. In a volume-controlled mode, the inspiratory pause was added to allow estimation of plateau pressure. In a pressure-controlled mode this was the set inspiratory pressure. In both cases, the value above PEEP was recorded, not the absolute value. If the patient had only received inspiratory pressure support, the support (inspiratory) pressure above PEEP was recorded
		Arterial blood gases ($PaCO_2$, pH, PaO_2 and FiO_2)	The PaO_2 and FiO_2 measurements related to the required repeat arterial blood sample to confirm ARDS (taken at least 12 hours after the initial arterial blood sample). The sample had to demonstrate a PaO_2/FiO_2 ratio of ≤ 26.7 kPa (200 mmHg) for eligibility
Pre-randomisation/daily data in ICU	**Organ support:** (during the last 24 hours had the patient received any of the following)	Advanced respiratory support	This was indicated by one or both of the following: • Mechanical ventilatory support [excluding mask CPAP or non-invasive methods (e.g. mask ventilation)] • Extracorporeal respiratory support
		Basic respiratory support	This was indicated by one or more of the following: • More than 50% oxygen by face mask • Close observation owing to the potential for acute deterioration to the point of needing advanced respiratory support (e.g. severely compromised airway or deteriorating respiratory muscle function) • Physiotherapy or suction to clear secretions at least two hourly, whether via a tracheostomy, mini-tracheostomy or in absence of an artificial airway • Patients had recently extubated after a prolonged period of intubation and mechanical ventilation (e.g. more than 24 hours of tracheal intubation) • Mask CPAP or non-invasive ventilation • Patients who were intubated to protect the airway but needed no ventilatory support and who were otherwise stable

Time points	Measurement category	Measurements collected	Procedures and notes for data collection
Pre-randomisation/ICU data	**Organ support:** (during the last 24 hours had the patient received any of the following)	Advanced cardiovascular support	This was indicated by one or more of the following: • Multiple intravenous vasoactive and/or rhythm controlling drugs used to support arterial pressure, cardiac output or organ perfusion (e.g. inotropes, amiodarone, nitrates) • Patients resuscitated following cardiac arrest where intensive therapy was considered clinically appropriate • Intra-aortic balloon pumping • A functioning external pacemaker unit • Presence of a gastrointestinal tonometer
		Basic cardiovascular support	This was indicated by one or more of the following: • Treatment of circulatory instability owing to hypovolaemia from any cause • Use of a central venous catheter for basic monitoring or central venous access to deliver therapeutic agents • Use of an arterial line for basic monitoring of arterial pressure or sampling of arterial blood • Single intravenous vasoactive drug used to support arterial pressure, cardiac output or organ perfusion • Intravenous drugs to control cardiac arrhythmias • Non-invasive measurement of cardiac output (e.g. echocardiography, thoracic impedance)
		Renal monitoring/support	This was indicated by acute renal replacement therapy (haemodialysis, haemofiltration, etc.)
		Gastrointestinal support	This was indicated by feeding with parenteral or enteral nutrition via a feeding tube
		Dermatological support	This was is indicated by one or more of the following: • Patients with major skin rashes, exfoliation or burns (e.g. > 30% body surface area affected) • Use of multiple, large trauma dressings (e.g. multiple limb or limb and head dressings) • Use of complex dressings (e.g. open abdomen or large skin area > 30% of body surface area)
		Liver support	This was indicated by extracorporeal liver replacement device such as a MARS device, bioartificial liver or charcoal haemoperfusion

continued

TABLE 4 Hospital assessments and the procedures used to collect the data (*continued*)

Time points	Measurement category	Measurements collected	Procedures and notes for data collection
		Antimicrobial use	'Yes' was ticked if the patient had received one or more doses of drugs primarily used for the treatment of bacterial, viral or fungal infections (as in *Box 1*). Drugs used to treat tuberculosis, HIV infection or parasitic diseases were excluded
Pre-randomisation/ICU data	**Organ support:** (during the last 24 hours had the patient received any of the following)	Sedative use	'Yes' was ticked if (in the 24-hour period) the patient has received an intravenous bolus dose or an infusion of drugs primarily for sedation rather than for analgesia, treatment of insomnia, treatment of psychosis or antiepileptic actions. If patients were receiving opiates alone primarily for analgesia the 'No' box was ticked. See *Table 5*
		Muscle relaxants	If patient had received muscle relaxant drugs (neuromuscular junction blocking agent), then this was ticked 'yes'
		Proned	Ventilation had to be in the prone position (fully prone – face down and no lateral tilt). Chest weighting in the supine position was not considered to be prone
		Receiving inhaled nitric oxide	This was recorded as 'yes' if patient was receiving any concentration of therapeutic inhaled nitric oxide
Immediately post randomisation	Patient's clinical data	Sex	
		Age	
		Weight	
ICU data	HFOV measurements	Frequency	The set HFOV oscillation frequency
		Mean airway pressure	The set mean airway pressure
		Amplitude	The measured amplitude in cmH_2O
		Arterial blood gases	Not venous gas results
		Hours on HFOV	This is the total number of completed hours on HFOV since 8 a.m. the previous day
		Cuff leak	Was a deliberate cuff leak introduced to improve CO_2 clearance at any point in the last 24 hours?
		Set cycle volume	This is set (not measured) volume
		The set base flow	As recorded on the HFOV device

CPAP, continuous positive airway pressure; MARS, Molecular Adsorbents Recirculation System.

BOX 1 Antimicrobial use drugs (pre randomisation and ICU). Drugs in this list were considered antimicrobial unless administered for another purpose (e.g. erythromycin as a prokinetic agent)

Acyclovir.

Amikacin.

Amoxicillin.

Ampicillin.

Amphotericin.

Aztreonam.

Benzylpenicillin.

Caspofungin.

Cefamandole.

Cefazolin.

Cefotaxime.

Cefoxitin.

Cefpirome.

Cefradine (cephradine).

Ceftazidime.

Ceftriaxone.

Cefuroxime.

Chloramphenicol (i.v.).

Ciprofloxacin.

Clarithromycin.

Clindamycin.

Co-amoxiclav.

Colistin.

Co-trimaxazole.

Ertapenem.

Erythromycin (not prokinetic doses).

Flucloxacillin.

Fluconazole.

Flucytosine.

BOX 1 Antimicrobial use drugs (pre randomisation and ICU). Drugs in this list were considered antimicrobial unless administered for another purpose (e.g. erythromycin as a prokinetic agent) (*continued*)

Foscarnet.

Ganiclovir.

Gentamicin.

Imipenem.

Itraconazole.

Ketoconazole.

Levofloxacin.

Linezolid.

Meropenem.

Metronidazole.

Netilmycin.

Ofloxacin.

Piperacillin.

Quinupristin/dalfopristin (Synercid®, Pfizer).

Sodium fusidate.

Sulfadiazine.

Teicoplanin.

Tazocin (piperacillin + tazobactam).

Ticarcillin.

Tigercycline.

Tobramycin.

Vancomycin.

Voriconazole.

i.v., intravenous.

TABLE 5 Drugs which were used as a sedative (pre randomisation/ICU)

Drug class	Drug
Primarily used as sedative	Chlorpromazine
	Chlordiazepoxide
	Diazepam
	Haloperidol
	Isoflurane
	Ketamine
	Lorazepam
	Methohexitone
	Midazolam
	Paraldehyde
	Phenobarbitone
	Promazine
	Propofol
	Thiopentone
Opiates primarily used as sedative	Alfentanil
	Diamorphine
	Fentanyl
	Morphine
	Remifentanil
	Papaveretum
If used alone, these are **not** considered primarily sedative	Alpha 2-adrenoceptor agonists (clonidine, dexmedetomidine)
	Buprenorphine
	Codeine phosphate
	Methadone
	Pethidine
	Tramadol

First 24 hours in intensive care unit

The ICU date and time of entry and the details of the patient's past medical history required to calculate the risk of in-hospital death using the Acute Physiology and Chronic Health Evaluation II (APACHE II) algorithm[79] were recorded using definitions slightly modified from those used by the ICNARC Case Mix Programme, a UK-wide ICU audit programme (*Box 2*). The patient's primary condition was also recorded using the ICNARC coding method convention.[80]

Clinical data were also recorded to calculate the APACHE II score. The procedure for recording the data is listed in *Box 3*, which is an updated version of the definitions used in the original APACHE II study.[79]

BOX 2 Past medical history for APACHE II scoring, which are updated versions on the definitions used by ICNARC

Portal hypertension

- Evidence of portal hypertension was the presence of oesophageal or gastric varices demonstrated by surgery, imaging or endoscopy or the demonstration of retrograde splenic venous flow by ultrasound.
- Did not include gastrointenstinal bleeding without evidence of portal hypertension.

Hepatic encephalopathy

- Episodes of hepatic encephalopathy, Grade 1 or greater.
- *Grade 0* No abnormality detected; *Grade 1* Slowness in cerebration, intermittent mild confusion and euphoria; *Grade 2* Confused most of the time, increasing drowsiness; *Grade 3* Severe confusion, rousable, responds to simple commands; *Grade 4* Unconscious, responds to painful stimuli.

Very severe cardiovascular disease

- Fatigue, claudication, dyspnoea or angina at rest, where any activity increased symptoms. Symptoms must have been attributable to myocardial or peripheral vascular disease. Functionally, this patient could not stand alone, walk slowly or dress without symptoms.

Severe respiratory disease

- Had permanent shortness of breath with light activity attributable to pulmonary disease. Functionally, this patient was unable to work and has shortness of breath performing most normal activites of daily living (e.g. walking 20 metres on level ground, walking slowly in the house, climbing one flight of stairs, dressing or standing).

Home ventilation

- Had used or was using home ventilation.
- Ventilation was defined where all or some of the breaths or a portion of the breaths (pressure support) were delivered by a mechanical device. Ventilation could be simply defined as a treatment where some or all of the energy required to increase lung volume during inspiration is supplied by a mechanical device.
- CPAP is excluded.

Chronic renal replacement

- Required chronic renal replacement therapy (either chronic haemodialysis, chronic haemofiltration or chronic peritoneal dialysis) for irreversible renal disease.

Acquired immunodeficiency syndrome

- HIV-positive with clinical complications.
- Clinical complications include *Pneumocystis carinii* (*P. jirovecii*) pneumonia, Karposi's sarcoma, lymphoma, tuberculosis and toxoplasma infection.
- Did not include AIDS-related complex or positive HIV test without clinical manifestations.

Steroid treatment

- Had received ≥ 0.3 mg/kg prednisolone or an equivalent dosage of another corticosteroid, **daily** for the 6 months prior to admission to your unit.

Radiotherapy

- Had received externally administered radiotherapy, excluding all of the following: radiotherapy for non-invasive skin tumours; enteral or parenteral radioisotope therapy; radioactive implants; radiotherapy for prevention of heterotopic bone formation.

BOX 2 Past medical history for APACHE II scoring, which are updated versions on the definitions used by ICNARC (*continued*)

Chemotherapy

- Had received drug treatment resulting in a lower resistance to infection.
- Examples include drug treatment malignancy, vasculitides, rheumatoid arthritis, inflammatory bowel disease, etc.

Metastatic disease

- Had distant (not regional lymph node) metastates, documented by surgery, imaging or biopsy.

Acute myelogenous/lymphocytic leukaemia or multiple myeloma

- Acute myelogenous leukaemia, acute lymphocytic leukaemia or multiple myeloma must have been evident in the 6 months prior to admission to your ICU.

Chronic myelogenous/lymphocytic leukaemia

- Chronic myelogenous leukaemia or chronic lymphocytic leukaemia must have been evident in the 6 months prior to admission to your unit.

Lymphoma

- Had active lymphoma, documented by surgery, imaging or biopsy.

Congential immunohumoral or cellular immune deficiency

- Had documented congenital immunohumoral or congenital cellular immune deficiency state.
- Examples include CVID, agammaglobulinaemia including XLA, SCID, chronic granulomatous disease, lgA deficiency, lgG deficiency, functional antibody deficiency, hyper lgE syndrome, Wiskott–Aldrich syndrome, CMCC, DiGeorge syndrome, ataxia telangiectasia, leucocyte adhesion defect, complement deficencies, C1 esterase inhibitor deficiency, Kostmann syndrome.

AIDS, acquired immunodeficiency syndrome; CMCC, chronic mucocutaneous candidiasis; CPAP, continuous positive airway pressure; CVID, common variable immunodeficiency; HIV, human immunodeficiency virus; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.

BOX 3 Procedure for collecting physiological variables for the first 24 hours of ICU admission

Central temperature

- Tympanic membrane, nasopharyngeal, oesophageal, rectal, pulmonary artery, bladder are considered as central temperature measurement sites.

Blood pressure

- The readings at the most extreme. (If there was a decision to be made between two readings take the one that gave the most extreme MAP.)

Heart rate

- For admissions who were paced, the actual measured ventricular rate is recorded.
- Ventricular rate is not recorded for any admissions during periods of iatrogenic disturbance (e.g. physiotherapy, turning, periods of crying, etc.).

Non-ventilated/ventilated respiratory rate

- A respiratory rate is defined as ventilated when all or some of the breaths or a portion of the breaths (pressure support) are delivered by a mechanical device. Ventilation can be simply defined as a treatment where some or all of the energy required to increase lung volume during inspiration is supplied by a mechanical device.
- High-frequency and jet ventilators, negative pressure ventilators and BIPAP are considered as ventilated.
- Hand ventilation by a member of your team is considered as ventilated.
- CPAP and ECMO are considered as not ventilated.
- For admissions who were ventilated, the respiratory rate is to be the sum of both ventilated and spontaneous breaths in a minute.

Intubated arterial blood gas with highest fractional concentration of inspired oxygen

- A patient is considered intubated if they have a laryngeal mask or an endotracheal, endobronchial or tracheostomy tube in place.

Serum sodium/potassium/creatinine/haematocrit/haemoglobin/white blood cell count

- Laboratory results only, performed either in the departments of clinical chemistry or haematology or in near patient testing laboratories with formal quality control programmes in operation. For white blood cell count, the effects of steroids, inotropes and splenectomy are ignored.

Urine output

- No account is taken of the effect of diuretics.

Assessment of Glasgow Coma Scale score

Glasgow Coma Scale scores assessed only when the patient was free from the effects of sedative and/or paralysing or neuromuscular blocking agents are valid (*Table 6*). For patients sedated or paralysed for part of the first 24 hours, the lowest Glasgow Coma Scale score is during the periods they are free of drug effects.

BIPAP, biphasic positive airway pressure; CPAP, continuous positive airway pressure; MAP, mean arterial pressure.

TABLE 6 Assessment of the Glasgow Coma Scale score

Feature	Response	Score
The best eye opening response	Spontaneous	4
	To verbal command	3
	To pain	2
	No response	1
The best verbal response	Orientated and converses	5
	Disorientated and converses	4
	Inappropriate words	3
	Incomprehensible sounds	2
The best motor response	Obeys verbal command	6
	Localises pain	5
	Flexion withdrawal	4
	Flexion-abnormal/decorticate rigidity	3
	Extension/decerebrate rigidity	2
	No response	1
If a patient is **intubated**, use clinical judgement to score verbal response as follows	Appears orientated	5
	Responsive but ability to converse questionable	3
	Generally unresponsive	1

Daily data in intensive care unit

Following ICU admission, data were collected every morning, starting at 8 a.m. (or as near as possible) the day after randomisation.

The data collected on all patients were details of organ support, antimicrobial use, sedative use, muscle relaxant use, nitric oxide use and information on prone positioning. For patients on conventional ventilation, exhaled minute volume, total respiratory rate (and hence tidal volume), PEEP and plateau pressures, blood gases and inspired oxygen were recorded. For the patients on HFOV, the frequency, mean airway pressure, measured amplitude, cycle volume, bias flow, completed hours on HFOV and the use of a cuff leak were recorded, along with arterial blood gases and inspired oxygen.

Transition from high-frequency oscillatory ventilation to conventional ventilation for weaning

As noted earlier, there is no facility for spontaneous breaths while a patient is receiving HFOV. As weaning from artificial ventilation back to spontaneous (unassisted) breathing involves a gradual removal of artificial ventilator support with a concomitant increase in spontaneous breathing, this could not be undertaken on the HFOV ventilator. When a patient randomised to HFOV had improved sufficiently (i.e. FiO_2 was ≤ 0.4 or less and the mean airway pressure was $\leq 25\ cmH_2O$) the patient was switched to conventional ventilation, initially using the conventional ventilation mode on the Vision Alpha ventilator for up to 48 hours and then using the ICU's normal ventilators. If, during the first 48 hours on conventional ventilation (either Vision Alpha or standard conventional ventilator), the consultant had decided that the patient might benefit from further high-frequency ventilation, the patient was placed back on HFOV and this was recorded accordingly. *Figure 3* summarises the patient treatment and weaning flow chart.

The point at which patients could be fully weaned from conventional artificial ventilation depended on a large number of factors that could not be protocolised. The assessments made whilst weaning a patient off HFOV are illustrated in *Figure 3*.

Hospital stay and after hospital discharge

Patients either died on the ICU or survived and were transferred to a hospital ward. The date, time and vital status at ICU discharge were recorded. No data were collected while in the hospital ward, except the hospital discharge date.

Patients were 'flagged' on the Office for National Statistics (ONS) database to ensure reliable collection of the survival data. Lists of survivors to hospital discharge were sent to the ONS regularly where two checks were carried out. The first was list cleaning, which maximised the chances of identifying individual patients on the ONS databases. The second check was to reveal any patients who have died after hospital discharge to ensure follow-up questionnaires were not posted out to deceased patients. For some patients it was necessary to contact the patient's general practitioner to obtain the patient's vital status.

Follow-up assessments

This section describes the methods used for patient follow-up to 1 year after randomisation, to obtain data on health-related QoL and health-care costs. As the trial recruitment period was extended into the period planned for follow-up, the follow-up data are incomplete at the time of writing, and so only a limited number of results are reported in *Chapter 4*.

Patients were followed up at 6 and 12 months after randomisation using self-completed postal questionnaires. Return of questionnaires was tracked carefully by the OSCAR trial office. Patients who died after hospital discharge but prior to the mailing were identified from the ONS returns and removed from the mailing list. The questionnaire included standard instruments to measure health-related QoL and calculate utility indices for the first year after ICU discharge [Short Form questionnaire-12 items (SF-12) and EQ-5D, see *Chapter 1*]. Questions on social- and health-service use were included to allow a health economic analysis. Freepost envelopes were provided to maximise the response rate.

A letter was sent out to survivors 2 weeks ahead of the first follow-up questionnaire at 6 months and the second questionnaire at 12 months. This letter was added in as a substantial amendment to the protocol (see *Appendix 1, List 5: substantial amendment 4*) as a reminder to the participant that they would be receiving a questionnaire related to their health in the near future, in an attempt to maximise the response rate. If the questionnaire was not returned a month after it was posted, the vital status of the patient was rechecked using ONS and a reminder letter and another questionnaire were posted. This reminder letter was added in as a substantial amendment to the protocol (see *Appendix 1, List 3: substantial amendment 2*).

A carer's questionnaire was also included as part of the follow-up package. This was added in as a substantial amendment to the protocol (see *Appendix 1, List 2: substantial amendment 1, No. 9*), as part of the study involved learning about the carers and the financial impact on them as a result of providing care to someone who has been treated on an ICU. Collecting the data on carers allowed an insight into the cost of the interventions not just to the NHS but to the wider society.

Outcomes

The outcomes are listed in *Table 7*.

TABLE 7 Primary and secondary outcomes

Type of outcome	Time point	Outcome		Derived
Primary	Post randomisation	Mortality (all cause) at 30 days		Status of the patient at 30 days (dead/alive)
Safety	Throughout the trial	SAEs		–
Secondary	ICU	Mortality rate at first discharge from ICU		Mortality rate from randomisation to first ICU discharge
		ICU length of stay		Discharged from ICU/death date
		Number of ventilator-free days (up to 30 days)		Number of days free of advanced respiratory support up to day 30, ICU discharge if prior to day 30 or death
		Advanced respiratory support-free days		Number of 'no' responses for advanced respiratory support from ICU entry to ICU discharge
		Basic respiratory support-free days		Number of 'no' responses for basic respiratory support from ICU entry to ICU discharge
		Number of days on renal support		Number of 'yes' responses for renal support from ICU entry to ICU discharge
		Number of days on gastrointestinal support		Number of 'yes' responses for gastrointestinal support from ICU entry to ICU discharge
		Number of days on dermatological support		Number of 'yes' responses for dermatological support from ICU entry to ICU discharge
		Number of days on liver support		Number of 'yes' responses for liver support from ICU entry to ICU discharge
		Exhaled minute volume		–
		Total respiratory rate		–
		PEEP		–
		Plateau pressure		–
		Arterial blood gas	*P*aO_2	–
			*P*aCO_2	–
			pH	–
			*F*iO_2	–
	Hospital discharge	Mortality rate at first discharge from hospital		Mortality rate from randomisation to first hospital discharge
		Length of acute hospital stay		Date of discharge from hospital/death
	Follow-up (6 months after randomisation)	SF-12 Health Survey questionnaire (version 2)		Scoring of the SF-12 was carried out using the *How to Score Version 2 of the SF-12 Health Survey: With a Supplement Documenting Version 1* manual[81]
		EQ-5D scale		ED-5D was scored using the devised algorithm and summarised as detailed in the EQ-5D-3L *User Guide* version 4.0[82]

continued

TABLE 7 Primary and secondary outcomes (*continued*)

Type of outcome	Time point	Outcome	Derived
	Follow-up (12 months after randomisation)	Mortality rate 1 year after randomisation	–
		Respiratory function (SGRQ)	This was scored as outlined in the text
		EQ-5D scale	As at 6 months
		SF-12 Health Survey questionnaire (version 2)	As at 6 months
	ICU	Number of days antimicrobial use: received in past 24 hours	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days antimicrobial use: treating pulmonary infection	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days antimicrobial use: given intravenously	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for sedative use: received in past 24 hours	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for sedative use: given as an intravenous bolus dose	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for sedative use: given by infusion	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for sedative use: more than one class of sedative	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for sedative use: more than two classes of sedative	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for sedative use: more than three classes of sedative	Number of 'yes' responses on this variable from ICU entry to ICU discharge

SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire.

Primary outcome

The primary outcome was all-cause mortality 30 days after randomisation. This allows comparison with previous studies and is the FDA's preferred ICU mortality outcome. Most deaths in observational/interventional studies of ARDS occur within 30 days.

Secondary outcomes

Prior to hospital discharge

In the original protocol, the secondary effectiveness outcomes which were to be assessed prior to follow-up included:

i. mortality at ICU discharge
ii. mortality at hospital discharge
iii. non-respiratory organ failure during intensive care treatment (measured using the Critical Care Minimum Data Set which all ICUs in the UK collect).

An amendment to the protocol was added in (see *Appendix 1, Listing 2: Substantial amendment 1, No. 2*) to allow for ventilation-free days, antimicrobial-free and sedative-free days to be secondary outcome measures.

The amendment to change to organ or treatment-free days was felt necessary because differing total mortality, or differing patterns of mortality over time, interacts with the number of days of organ failure or treatment. Early deaths decrease the interval available to accrue days of organ failure or treatment. Ventilation-free days are calculated by assigning a census day (day 28 post randomisation) and all patients who die before that date are assigned 28 days of ventilation. All survivors at day 28 are assigned the actual number of days they received ventilation. Other treatment-free days are calculated in the same way.

Follow-up at 6 and 12 months

i. Mortality 1 year after randomisation.
ii. Health-related QoL (at 6 months and 12 months) using SF-12 and EQ-5D.
iii. Respiratory function questionnaires [St. George's Respiratory Questionnaire (SGRQ)] to measure long-term lung damage.
iv. Cognitive function.

It was originally anticipated that we would use the SF-36 health-related QoL questionnaire. However, amendments to the protocol were made (see *Appendix 1, Listing 2: Substantial amendment 1, No. 3* and *No. 7*) which allowed us to use the SF-12 questionnaire. The reasons for the change were that it would reduce responder burden and many ARDS studies were using SF-12 which would make pooling of results easier.

Respiratory function was measured using the SGRQ.[83]

Cognitive function was not measured in this study. After an extensive literature review, no self-completed questionnaire was found which could be used to adequately record cognitive function at the follow-up times. An amendment (see *Appendix 1, Listing 2: substantial amendment 3*) was submitted to remove this from the protocol.

Short-Form questionnaire-12 items health-related quality-of-life instrument

Scoring

The SF-12 manual[84] was used to score the eight concepts included in the SF-12: general health, vitality, social functioning, role functioning physical, role functioning emotional, mental health, physical functioning, and bodily pain. Results were expressed in terms of two meta-scores: physical and mental components.

Interpretation

The SF-12 is scored so that a high score indicates better physical functioning. The physical and mental scores have a range of 0 to 100 and were designed to have a mean score of 50 and a standard deviation (SD) of 10 in a representative sample of the US population. A SF-12 score that is > 50 represents above-average health status. On the other hand, people with a score of 40 function at a level lower than 84% of the population (1 SD) and people with a score < 30 function at a level lower than approximately 98% of the population (2 SDs). An example of the scores recorded in a mixed population in the USA is shown in *Table 8*.

TABLE 8 Short Form questionnaire-12 items mean scores (general US population)

Age (years)	Mean physical component score	Mean mental component score
45–54	50	50
55–64	47	51
65–74	44	52
> 75	39	50

European Quality of Life-5 Dimensions

In order to conduct an economic evaluation, it was also necessary to have a single index measure of health status differences. The EQ-5D is one of the most commonly used tools. It measures health on five dimensions and a tariff is available for deriving a single utility score. Completion takes < 5 minutes. We used the three-level version of the instrument.

Scoring

The instrument contains a description of the health state in five dimensions or items: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The items are always presented in the same order and there are three levels of severity for each item: 1 (no problems), 2 (some problems) and 3 (unable to do/extreme problems). For each item, the respondent must indicate the level of severity that best describes his/her personal health state at the time of giving the answers. The subject's global health state is defined as the combination of the level of problems described for each of the five dimensions contained in the EQ-5D. Health states defined by the EQ-5D can be converted to a single summary by applying scores from a standard set of values (or preferences) derived from general population samples.[84]

Interpretation

The numbers or weightings representing the strength of society's preferences for an experienced or described health state are scored between 0 (death or worst imaginable health state) and 1 (full health or best imaginable health state). The quality adjustment is then multiplied by the expected life-years (LYs) in the assessed health state to arrive at the number of QALYs achieved. The expected utility associated with a health-care intervention is then the sum of the probability of entering a health state multiplied by the utility (QALY) associated with that state.

St. George's Respiratory Questionnaire

The SGRQ is a self-reported, disease-specific, health-related QoL questionnaire.[83] It was originally developed to measure the impact of chronic obstructive pulmonary disease (COPD) on a person's life, but has also been studied and applied to non-COPD pulmonary disease populations.

Scoring

Each of the questionnaire responses has a unique empirically derived weight. The lowest possible weight is 0 and the highest is 100.

Each component of the questionnaire is scored as follows:

i. The weights for all items with a positive response are summed.
ii. The weights for all missed items are deducted from the maximum possible weight for the total score.
iii. The total score is calculated by:

$$\text{Score} = 100 \times \text{summed weights from positive items in the questionnaire/sum of weights for all items in the questionnaire.} \quad (1)$$

Interpretation

A total score is calculated which summarises the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.

Tertiary outcomes and process variables

Other outcome measures and process variables were collected and are listed in *Table 9*. Oxygenation is not listed as a process variable because, as expected, the patients receiving HFOV initially had an improved oxygenation compared with conventionally ventilated patients (mean P : F ratio 25.8 kPa vs. 20.9 kPa) which persisted for the first 4 days. It then declined as the recovering patients were converted to conventional ventilation and so, over time, only the 'sicker' patients who are not responding to HFOV dominated the results.

TABLE 9 Tertiary outcomes and process variables

Type of outcome	Time point	Outcome	Derived
Tertiary outcomes	ICU	APACHE II score	APACHE II score and associated predicted mortality was derived using the specified algorithm[79]
		Number of days for muscle relaxants use: received in past 24 hours	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for muscle relaxants use: given as an intravenous bolus dose	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days for muscle relaxants use: given by infusion	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days prone in last 24 hours	Number of 'yes' responses on this variable from ICU entry to ICU discharge
		Number of days patient received inhaled nitric oxide in past 24 hours	Number of 'yes' responses on this variable from ICU entry to ICU discharge
Process	Hospital admission/ICU	Time from hospital admission to ICU admission	Time (date and time) of ICU admission
	Hospital admission/ randomisation	Time from hospital admission to randomisation	Time (date and time) of randomisation – time (date and time) of hospital admission
	ICU/randomisation	Time from ICU to randomisation	Time (date and time) of randomisation – time (date and time) of ICU admission
	ICU	Exhaled minute volume (conventional ventilation only)	–
		Total respiratory rate (conventional ventilation only)	–
		PEEP level (conventional ventilation only)	–
		Plateau pressure (conventional ventilation only)	–
		HFOV settings on ventilation	–

Health economic outcomes

The EQ-5D was the main measure of health economics and it was planned to collect data on non-public sector resource utilisation.[85]

However, an amendment submitted (see *Appendix 1, Listing 2: substantial amendment 1, No. 4* and *No. 8*) also allowed the data collection on social- and health-service use and care both from a patient's point of view as well as the carer's.

Quality assurance

There was no formalised quality assurance check of individual site delivery of the protocol but two OSCAR research nurses continually visited sites both to train staff and discuss the operational aspects of the trial with local staff.

Compliance

The primary responsibility for the care of ventilated patients on ICUs passed from one consultant to the next on a daily or weekly basis depending on the type of duty roster. To ensure that there was compliance with the trial protocol throughout a patient's stay, and to avoid crossover after allocation, units were only signed up to the trial if all the consultant staff agreed to abide by the randomisation for study patients under their care.

Adverse events

Serious adverse events

The reporting guidelines from the National Research Ethics Service (NRES) for safety reporting in research other than clinical trials of investigational medicinal products were used for serious adverse events (SAEs).

A SAE was considered as an untoward and unexpected occurrence that a research participant experienced which: (i) resulted in death; (ii) was life-threatening; (iii) required hospitalisation or prolongation of existing hospitalisation; (iv) resulted in persistent or significant disability or incapacity; (v) consisted of a congenital anomaly or birth defect.

A SAE was recorded on the appropriate trial form by the clinician caring for the patient and reported immediately to the Principal Investigator at that centre. The Principal Investigator then reported the SAE to the Chief Investigator of the OSCAR trial. The Chief Investigator gave an opinion on whether or not the event was:

- 'related' (resulted from administration of any of the research procedures), and
- 'unexpected' (the type of event was not listed in the protocol as an expected occurrence).

A confirmed, related SAE was submitted to a MREC (England or Scotland) within 15 days of the Chief Investigator becoming aware of the event using the NRES report of SAE form. Events were also reported to the Data Monitoring and Ethics Committee (DMEC).

Expected events

Most known events related to artificial ventilation should occur equally in both groups. Exceptions that were noted that might occur more frequently in the HFOV group were:

1. air trapping
2. secondary effects of air trapping such as reduced carbon dioxide clearance, and impaired venous return to the thorax.

Sample size

In the original protocol, the sample size was 1006 patients randomised in equal allocation to either group.

The sample size calculations were based on the primary outcome measure, 30-day all-cause mortality. Data to inform the sample size estimation were available for all-cause mortality in patients meeting the entry criteria for the proposed study from a number of sources, to assist with sample size calculations.

Large epidemiological studies of ARDS in Europe had been undertaken at regular intervals over the last decade. The most recent was the ALIVE study,[3] which collected data from February 1999 to March 1999 from 78 ICUs across Europe. Cases of ARDS were identified at any point in the ICU stay using the American-European consensus conference criteria. A total of 401 cases of ARDS were identified among 6522 admissions. Hospital mortality was 57.9% but 30-day mortality was not recorded. These data were robust but were an average across multiple European ICUs. However, they were outdated (7 years old at the study start) and the 30-day mortality was not known.

Data collected and analysed by the ICNARC were presented at the US Society of Critical Care Medicine in January 2006. The data came from 261,193 cases admitted to 174 adult, general ICUs in England, Wales and Northern Ireland, from December 1995 to July 2005. Cases were identified using the lowest P : F ratio recorded in the first 24 hours after ICU admission, and categorised into ALI and ARDS using the American-European Consensus Conference on ARDS definitions[20] but excluding the chest radiograph requirement. Overall (patients with either ALI or ARDS) the hospital mortality was 44%, but only 61% of these patients were artificially ventilated on ICU admission. For those with ARDS who required artificial ventilation at the time of admission the hospital mortality was 42.4%. The 30-day mortality was not presented and median length of hospital stay was 16 days.

The main drawbacks with the ICNARC data were that they only identify patients who meet the study entry criteria in the first 24 hours following ICU admission, they were based on single blood gas estimation, there was no chest radiograph data, and the quoted mortality was hospital, not 30-day mortality.

The Chief Investigator of the OSCAR trial undertook a similar study using data on admissions to the adult ICU at the John Radcliffe Hospital, Oxford, for the calendar year 2005. Of 973 admissions, 850 had simultaneous arterial blood gas analyses and FiO_2 records which allowed P : F ratios to be calculated. The incidence of ARDS, defined using a P : F ratio of < 23.7 kPa at any point during the patient's stay, was 78.9%. However, only 2.5% of the patients had both a P : F ratio of < 26.7 kPa and any mention of ARDS in the discharge summary. These patients had a 38% 30-day mortality.

The limitation of the Oxford data was that true incidence of ARDS in ICU patients was almost certainly greater than the 2.5% we identified by retrospectively searching the database of discharge summaries. As a result the mortality estimate may be erroneous.

The SICSAG published data from 23 of the 26 ICUs in Scotland for an audit run between May 1999 and December 1999.[5] They only recorded patients meeting the diagnostic criteria for ARDS, but unlike ICNARC determined whether or not patents had ARDS on a daily basis, rather than only on admission, and

included chest radiographs in the inclusion criteria. They reported 61% hospital mortality for patients meeting the ARDS criteria at any point in their ICU stay. The main drawbacks of the SICSAG data were that they were outdated (7 years old) and the data were hospital not 30-day mortality.

In calculating the original sample size, we assumed that hospital mortality was close to 30-day mortality, and chose a middle value from the available data, namely 45%. We had used the effect size from the only intervention known to alter mortality in ARDS[12] as our predicted effect size (9% absolute mortality reduction). This was close to the effect size in the unweighted pooled data from the two RCTs performed to date at the time (8.1% absolute mortality reduction). We knew that the loss of patients to the PAC-Man study[54] owing to withdrawals was in the order of 3%. Crossovers were to be analysed on an intention-to-treat basis and so no correction was required. Using an 80% certainty of detecting this difference at $p = 0.05$ with a control group mortality of 45% required 503 patients in each group, a total study size of 1006.

Planned recruitment rate

Recruiting patients from 12 large UK ICUs admitting at least 650 patients per year each allowed a potential pool of patients of 7800 admissions per annum or 23,400 in the 36 months OSCAR was planned to recruit over. Based on the incidence of ARDS found in Scotland[5] of 8.1%, this gave a potential pool to recruit from of 1895 patients. From previous studies in ICU (the completed PAC-Man study[54] and the then ongoing TracMan,[86] PERMIT and SimSepT studies) we knew that the refusal rate for consent to research in ICU was approximately 30%. This would leave about 1320 potential patients for the OSCAR study, about 30% more than required. The required recruitment rate was just over two patients per month per site.

Revised recruitment target

From 1 December 2007 (start of recruitment) to 1 April 2009, the observed rate of recruitment had averaged to 1.01 per centre per month, approximately half of what was expected and thus the trial was severely underrecruiting.

After reviewing various strategies of increasing recruitment with experts in this research field, the DMEC and the Trial Steering Committee (TSC), it was agreed that the effect size based on the clinical relevant difference should be revisited and closely assessed. In addition, the assumptions around control group mortality should be checked by the study statistician reviewing the control group 30-day mortality. It was agreed that this information should be shared with the trial statistician and the HTA only. The sample size was recalculated using a 10% absolute change in mortality, with 80% power and 5% significance level and the control group mortality, giving a total of 802 patients (with 401 per treatment group), allowing for a 3% withdrawal rate. This recalculated sample size was discussed with clinical members of the TSC, who felt this represented a reasonable compromise between an achievable and clinically credible improvement in mortality, and the need to reduce the sample size and hence costs.

Data management

Before the start of the trial, data collection forms were piloted to determine ease of use and other practical issues.

Electronic databases were developed using specialised software. These were developed by the programmers at the Warwick Clinical Trials Unit, in collaboration with the trial manager and statistician. Computerised validation checks were incorporated into the databases to minimise data entry errors.

Validation checks were conducted at every interim analysis (once per year) and once the data had started to accumulate at a rapid rate (i.e. after January 2011), the validation checks were carried out every 6 months, until a final completely validated data set was produced. All items from the CRFs and as entered on the database were checked in the validation process.

Statistical analysis

The trial has been reported in accordance with the CONSORT[78] guidelines. All statistical tests were two-sided. The statistical analysis was carried out in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata 9 (StataCorp LP, College Station, TX, USA).

Formal interim analyses

At the request of the DMEC, the following were pre-specified:

- Two definite equally spaced formal interim analyses (one approximately 1/3 of the way and another 2/3 of the way through the trial).
- It was decided a priori that if any of the stopping guidelines (detailed in *Table 10*) were met at the first interim analysis, then the DMEC decided whether or not a closer monitoring of the trial was required. In this case, it was anticipated that another interim analysis would be planned half way through recruitment.
- It was not appropriate to specify fixed stopping rules, but the *p*-values given in *Table 10* were used as guidance for reviewing the primary end point, to assist decision-making around stopping or modifying the trial prematurely. *Table 10* illustrates the *p*-values if the data were reviewed three times (at equal time intervals), or four times (with unequal time spacing). The pre-specified reasons for stopping/modifying the trial were:
  - treatments were convincingly different in terms of mortality at 30 days
  - there were an unacceptable number of SAEs.
- Two formal interim analyses were conducted as detailed above and at each stage there was no cause for concern to stop or modify the trial.

TABLE 10 Stopping guidelines for the planned interim analyses

Number of planned interim analysis	Interim analysis	O'Brien–Fleming	Alpha spending function (Lan-DeMets)
3	1	0.00021	–
3	2	0.01210	–
3	3 (final)	0.05000	–
4	1	–	0.00019
4	2	–	0.00305
4	3	–	0.01235
4	4 (final)	–	0.05000

Final statistical analyses

Data sets used for the analysis

Intention to treat (observed data set)
The primary data analysis was 'intention to treat' (effectiveness analysis), using the observed data. The patients were analysed according to the intervention they had been randomised to, irrespective of the treatment they actually received.

Intention to treat (imputed data set)
A sensitivity analysis to assess the impact of missing data was carried out on the main observed data. The ICU data were not imputed as the assumption 'missing completely at random' could not be made due to the nature of the trial – missing data may be a result of poor prognosis of a patient in ICU.

However, questionnaire data at follow-up, in particular the items on a questionnaire, were imputed. Multiple imputation methods were used to impute missing data. Prior to an imputation, the data mechanisms (MAR – missing at random; NMAR – not missing at random; MCAR – missing completely at random) were assessed to make sure that multiple imputation was viable. This was done by looking at any patterns of missingness and only data that were validly missing were imputed. In the case of multivariate normal data, the multiple imputation methods assuming normality was used. In the case where we could not assume a distribution of the data, the ICE procedure[87] was used.

Per protocol
A secondary analysis was an efficacy analysis, which was restricted to patients who fulfilled the protocol and adhered perfectly to the clinical trial instructions as stipulated in the protocol.

Patients who were excluded from this analysis were:

i. those who had ventilator problems
ii. those who were randomised to HFOV and crossed over to conventional ventilation within 30 days of randomisation
iii. those who were randomised to conventional ventilation but crossed over to HFOV within 30 days of randomisation
iv. those who received less than the protocol 12 hours of HFOV
v. those that were taken off the ventilator due to clinical concerns
vi. those that were taken off the ventilator as staff were not confident with the ventilator.

CONSORT flow chart

The CONSORT flow chart details the number of patients who were recruited into the trial and the passage of patients through the trial (randomisation, ICU, follow-up and primary data analysis).

Details of patient withdrawal, those not responding at follow-up and patients who deviated from the protocol are also given (number and percentage based on those randomised within intervention group).

Serious adverse events

The number (and percentage) of SAEs which have occurred within each intervention group and at each time point (in ICU, from ICU to hospital discharge, hospital discharge to 6 months, 6 months to 12 months) were summarised. The details of each SAE were described in a listing.

Not in the trial patients

A patient who was not eligible for the trial could fall into one of the categories detailed in *Table 11*.

TABLE 11 Reasons why patients may not be entered into the OSCAR trial

Reason[a]	Reason
A	Another trial patient is already on the Vision Alpha
B	Another non-trial patient is on the Vision Alpha
C	Oscillator not working/technical failure
D	Patient has been ventilated for > 7 days
E	Consultant predicts patient will need > 48 hours of artificial ventilation
F	Consultant not 'substantially uncertain'/wants to continue only with conventional ventilation
G	PERSONAL consultee refused agreement
H	Nominated PROFESSIONAL consultee refused agreement
I	Excluded as welfare guardian/nearest relative refused consent
J	Exclusion criteria: previously in OSCAR
K	Exclusion criteria: in another trial
L	Exclusion criteria: interpreter not available
M	Exclusion criteria: treatment withdrawal is planned
N	Exclusion criteria: left atrial hypertension from any cause
O	Exclusion criteria: moderate or severe airway disease
P	Exclusion criteria: lung biopsy or resection
Q	Exclusion criteria: patient has condition clinician believes would make HFOV hazardous
Z	Other reasons

a See *Table 12*.

For the CONSORT diagram, we could summarise these into the following:

TABLE 12 Reasons from *Table 11*

Reasons from *Table 11*	Categories for exclusion
D + E	Not meeting all inclusion criteria
A + B + C	Meeting all the inclusion criteria but ventilator not available
F + G + H	Meeting all the inclusion criteria but also met one or more of the exclusion criteria
I through to Z	Meeting all the inclusion criteria but excluded due to other reasons

The demography details (i.e. age and sex) of patients, who were not entered into the trial and those who were entered into the trial were assessed statistically, using *t*-tests and chi-squared tests, respectively. This was to ensure that those in the trial were similar in characteristics to patients from a large population.

Pre-randomisation, randomisation and immediately post-randomisation assessment

The categorical variables were summarised using number of patients and percentages and the continuous variables were summarised using mean, SD, median, range (minimum and maximum) and number of patients with data prior and after randomisation.

No formal statistical testing was carried out on these data.

First 24 hours in intensive care unit

Data collected in the first 24 hours in ICU were summarised in a similar way to the above. In addition, comparison of interventions was carried out and the 'unadjusted estimates' were obtained using analysis of variance. The 'adjusted estimates' were obtained using analysis of covariance, with adjustments made for centre, P : F ratio and sex.

Intensive care unit and hospital stay data

These data were presented as tables and analysed using a linear regression model. The data were not split into survivors and non-survivors.

Primary outcome measure

For mortality at 30 days post-randomisation frequencies and percentages per intervention group were presented in a table. Mortality at 30 days was compared between treatment groups using chi-squared test (for an unadjusted estimate) and logistic regression model (for the adjusted estimates). For the latter model, the dependent variable was survived/died and independent variables were treatment and other important predictors (e.g. centre, age, P : F ratio and APACHE II score). An odds ratio measuring the treatment effect and its 95% CI was reported.

Survival time from randomisation to 30 days was analysed using a log-rank test. The event here was 'death up to 30 days'. Thus, any patient who was alive up to day 30 or after or had withdrawn prior to day 30 (after randomisation) was censored. The proportion dying over time was illustrated using a Kaplan–Meier curve for each of the ventilator groups. The *p*-values and a hazard ratio with its 95% CI obtained from a Cox-proportional hazards model were also presented (adjusted for centre, age, P : F ratio and APACHE II score). The proportional hazard assumption across treatment groups was checked graphically using a log-cumulative hazard plot.

The Kaplan–Meier curve with the probability of survival up to 30 days post randomisation, for each intervention was plotted. For this plot, the event was 'mortality up to 30 days post randomisation'. In the case where the event did not occur (i.e. where patients lived beyond 30 days or had any withdrew prior to 30 days), the observations were censored (i.e. the event was not observed). Thus, at the end of each day, taking account of all those who have died in the study to that day, the probability of death is computed, and from that the probability of survival is obtained [i.e. 1 – Pr(dying)].

Secondary and tertiary outcomes and process variables (during intensive care unit and follow-up)

In terms of other outcomes and variables, three different types of data were presented:

- *Categorical data* Categorical data were analysed using logistic regression models, with intervention as an independent variable with other important predictors (e.g. centre, age, P : F ratio and APACHE II score). The summary statistics were based on proportions and the 95% CI.
- *Continuous data* Continuous data were analysed using linear regression models, with intervention as an independent variable with other important predictors (e.g. centre, age and P : F ratio and APACHE II score). Intervention difference was based on adjusted mean estimates (and 95% CIs).
- *Time to an event* Time to ICU discharge from randomisation (i.e. length of intensive care stay), time to hospital discharge from randomisation (i.e. length of acute hospital stay) and 'survival time to 12 months' were summarised in tables. The analysis based on the comparison of the ventilation groups was done using survival analysis (in a similar way stated for the 'Primary outcome' above). The events of interest were 'died during ICU stay', 'died during hospital stay' and 'died by 12 months'. Thus, any patients who did not have the event (e.g. alive or withdrew prior to the event or non-responders) were treated as censored observations in the survival analysis.

Subgroup analyses

The most scientifically robust method of subgroup analysis is a test of interaction between treatment and outcome that has been appropriately powered. It is widely recognised that powering a study for subgroup analysis can dramatically increase sample size requirement. A rough rule is that detection of interactions approximately twice the size of the main effect requires no increase in the sample size, provided that the subgroups are of equal size, the subgroup comparisons are limited and pre-specified, and the results are considered hypotheses generating as opposed to confirmatory.[88] Three pre-specified analyses were alongside the main trial results. For each of these, the outcome was modelled with the intervention, subgroupings and interaction of intervention and subgroups. These analyses explored:

- The effect of HFOV on length of acute hospital stay, 30-day and hospital mortality in subgroups with different severity of illness determined by APACHE II scoring on ICU admission.
- The effect of HFOV on length of acute hospital stay, 30-day and hospital mortality in broad ARDS subgroups (pulmonary or extrapulmonary cause, sepsis, trauma, burns).
- The effect of HFOV on length of acute hospital stay, 30-day and hospital mortality in patients with differing severity of lung injury determined from their P : F ratio.

For each subgroup analysis, the Cox's proportional hazard's model and Kaplan–Meier plots were used to assess the difference in treatment effect and each subgrouping.

Health economic analysis

As noted above, data collection for the health economic analysis is ongoing.

In the original protocol, the primary measure of health-care system benefit was within-trial cost-effectiveness analysis (CEA) to estimate the cost per QALY gained for HFOV compared with conventional ventilation at 1 year. A long-term CEA was planned by implementing a decision analytic cost-effectiveness model with a lifetime time horizon. The parameters for the CEA were obtained by a Bayesian synthesis of the trial evidence with evidence identified by a systematic review and a costing study in a guided sample of ICUs. The primary analysis followed National Institute for Health and Care Excellence (NICE) guidance.

Secondary analysis adopted a full societal perspective. Data on non-public sector resource utilisation was being collected from the patients at 6 and 12 months.

Analyses for this study was undertaken from a NHS perspective. The main health economic outcome was the health status of survivors of ARDS at 6 months (from EQ-5D data) which were converted into QALYs to allow cost-utility modelling. Additionally, a range of modelling techniques was used to estimate longer-term cost-utility from 1-year follow-up data. Epidemiological and economic models were used to estimate lifetime gains or losses in QALYs from HFOV and savings in health-care expenditures. A full literature review was undertaken to explore the potential for providing monetary estimates of the long-term impacts of HFOV. This work was being undertaken at the University of Leeds.

To inform the economic analysis, a representative sampling framework for UK ICUs based on size (number of beds), consultant/bed ratio, nurse/bed ratio; and median APACHE II score of admissions was prepared, and in at least one unit from each cell in the sampling frame we undertook a micro costing study for patients with ARDS.

A research assistant visited these units to observe the care patients with ARDS receive and then cost it, along with representative patients not suffering from ARDS. The units did not have to be the same as those recruiting patients to the trial to obtain data on resource use in patients not receiving HFOV. Trial units, and in addition some non-trial ICUs undertaking HFOV, were used to determine resource use for HFOV in both the trial setting and in the more 'mature' use of HFOV in ARDS.

To provide some estimate of QoL beyond 12 months, patients recruited in the first year received an additional EQ-5D questionnaire and questions concerning social and health service use at 24 and 30 months. The patients recruited in the second year received an additional EQ-5D questionnaire and questions concerning social and health service use at 18 months. This allowed us to model the time for health-related QoL to return to population normal levels after ICU by group.

Trial organisation

The Data Monitoring and Ethics Committee

The DMEC comprised a senior statistician, a senior clinician and a senior triallist (chairperson); see *Appendix 4* for membership details.

Standard operating procedures for the DMEC were:

i. During the period of recruitment into the study, interim analyses of the proportion of patients alive at 30 days and analyses of deaths from all causes at 30 days were supplied, in strict confidence, to the chairperson of the DMEC, along with any other analyses that the committee requested.
ii. In the light of these analyses, the DMEC advised the chairperson of the Steering Committee if, in their view, the randomised comparisons provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment was clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management.
iii. Data relating to the safety of patients were reviewed by the Chair of the DMEC. The data reviewed were specifically related to:

   – procedure related 'serious, unanticipated adverse events' (death or serious disability)
   – procedure related adverse events/complications
   – deaths at 30 days (any cause).

The DMEC met to review progress at 1 year and when a formal interim analysis was due.

The Trial Steering Committee

The trial was guided by a group of respected and experienced critical care personnel and triallists as well as a public and patient representative. Face-to-face meetings were held at regular intervals determined by need but not less than once a year.

Standard operating procedures for the TSC were:

The TSC, in the development of this protocol and throughout the trial, was responsible for:

- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial
- reviewing relevant information from other sources
- considering recommendations from the DMEC
- informing and advising on all aspects of the trial.

Project management groups' responsibilities

This group was made up of the investigators on the grant application to the HTA programme plus the OSCAR co-ordinating team (see *Appendix 3* for membership details). They were responsible for:

- monitoring the progress of the trial and discussing project milestones
- reviewing centre and patient recruitment to the trial
- discussing day-to-day management issues that arise.

Collaborators' responsibilities

Co-ordination within each participating hospital was through a local collaborator who:

- complied with the protocol at all times
- discussed the trial with medical and nursing staff who treated ICU patients and ensured that they remained aware of the state of the current knowledge, the trial and its procedures (posters and other 'reminders' were provided by the trial office)
- ensured that patients in the ICU were considered promptly for the trial
- ensured that the trial CRFs and consent forms were completed in full
- ensured the trial was conducted in accordance with the Research Governance Framework and Good Clinical Practice (GCP) and fulfilled all national and local regulatory requirements
- allowed access to source data for audit and verification.

Co-ordinating centre responsibilities

The trial was co-ordinated by the Intensive Care Society (ICS) Trials Group based at the Kadoorie Centre for Critical Care Research and Education at the John Radcliffe Hospital in Oxford. Administrative support was supplied by the Nuffield Department of Anaesthetics, University of Oxford. Assistance with trial management and the statistical elements of the trial was supplied by the Clinical Trials Unit at Warwick University. Health economic support and analysis was provided by the Academic Unit of Health Economics at the University of Leeds. Randomisation services were provided by the University of Aberdeen.

The co-ordinating centre had the responsibility to:

- assist and facilitate the setting up of centres wishing to collaborate
- organise training in the use of the Vision Alpha high-frequency oscillatory ventilator
- provide study materials and organise a 24-hour randomisation service
- respond to any questions from collaborators about the trial
- give collaborators regular information about the progress of the study
- monitor the collection of data, process and seek missing data
- assure data security and quality

- organise any interim and main analyses
- organise TSC, DMEC and collaborators meetings
- carry out the trial according to the Research Governance Framework and GCP.

Good Clinical Practice and research governance

The OSCAR trial did not fall under the EU Clinical Trials Directive (Directive 2001/20/EC) as it was not a medicinal product trial (Clinical Trial of an Investigational Medicinal Product). It was therefore not required by law to work to International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP although we worked to the principles outlined in ICH GCP, as well as following the Medical Research Council's GCP guidelines and the Department of Health's Research Governance Framework.

Health economics methods

The health economics methods are given in *Chapter 5*.

Chapter 4 Results

The OSCAR trial was generally complex, used different sites for different periods of the study, used a combination of unit- and study-owned ventilators, and recruited patients with a condition which is known to vary in incidence over the year. A figure summarising active sites and recruitment rates month-by-month in the study is shown in *Figure 5*, with periods of peak H1N1 influenza infection incidence marked. The overall recruitment/retention is listed in *Table 13*.

CONSORT flow chart

Summary of CONSORT flow chart

Figure 6 illustrates the CONSORT diagram[78] of the OSCAR trial.

In brief:

- Two thousand seven hundred and sixty-nine patients were screened for the OSCAR trial.
- Of these, 1974 (71.4% of those screened) did not meet the inclusion criteria or met the inclusion criteria and were excluded for another reason.
- The total number randomised was 795 (28.7% of those screened).
- Of these, one patient remained in ICU and six patients were in hospital when the database was closed for the analysis for this report (14 October 2012).
- Of the patients randomised, three withdrew from follow-up (one who had received HFOV and two who had received conventional ventilation). The withdrawal rate was 0.3% of those randomised (the anticipated withdrawal rate used for the sample size calculation was 3%).
- The number of patients who did not receive the randomised intervention was very similar between the two intervention groups.
- Follow-up data have been collected on 215 patients (64% of those approached for follow-up) at 6 months and on 179 patients (60% of those approached for follow-up) at 12 months (as of database closure on 14 October 2012). Follow-up of the remaining patients continues but the results will not be included in this report.
- All randomised patients had the primary outcome data recorded.

Patient flow in the trial

Of the 795 patients randomised, at database closure (14 October 2012) there was one patient in ICU [trial number (TNO) = 22035] and there were six patients who were in hospital and had not been discharged (TNO = 7043, 8005, 25030, 27021, 27054, 27037).

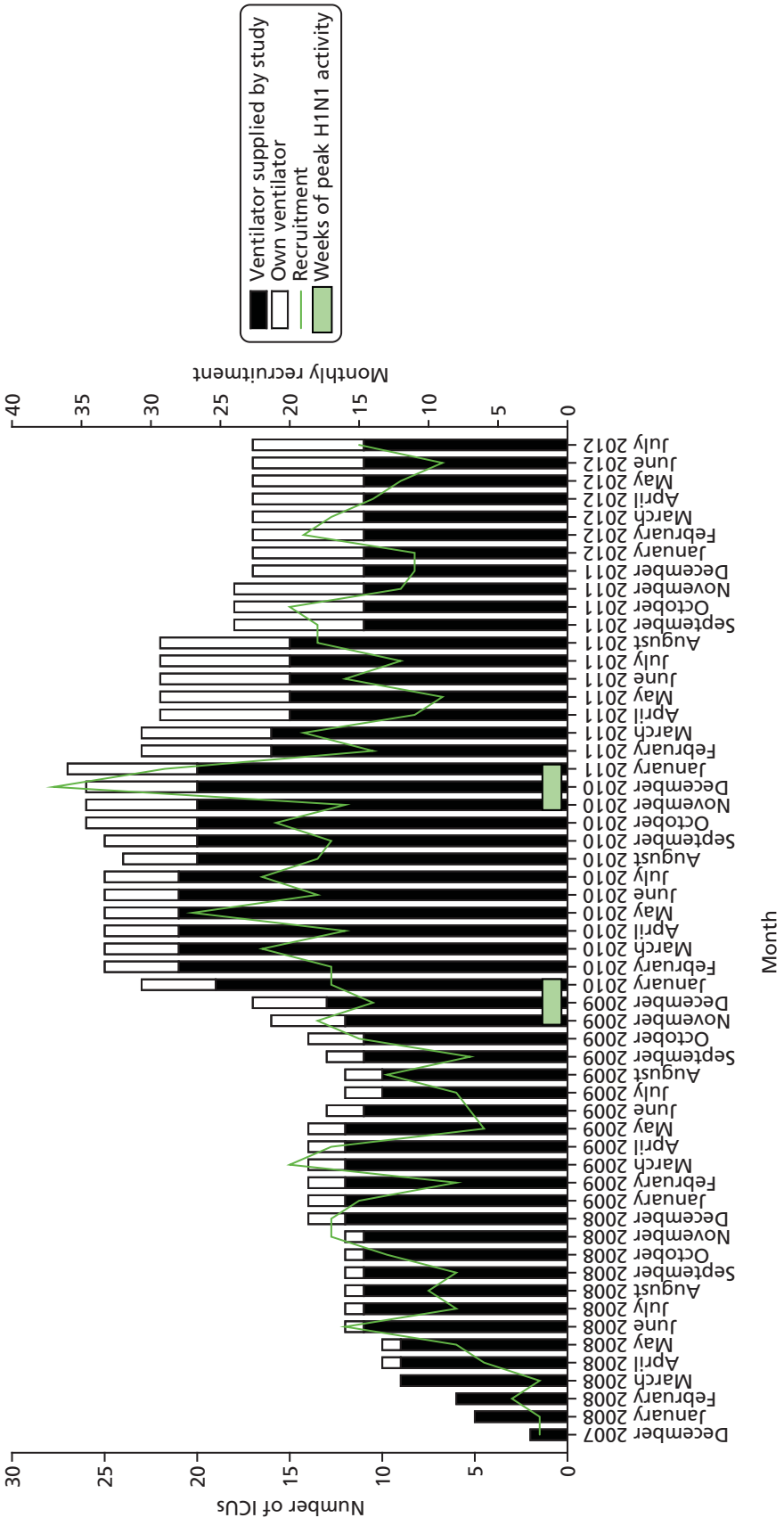


FIGURE 5 Recruitment summary for the study.

TABLE 13 Recruitment of patients into the OSCAR Trial

Stage	Category	Total
From screening to pre randomisation	All patients approached (on the not in the trial and those randomised)	2769
	Excluded patients: not in the trial	1974
Pre randomisation	Patients with pre-randomisation baseline data (form)	795
Randomised	Patients satisfying the entry inclusion criteria – randomised	795
	Patients satisfying the entry inclusion criteria – not randomised	0
	Patients randomised but ineligible	0
Died	From randomisation to first discharge ICU	342 (43.1%)
	30 days post randomisation	329 (41.4%)
	From randomisation to hospital discharge	388 (48.8%)
	6 months follow-up	395 (49.7%)
	12 months follow-up	405 (50.9%)
Survivors (in trial)	From randomisation to first discharge ICU	452 (56.9%)
	30 days post randomisation	466 (58.6%)
	From randomisation to hospital discharge	400 (50.3%)
	6 months follow-up	400 (50.3%)
	12 months follow-up	390 (49.1%)
Withdrawals	In ICU (immediately post randomisation to ICU discharge)	0 (0.0%)
	From 6 months follow-up	1 (0.1%)
	From 12 months follow-up	3 (0.4%)
Follow-up	Follow-up data at 6 months	215 (27.0%)
	Follow-up data at 12 months	179 (22.5%)
Non-responders (follow-up)	Up to 6 months follow-up	123 (15.5%)
	6–12 months follow-up	118 (14.8%)

% is based on randomised patients within treatment group.

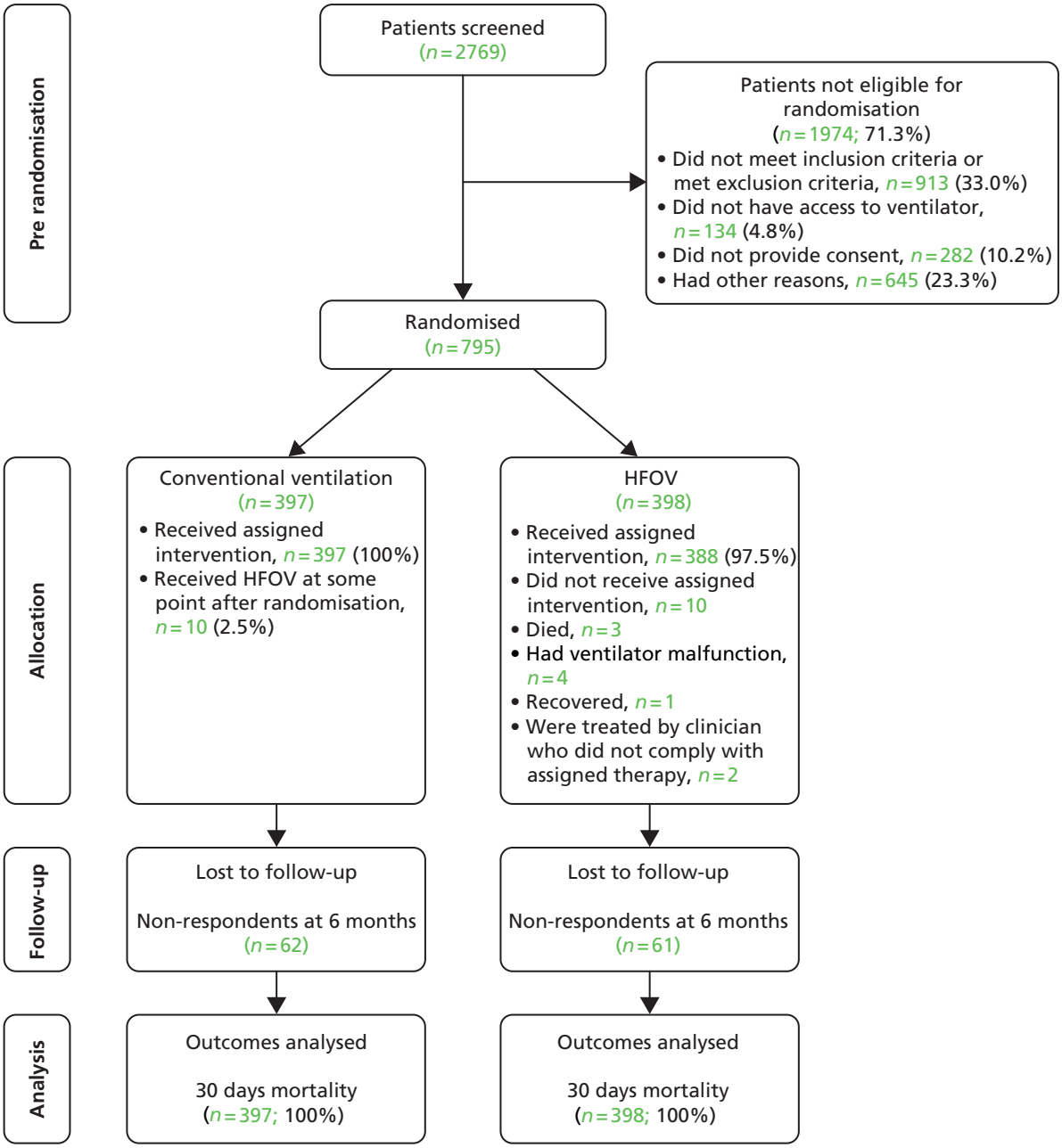


FIGURE 6 The CONSORT flow chart for the OSCAR trial. 'Not meeting all inclusion criteria' are reasons D + E in *Table 12*; 'meeting all inclusion criteria but ventilator not available' are reasons A + B + C in *Table 12*; 'meeting all the inclusion criteria but also met one of more of the exclusion criteria' are reasons F + G + H in *Table 12* and 'meeting all the inclusion criteria but excluded due to the other reasons' are reasons I to Z in *Table 12*.

Withdrawals

There were three patients who withdrew during the trial from follow-up (as in *Tables 14* and *15*) as follows:

- One patient (TNO = 8011: allocated conventional ventilation) withdrew in ICU from all follow-up (both 6 and 12 months).
- Two patients withdrew after 6 months follow-up from any further follow-up (TNO = 5022 allocated conventional ventilation; TNO = 6002 allocated HFOV).

All three patients provided data from randomisation to hospital discharge.

Responders at follow-up

The responders are detailed in *Table 16*.

TABLE 14 Withdrawals (throughout the trial)

Time period	Conventional ventilation	HFOV	Total
In ICU (immediately post randomisation to ICU discharge)	0 (0.0%)	0 (0.0%)	0
From 6-month follow-up	1 (0.3%)	0 (0.0%)	1
From 6- and 12-month follow-up	1 (0.3%)	1 (0.3%)	2

% is based on randomised patients within treatment group.

TABLE 15 Withdrawal details (in ICU)

Time period	Initiator of withdrawal	Conventional ventilation ($n = 397$)	HFOV ($n = 398$)	Total
Patients allocated treatment withdrawn	Patient	0 (0.0%)	0 (0.0%)	0
	Consultee	0 (0.0%)	0 (0.0%)	0
Permission withdrawn to allow trial to use ICU data	Patient	0 (0.0%)	0 (0.0%)	0
	Consultee	0 (0.0%)	0 (0.0%)	0
Permission withdrawn to allow follow-up (by questionnaires)	Patient	1 (0.3%)	0 (0.0%)	0
	Consultee	0 (0.0%)	0 (0.0%)	0

% is based on randomised patients within treatment group.

TABLE 16 Non-responders (during follow-up)

Non-responders	Conventional ventilation	HFOV	Total
Up to 6 months follow-up	62 (15.6%)	61 (15.3%)	123
Up to 12 months follow-up	62 (15.6%)	56 (14.1%)	118

% is based on randomised patients within treatment group.

Protocol deviations

There were, in total, 84 deviations from the protocol.

Eleven patients (2.8% of those randomised to conventional ventilation) received HFOV. Nine patients (2.3% of those randomised to HFOV) did not receive HFOV. The breakdown of these nine patients is illustrated in *Table 17*. There were 64 patients (16.1%) who were randomised to HFOV but had some problem with the ventilator during weaning or received < 12 hours of HFOV that was required (see *Table 17* for details).

TABLE 17 Protocol deviations

Category	Reasons	Conventional ventilation	HFOV	Total
Randomised to HFOV but did not receive it	Patient recovered before HFOV used	N/A	1 (0.3%)	1
	Patient died before HFOV used	N/A	2 (0.5%)	2
	Transferred out of unit before treatment	N/A	0 (0.0%)	0
	Oscillator being used for non-trial patient	N/A	0 (0.0%)	0
	Oscillator being used for another trial patient	N/A	0 (0.0%)	0
	Failure to recruit lung	N/A	0 (0.0%)	0
	Failure attributable to haemodynamic compromise	N/A	0 (0.0%)	0
	Clinician's instruction not to use	N/A	2 (0.5%)	2
	Oscillator technical failure	N/A	4 (1.0%)	4
	Others	N/A	0 (0.0%)	0
Randomised to HFOV but received < 12 hours of HFOV	–	N/A	33 (8.3%)	33
Problems with ventilator when HFOV weaning	–	N/A	16 (4.0%)	16
Other reasons	–	N/A	15 (3.8%)	15
Randomised to conventional ventilation but received HFOV	–	11 (2.8%)	–	11
Total	–	11	73	84

N/A, not applicable.
% is based on randomised patients within treatment group.

Serious adverse events

There are four SAEs recorded for four patients in the trial. All of these were in ICU while on HFOV. All of these events were thought to be related to the trial treatment and they were life-threatening. Details are in *Table 18*.

Serious adverse event details are listed as reported to the trial office in *Table 19*.

Not in trial patients

From *Table 20*, of the 1974 patients not taking parting in the trial:

- University College Hospital had the highest proportion of patients who were not randomised into the study ($n = 307$; 15.6%).
- Queen Margaret Hospital and York Hospital had the lowest proportion of patients who were not randomised into the study (each had $n = 6$; 0.3%).
- The single most common reason for not including patients into the study was 'consultant predicts patient will need < 48 hours artificial ventilation' ($n = 195$; 9.9%).
- The single least common reason for not including patients into the study was 'another non-trial patient is on the Vision Alpha' ($n = 2$; 0.1%).
- The 'others' category made up for 32.7% ($n = 645$) of the patients who were not included into the study.

TABLE 18 Serious adverse events

Location	Category	SAE subgroup	Conventional ventilation	HFOV	Total
In ICU	SAE details	Unexpected for the treatments offered	0 (0.0%)	3 (0.8%)	3
		Related directly to the treatments offered	0 (0.0%)	4 (1.0%)	4
		Unexpected and related to the treatments offered	0 (0.0%)	3 (0.8%)	3
	SAEs	Patient died	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event was life-threatening	0 (0.0%)	4 (1.0%)	4
		Event involved prolonged hospitalisation	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved persistent or significant disability/incapacity	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Others	0 (0.0%)	2 (0.5%)	0 (0.0%)
	SAE was caused by OSCAR trial participation	Yes	0 (0.0%)	4 (1.0%)	4
		No	0 (0.0%)	0 (0.0%)	0 (0.0%)
From ICU to hospital discharge	SAE details	Unexpected for the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Related directly to the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Unexpected and related to the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)

continued

TABLE 18 Serious adverse events (*continued*)

Location	Category	SAE subgroup	Conventional ventilation	HFOV	Total
	SAEs	Patient died	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event was life-threatening	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved prolonged hospitalisation	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved persistent or significant disability/incapacity	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Others	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SAE was caused by OSCAR trial participation	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
		No	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hospital discharge to 6 months	SAE details	Unexpected for the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Related directly to the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Unexpected and related to the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SAEs	Patient died	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event was life-threatening	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved prolonged hospitalisation	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved persistent or significant disability/incapacity	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Others	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SAE was caused by OSCAR trial participation	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
		No	0 (0.0%)	0 (0.0%)	0 (0.0%)
6 to 12 months	SAE details	Unexpected for the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Related directly to the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Unexpected and related to the treatments offered	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SAEs	Patient died	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event was life-threatening	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved prolonged hospitalisation	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Event involved persistent or significant disability/incapacity	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Others	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SAE was caused by OSCAR trial participation	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
		No	0 (0.0%)	0 (0.0%)	0 (0.0%)

% is based on randomised patients within treatment group.

TABLE 19 Serious adverse event details as reported to the trial office. Sexes and dates have been removed to preserve anonymity

Reporting heading	Data supplied
Patient	***ID = 2002***
Centre	Derriford Hospital
Age	36 years
Sex	[*Sex removed*]
Event details	Difficulty in reintubating patient at time of ETT change owing to oropharyngeal swelling
Event caused by trial?	Patient was grade 1 intubation grade at intubation initially. At time of ETT change, 36 hours later the view was significantly reduced by oropharyngeal oedema
Patient	***ID = 7036***
Centre	University College Hospital
Age	63 years
Sex	[*Sex removed*]
Event details	Nurse deviated from protocol by progressively increasing mean airway pressure despite acceptable oxygenation, pressure up 28 cmH_2O to 38 cmH_2O. The higher pressure impaired the patient's right ventricle
Other event details	Atrial fibrillation was associated with loss of blood pressure requiring cardiopulmonary resuscitation at [*date/time removed*]
Event caused by trial?	Raised intrathoracic pressure impaired right ventricular function leading to cardiovascular collapse – this occurred as a deviation from protocol
Patient	***ID = 18004***
Centre	Ipswich Hospital
Age	38 years
Sex	[*Sex removed*]
Event details	PEA cardiac arrest – drop in blood pressure and heart rate leading to loss of cardiac output. HFOV stopped, CPR commenced. CXR no pneumothorax. Oscillation restarted
Other event details	Second arrest at [date/time removed]. Again PEA arrest. Shocked – resuscitated. Decision made by resident doctor to discontinue oscillation. CXR no pneumothorax
Event caused by trial?	Probable combination of high acidosis from ineffective CVVHDF (haemofilter clotting off) and high $PaCO_2$ since being on oscillation despite 'accelerated' changes
Patient	***ID = 24015***
Centre	Royal Blackburn Hospital
Age	47 years
Sex	[*Sex removed*]
Event details	Patient on HFOV, arterial blood gas pH 6.8 $PaCO_2$ off the measurable scale of blood gas machine. O_2 4 kPa. Periarrest. Life-threatening? Bronchospasm? ETT problem
Event caused by trial?	Patient was randomised to HFOV group of trial. The above problem only occurred post randomisation once the patient was on HFOV

CPR, cardiopulmonary resuscitation; CVVDHF, continuous venovenous haemodiafiltration; CXR, chest X-ray; ETT, endotracheal tube; ID, identifier; PEA, pulseless electrical activity.

TABLE 20 Patients who were not randomised[a]

Centre	Reasons for patients not in the trial								Total (within centre)
	A	B	C	D	E	F	G	H	
John Radcliffe, Oxford	2 (2.2%)	0 (0.0%)	0 (0.0%)	7 (7.7%)	25 (27.5%)	0 (0.0%)	6 (6.6%)	0 (0.0%)	91
Derriford Hospital, Plymouth	13 (9.2%)	0 (0.0%)	0 (0.0%)	9 (6.4%)	2 (1.4%)	0 (0.0%)	10 (7.1%)	0 (0.0%)	141
Aberdeen Royal Infirmary	1 (1.3%)	1 (1.3%)	0 (0.0%)	7 (9.0%)	6 (7.7%)	8 (10.3%)	0 (0.0%)	0 (0.0%)	78
Medway Maritime Hospital	6 (4.1%)	0 (0.0%)	1 (0.7%)	2 (1.4%)	18 (12.2%)	12 (8.2%)	11 (7.5%)	5 (3.4%)	147
Selly Oak/Queen Elizabeth, Birmingham	13 (12.4%)	0 (0.0%)	5 (4.8%)	4 (3.8%)	5 (4.8%)	4 (3.8%)	26 (24.8%)	14 (13.3%)	105
Royal Sussex County Hospital	5 (2.9%)	0 (0.0%)	3 (1.7%)	8 (4.6%)	7 (4.0%)	3 (1.7%)	12 (6.9%)	1 (0.6%)	175
University College Hospital	15 (4.9%)	0 (0.0%)	0 (0.0%)	26 (8.5%)	8 (2.6%)	4 (1.3%)	28 (9.1%)	37 (12.1%)	307
University Hospital of Wales	9 (7.9%)	0 (0.0%)	0 (0.0%)	5 (4.4%)	11 (9.7%)	0 (0.0%)	8 (7.0%)	0 (0.0%)	114
Royal United Hospital	3 (6.8%)	0 (0.0%)	3 (6.8%)	4 (9.1%)	1 (2.3%)	0 (0.0%)	6 (13.6%)	0 (0.0%)	44
Manchester Royal Infirmary	16 (9.6%)	0 (0.0%)	0 (0.0%)	4 (2.4%)	20 (12.0%)	1 (0.6%)	28 (16.8%)	1 (0.6%)	167
Ysbyty Maelor Hospital	5 (5.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)	10 (10.0%)	6 (6.0%)	7 (7.0%)	0 (0.0%)	100
Queen Elizabeth Hospital, Gateshead	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9
Royal Cornwall Hospital	5 (7.4%)	0 (0.0%)	0 (0.0%)	2 (2.9%)	8 (11.8%)	0 (0.0%)	5 (7.4%)	0 (0.0%)	68
Stirling Royal Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	20
James Paget University Hospital	1 (1.9%)	0 (0.0%)	0 (0.0%)	4 (7.6%)	10 (18.9%)	0 (0.0%)	6 (11.3%)	3 (5.7%)	53
Queen Alexandra Hospital	9 (14.5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	8 (12.9%)	0 (0.0%)	8 (12.9%)	1 (1.6%)	62
Wythenshawe Hospital	4 (5.3%)	1 (1.3%)	0 (0.0%)	10 (13.3%)	16 (21.3%)	0 (0.0%)	5 (6.7%)	0 (0.0%)	75

Centre	Reasons for patients not in the trial										Total (within centre)
	A	B	C	D	E	F	G	H			
University Hospital, North Straffordshire	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.4%)	0 (0.0%)	2 (8.7%)	12 (52.2%)	0 (0.0%)			23
Ipswich Hospital	2 (20.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)			10
Queen Margaret Hospital	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			6
Southampton General Hospital	2 (4.9%)	0 (0.0%)	0 (0.0%)	2 (4.9%)	8 (19.5%)	0 (0.0%)	2 (4.9%)	0 (0.0%)			41
York Hospital	1 (16.7%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			6
Victoria Hospital Blackpool	4 (5.1%)	0 (0.0%)	1 (1.3%)	2 (2.6%)	21 (26.9%)	0 (0.0%)	7 (9.0%)	0 (0.0%)			78
Newcastle upon Tyne Hospital	1 (2.3%)	0 (0.0%)	0 (0.0%)	2 (4.6%)	6 (13.6%)	1 (2.3%)	2 (4.6%)	0 (0.0%)			44
James Cook University Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			10
Total (of each reason)	119	2	13	107	195	41	190	62			1974
	I	***J***	***K***	***L***	***M***	***N***	***O***	***P***	***Q***	***Z***	
John Radcliffe, Oxford	0 (0.0%)	0 (0.0%)	2 (2.2%)	0 (0.0%)	15 (16.5%)	2 (2.2%)	1 (1.1%)	0 (0.0%)	7 (7.7%)	24 (26.4%)	***91***
Derriford Hospital, Plymouth	0 (0.0%)	1 (0.7%)	7 (5.0%)	0 (0.0%)	3 (2.1%)	5 (3.6%)	5 (3.6%)	1 (0.7%)	33 (23.4%)	52 (36.9%)	***141***
Aberdeen Royal Infirmary	20 (25.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (14.1%)	6 (7.7%)	2 (2.6%)	0 (0.0%)	5 (6.4%)	11 (14.1%)	***78***
Medway Maritime Hospital	0 (0.0%)	2 (1.4%)	2 (1.4%)	0 (0.0%)	23 (15.7%)	2 (1.4%)	13 (8.8%	1 (0.7%)	21 (14.3%)	28 (19.1%)	***147***
Selly Oak/Queen Elizabeth, Birmingham	0 (0.0%)	2 (1.9%)	5 (4.8%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	1 (1.0%)	2 (1.9%)	0 (0.0%)	22 (21.0%)	***105***
Royal Sussex County Hospital	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	19 (10.9%)	18 (10.3%)	15 (8.6%)	0 (0.0%)	21 (12.0%)	61 (34.9%)	***175***
University College Hospital	0 (0.0%)	0 (0.0%)	40 (13.0%)	0 (0.0%)	6 (2.0%)	6 (2.0%)	6 (2.0%)	0 (0.0%)	1 (0.3%)	130 (42.4%)	***307***
University Hospital of Wales	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.8%)	11 (9.7%)	10 (8.8%)	2 (1.8%)	3 (2.6%)	8 (7.0%)	44 (38.6%)	***114***
Royal United Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (11.4%)	3 (6.8%)	3 (6.8%)	1 (2.3%)	7 (15.9%)	8 (18.2%)	***44***

continued

TABLE 20 Patients who were not randomised[a] (*continued*)

Centre	Reasons for patients not in the trial										Total (within centre)
	A	B	C	D	E	F	G	H			
	I	*J*	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	*Z*	
Manchester Royal Infirmary	0 (0.0%)	0 (0.0%)	2 (1.2%)	3 (1.8%)	37 (22.2%)	3 (1.8%)	6 (3.6%)	0 (0.0%)	21 (15.6%)	25 (15.0%)	***167***
Ysbyty Maelor Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (12.0%)	1 (1.0%)	11 (11.0%)	0 (0.0%)	3 (3.0%)	43 (43.0%)	***100***
Queen Elizabeth Hospital, Gateshead	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	1 (11.1%)	5 (55.6%)	***9***
Royal Cornwall Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (11.8%)	2 (2.9%)	7 (10.3%)	0 (0.0%)	2 (2.9%)	29 (42.7%)	***68***
Stirling Royal Hospital	9 (45.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (45.0%)	***20***
James Paget University Hospital	0 (0.0%)	0 (0.0%)	2 (3.8%)	0 (0.0%)	5 (9.4%)	0 (0.0%)	2 (3.8%)	0 (0.0%)	2 (3.8%)	18 (34.0%)	***53***
Queen Alexandra Hospital	0 (0.0%)	0 (0.0%)	2 (3.2%)	0 (0.0%)	3 (4.8%)	1 (1.6%)	1 (1.6%)	0 (0.0%)	2 (3.2%)	26 (41.9%)	***62***
Wythenshawe Hospital	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	10 (13.3%)	4 (5.3%)	2 (2.7%)	0 (0.0%)	3 (4.0%)	19 (25.3%)	***75***
University Hospital, North Straffordshire	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.7%)	1 (4.4%)	1 (4.4%)	0 (0.0%)	1 (4.4%)	3 (13.0%)	***23***
Ipswich Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (50.0%)	***10***
Queen Margaret Hospital	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (66.7%)	***6***
Southampton General Hospital	0 (0.0%)	0 (0.0%)	2 (4.9%)	0 (0.0%)	7 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.9%)	16 (39.0%)	***41***
York Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	***6***
Victoria Hospital Blackpool	0 (0.0%)	1 (1.3%)	7 (9.0%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (1.3%)	31 (39.7%)	***78***
Newcastle upon Tyne Hospital	0 (0.0%)	0 (0.0%)	4 (9.1%)	0 (0.0%)	3 (6.8%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	24 (54.6%)	***44***
James Cook University Hospital	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	7 (70.0%)	***10***
TOTAL (of each reason)	30	7	78	5	184	64	82	8	142	645	***1974***

a These patients meet the initial inclusion criteria of: (i) age ≥ 16 years; (ii) weight ≥ 35 kg; (iii) receiving artificial ventilation via an endotracheal or tracheostomy tube; (iv) has ARDS as defined by the trial protocol.

Patients who were not randomised to the trial

From *Table 21* and *22*:

- Patients who are not in the trial are statistically significantly ($p < 0.0001$; based on a two-sample *t*-test) older than those randomised into the trial.
- The proportion within each sex group was found to be similar across for those that were randomised and not randomised ($p = 0.2971$; based on chi-squared test).
- Almost two-thirds of the patients approached for the trial were male.

Pre-randomisation assessments

All potential patients who were eligible for randomisation had pre-randomisation assessments completed (i.e. $n = 795$).

From *Table 23*, there is indication that the assessments are similar across the two intervention groups.

TABLE 21 Summary of age (in years) of patients who were in the trial/not in the trial

Category	Mean	*n*	Median	SD	Minimum	Maximum	Missing
Randomised	55.4	795	57.2	16.8	16.2	90.1	0
Not in the trial	58.6	1720	61.1	16.9	16.1	95.1	254
Total	57.6	2515	59.9	16.9	16.1	95.1	254

Based on the two-sample *t*-test [comparison of age (randomised vs. not in trial)]: $p < 0.0001$ [diff: 3.2 (standard error = 0.72)].

TABLE 22 Sex of patients who were in the trial/not in the trial

Sex	Randomised	Not in the trial	Total
Missing	0 (0.0%)	18 (0.9%)	18 (0.7%)
Male	495 (62.3%)	1176 (59.6%)	1671 (60.3%)
Female	300 (37.7%)	780 (39.5%)	1080 (39.0%)
Total	795	1974	2769

% are based on the columns.
Chi-squared test statistic [comparison of sex (randomised vs. non-randomised)]: $p = 0.2971$.

TABLE 23 Pre randomisation clinical variables

						Arterial blood gas				
Ventilation	Measure	Exhaled minute volume (l/minute)	Total respiratory rate (breaths/minute)	PEEP (cmH_2O)	Plateau pressure (cmH_2O)	PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	Hydrogen ion concentration (nmol)	Associated FiO_2
Conventional ventilation	Mean	10.2	21.1	11.3	22.3	10.4	6.9	7.3	49.4	0.7
	n	396	397	391	381	397	397	392	5	397
	SD	3.5	8.2	3.3	9.1	2.5	1.8	0.1	6.5	0.2
	Median	9.9	20.0	10.0	24.0	10.0	6.7	7.3	49	0.7
	Minimum	0.3	8.0	5.0	0.0	5.0	3.5	7.0	43	0.4
	Maximum	33.4	70.0	36.0	48.0	24.2	16.3	7.5	57	1.0
	Missing	1	0	6	16	0	0	5	392	0
HFOV	Mean	10.4	20.8	11.4	22.1	10.3	6.9	7.3	47.8	0.7
	n	398	398	391	386	398	398	390	8	398
	SD	3.3	7.9	3.5	9.1	2.3	1.9	0.1	11.0	0.2
	Median	10.1	20.0	10.0	23.0	10.0	6.6	7.3	47	0.7
	Minimum	3.0	0.0	5.0	0.0	5.9	3.6	6.9	31	0.4
	Maximum	30.8	69.0	33.0	43.0	23.6	19.6	7.7	67	1.0
	Missing	0	0	7	12	0	0	8	390	0
Total	Mean	10.3	21.0	11.4	22.2	10.4	6.9	7.3	48.4	0.7
	n	794	795	782	767	795	795	782	13	795
	SD	3.4	8.0	3.4	9.1	2.4	1.9	0.1	9.2	0.2
	Median	10.0	20.0	10.0	23.0	10.0	6.7	7.3	49	0.7
	Minimum	0.3	0.0	5.0	0.0	5.0	3.5	6.9	31	0.4
	Maximum	33.4	70.0	36.0	48.0	24.2	19.6	7.7	67	1.0
	Missing	1	0	13	28	0	0	13	782	0

From *Table 24*:

Organ support:

- Almost all patients (99.6%) randomised received advanced respiratory support, as would be expected from the inclusion criteria. The proportion of patient receiving advanced respiratory support was similar across the two interventions.
- Most of the patients had basic cardiovascular support (as opposed to advanced cardiovascular support) and the proportion getting this support was similar across the intervention groups.
- Most of the patients required gastrointestinal support, with very few patients requiring renal, dermatological or liver support.

TABLE 24 Number of patients (and %) for each support/organ monitoring categories pre randomisation

Monitoring category		Response	Conventional ventilation	HFOV	Total
Organ support	Advanced respiratory support	No	2 (0.5%)	1 (0.3%)	3 (0.4%)
		Yes	395 (99.5%)	397 (99.7%)	792 (99.6%)
	Basic respiratory support	No	334 (84.1%)	341 (85.7%)	675 (84.9%)
		Yes	63 (15.9%)	57 (14.3%)	120 (15.1%)
	Advanced cardiovascular support	No	211 (53.1%)	231 (58.0%)	442 (55.6%)
		Yes	186 (46.9%)	167 (42.0%)	353 (44.4%)
	Basic cardiovascular support	No	149 (37.5%)	135 (33.9%)	284 (35.7%)
		Yes	248 (62.5%)	263 (66.1%)	511 (64.3%)
	Renal support	No	326 (82.1%)	311 (78.1%)	637 (80.1%)
		Yes	71 (17.9%)	87 (21.9%)	158 (19.9%)
	Gastrointestinal support	No	88 (22.2%)	90 (22.6%)	178 (22.4%)
		Yes	309 (77.8%)	308 (77.4%)	617 (77.6%)
	Dermatological support	No	384 (96.7%)	380 (95.5%)	764 (96.1%)
		Yes	13 (3.3%)	18 (4.5%)	31 (3.9%)
	Liver support	No	392 (98.7%)	397 (99.7%)	789 (99.2%)
		Yes	5 (1.3%)	1 (0.3%)	6 (0.8%)
Antimicrobial use	Antimicrobial drug received	No	12 (3.0%)	16 (4.0%)	28 (3.5%)
		Yes	385 (97.0%)	382 (96.0%)	767 (96.5%)
	Antimicrobial for pulmonary infection	No	62 (15.6%)	63 (15.8%)	125 (15.7%)
		Yes	323 (81.4%)	319 (80.2%)	642 (80.8%)
		Missing	12 (3.0%)	16 (4.0%)	28 (3.5%)
	Antimicrobial intravenous	No	3 (0.8%)	2 (0.5%)	5 (0.6%)
		Yes	382 (96.2%)	380 (95.5%)	762 (95.9%)
		Missing	12 (3.0%)	16 (4.0%)	28 (3.5%)

continued

TABLE 24 Number of patients (and %) for each support/organ monitoring categories pre randomisation (*continued*)

Monitoring category		Response	Conventional ventilation	HFOV	Total
Sedation use	Sedation received	No	7 (1.8%)	8 (2.0%)	15 (1.9%)
		Yes	390 (98.2%)	390 (98.0%)	780 (98.1%)
	Sedation intravenous	No	352 (88.7%)	339 (85.2%)	691 (86.9%)
		Yes	38 (9.6%)	51 (12.8%)	89 (11.2%)
		Missing	7 (1.8%)	8 (2.0%)	15 (1.9%)
	Sedation infusion	No	2 (0.5%)	4 (1.0%)	6 (0.8%)
		Yes	388 (97.7%)	386 (97.0%)	774 (97.4%)
		Missing	7 (1.8%)	8 (2.0%)	15 (1.9%)
	Sedation, more than one class of drug used	No	47 (11.8%)	54 (13.6%)	101 (12.7%)
		Yes	343 (86.4%)	336 (84.4%)	679 (85.4%)
		Missing	7 (1.8%)	8 (2.0%)	15 (1.9%)
	Sedation, more than two classes of drugs used	No	339 (85.4%)	342 (85.9%)	681 (85.7%)
		Yes	51 (12.9%)	48 (12.1%)	99 (12.5%)
		Missing	7 (1.8%)	8 (2.0%)	15 (1.9%)
	Sedation, more than three classes of drugs used	No	387 (97.5%)	386 (97.0%)	773 (97.2%)
		Yes	3 (0.8%)	4 (1.0%)	7 (0.9%)
		Missing	7 (1.8%)	8 (2.0%)	15 (1.9%)
Muscle relaxant drug use	Muscle relaxants received	No	223 (56.2%)	223 (56.0%)	446 (56.1%)
		Yes	174 (43.8%)	175 (44.0%)	349 (43.9%)
	Muscle relaxants primarily by intravenous bolus	No	89 (22.4%)	80 (20.1%)	169 (21.3%)
		Yes	85 (21.4%)	95 (23.9%)	180 (22.6%)
		Missing	223 (56.2%)	223 (56.0%)	446 (56.1%)
	Muscle relaxants primarily by intravenous infusion	No	72 (18.1%)	69 (17.3%)	141 (17.7%)
		Yes	102 (25.7%)	106 (26.6%)	208 (26.2%)
		Missing	223 (56.2%)	223 (56.0%)	446 (56.1%)
Others	Ventilated in the prone position	No	378 (95.2%)	378 (95.0%)	756 (95.1%)
		Yes	19 (4.8%)	20 (5.0%)	39 (4.9%)
	Inhaled nitric oxide treatment	No	389 (98.0%)	386 (97.0%)	775 (97.5%)
		Yes	8 (2.0%)	12 (3.0%)	20 (2.5%)

Antimicrobial use:

- Almost all patients received intravenous antimicrobial drugs for pulmonary infection. The proportions receiving these drugs were similar across the two interventions.

Sedation use:

- Almost all patients received sedation by infusion. Where sedation was given, a single sedative (as opposed to multiple drugs) was used in the majority of the patients. Again the proportions receiving sedation were similar across the interventions.

Muscle relaxants:

- These were used on a small proportion of patients and the proportions were similar across the interventions.

Prone position ventilated and nitric oxide received:

- Nearly all patients were ventilated in the supine position and very few received inhaled nitric oxide. This again was similar across the interventions.

Time to randomisation

- The times from hospital to ICU admission, and ICU admission to randomisation are given in *Table 25*.

TABLE 25 Time to randomisation and time to ICU

Interval	Measure	Conventional ventilation	HFOV	Total
Time from hospital admission to ICU admission (days)	Mean	3.8	5.0	4.4
	n	397	398	795
	SD	7.5	19.3	14.6
	Median	1	1	1
	Minimum	0	0	0
	Maximum	80	334	334
Time from hospital admission to randomisation (days)	Mean	8.3	7.9	8.1
	n	397	398	795
	SD	37.3	19.8	29.8
	Median	4	4	4
	Minimum	0	0	0
	Maximum	732	340	732
Time from ICU to randomisation (days)	Mean	4.5	2.9	3.7
	n	397	398	795
	SD	36.7	2.6	26.0
	Median	2	2	2
	Minimum	0	0	0
	Maximum	732	22	732

ICU date is necessarily prior to randomisation date.

Randomisation

Table 26 illustrates the randomised patients by each centre. There is evidence in this table that the proportion of patients recruited on each intervention is approximately the same within a centre.

Appendix 6 shows the allocation of patients within each of the randomisation strata (age and P : F ratio) within each centre. Again, there is an indication that the allocation of the proportion of patients within a centre is similar within a treatment group.

TABLE 26 Randomised patients by centre and ventilation treatment

Centre	Conventional ventilation	HFOV	Total
John Radcliffe, Oxford	8 (53.3%)	7 (46.7%)	15
Derriford Hospital, Plymouth	22 (47.8%)	24 (52.2%)	46
Aberdeen Royal Infirmary	8 (53.3%)	7 (46.7%)	15
Medway Maritime Hospital	14 (51.9%)	13 (48.2%)	27
Selly Oak/Queen Elizabeth, Birmingham	50 (49.0%)	52 (51.0%)	102
Royal Sussex County Hospital	22 (47.8%)	24 (52.2%)	46
University College Hospital	33 (52.4%)	30 (47.6%)	63
University Hospital of Wales	9 (56.3%)	7 (43.8%)	16
Royal United Hospital	11 (55.0%)	9 (45.0%)	20
Manchester Royal Infirmary	12 (50.0%)	12 (50.0%)	24
Ysbyty Maelor Hospital	17 (53.1%)	15 (46.9%)	32
Queen Elizabeth Hospital, Gateshead	7 (50.0%)	7 (50.0%)	14
Royal Cornwall Hospital	28 (50.0%)	28 (50.0%)	56
Stirling Royal Hospital	8 (42.1%)	11 (57.9%)	19
Manchester Royal Infirmary, Cardiac ICU	1 (100.0%)	0 (0.0%)	1
Leeds General Infirmary	14 (46.7%)	16 (53.3%)	30
James Paget University Hospital	12 (52.2%)	11 (47.8%)	23
Queen Alexandra Hospital	18 (48.7%)	19 (51.4%)	37
Royal Blackburn Hospital	13 (50.0%)	13 (50.0%)	26
Wythenshawe Hospital	7 (46.7%)	8 (53.3%)	15
University Hospital of North Staffordshire	7 (46.7%)	8 (53.3%)	15
Ipswich Hospital	1 (20.0%)	4 (80.0%)	5
Queen Margaret Hospital	5 (62.5%)	3 (37.5%)	8
Southampton General Hospital	8 (57.1%)	6 (42.9%)	14
St James's University Hospital	34 (50.0%)	34 (50.0%)	68
York Hospital	7 (53.8%)	6 (46.2%)	13
Victoria Hospital Blackpool	13 (46.4%)	15 (53.6%)	28
Southend Hospital	1 (33.3%)	2 (66.7%)	3
Newcastle upon Tyne Hospital	4 (50.0%)	4 (50.0%)	8
James Cook University Hospital	3 (50.0%)	3 (50.0%)	6
Total	397	398	795

% are based within each centre (row).

There were 31 patients who were randomised 'incorrectly' because their age or P : F ratio entered into the randomisation system did not match that recorded on the Case Report Form. There were eight patients who had their age group recorded as '> 55 years old', when in fact their date of birth indicated they were '< 55 years old'. There were 23 patients who had a P : F ratio recorded as '< 15 kPa', when their P : F ratio was '> 15 kPa'.

Tables 27–32 illustrate the demographic variables and those measured immediately post randomisation. In general, the variables presented in these tables are similar across the two treatment groups.

TABLE 27 Demographic details of randomised patients

Classifier	Conventional ventilation	HFOV	Total
Age group (years)			
≤ 55	174 (43.8%)	178 (44.7%)	352 (44.3%)
> 55	223 (56.2%)	220 (55.3%)	443 (55.7%)
Sex			
Male	239 (60.2%)	256 (64.3%)	495 (62.3%)
Female	158 (39.8%)	142 (35.7%)	300 (37.7%)
P : F ratio (kPa)			
≤ 15	234 (58.9%)	227 (57.0%)	461 (58.0%)
> 15	163 (41.1%)	171 (43.0%)	334 (42.0%)
Weight (kg)			
Mean	78.60	80.79	79.70
n	397	398	795
SD	20.9	21.7	21.4
Median	76.0	79.5	78.0
Minimum	37.0	35.0	35.0
Maximum	215.0	186.0	215.0
Patient's height or heel/crown measurement (m)			
Mean	1.7	1.7	1.7
n	386	383	769
SD	0.1	0.1	0.1
Median	1.7	1.7	1.7
Minimum	1.4	1.2	1.2
Maximum	2.0	2.0	2.0
Associated FiO_2			
Mean	0.7	0.7	0.7
n	397	398	795
SD	0.2	0.2	0.2
Median	0.7	0.7	0.7
Minimum	0.4	0.4	0.4
Maximum	1.0	1.0	1.0

TABLE 28 Causes of hypoxaemic respiratory failure (immediately post randomisation)

Cause	Conventional ventilation	HFOV	Total
Pulmonary	304 (76.6%)	302 (75.9%)	606 (76.2%)
Extrapulmonary	93 (23.4%)	96 (24.1%)	189 (23.8%)

TABLE 29 Initial ventilation data

Initiation of ventilation	Conventional ventilation	HFOV	Total
Ventilated before hospital admission	20 (5.0%)	13 (3.3%)	33 (4.2%)
Ventilated after hospital admission but prior to ICU admission	119 (30.0%)	118 (29.6%)	237 (29.8%)
First ventilated during ICU stay	257 (64.7%)	267 (67.1%)	524 (65.9%)
Where first ventilated not known	1 (0.3%)	0 (0.0%)	1 (0.1%)

First 24 hours in intensive care unit

TABLE 30 Admission to ICU

Surgical filters	Classifier	Conventional ventilation	HFOV	Total
Was the patient admitted to your ICU directly from the operating theatre/recovery area in your hospital?	No	347 (87.4%)	340 (85.4%)	687 (86.4%)
	Yes	50 (12.6%)	58 (14.6%)	108 (13.6%)
If 'yes',[a] was the surgery	Emergency?	21 (42.0%)	29 (50.0%)	50 (46.3%)
	Urgent?	17 (34.0%)	19 (32.8%)	26 (33.3%)
	Scheduled?	2 (4.0%)	3 (5.2%)	5 (4.6%)
	Elective?	10 (20.0%)	7 (12.1%)	17 (15.7%)

a The definitions used were those used by the National Confidential Enquiry into Peri-Operative Deaths (NCEPOD).[89]

TABLE 31 Past medical history

Status	Past medical history	Conventional ventilation	HFOV	Total
No past history	Yes	90 (22.7%)	74 (18.6%)	164 (20.6%)
	No	307 (77.3%)	324 (81.4%)	631 (79.4%)
Past history				
Biopsy-proven cirrhosis	Yes	6 (6.7%)	8 (10.8%)	14 (8.5%)
	No	84 (93.3%)	66 (89.2%)	150 (91.5%)
Portal hypertension	Yes	8 (8.9%)	11 (14.9%)	19 (11.6%)
	No	82 (91.1%)	63 (85.1%)	145 (88.4%)
Hepatic encephalopathy	Yes	7 (7.8%)	7 (9.5%)	14 (8.5%)
	No	83 (92.2%)	67 (90.5%)	150 (91.5%)
Very severe cardiovascular disease	Yes	6 (6.7%)	1 (1.4%)	7 (4.3%)
	No	84 (93.3%)	73 (98.7%)	157 (95.7%)
Severe respiratory disease	Yes	6 (6.7%)	7 (9.5%)	13 (7.9%)
	No	84 (93.3%)	67 (90.5%)	151 (92.1%)
Home ventilation	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	90 (100.0%)	74 (100.0%)	164(100.0%)
Chronic renal replacement	Yes	4 (4.4%)	2 (2.7%)	6 (3.7%)
	No	86 (95.6%)	72 (97.3%)	158 (96.3%)
AIDS	Yes	3 (3.3%)	5 (6.8%)	8 (4.9%)
	No	87 (96.7%)	69 (93.2%)	156 (95.1%)
Steroid treatment	Yes	15 (16.7%)	8 (10.8%)	23 (14.0%)
	No	75 (83.3%)	66 (89.2%)	141 (86.0%)
Radiotherapy	Yes	9 (10.0%)	7 (9.5%)	16 (9.8%)
	No	81 (90.0%)	67 (90.5%)	148 (90.2%)
Chemotherapy	Yes	39 (43.3%)	27 (36.5%)	66 (40.2%)
	No	51 (56.7%)	47 (63.5%)	98 (59.8%)
Metastatic disease	Yes	10 (11.1%)	4 (5.4%)	14 (8.5%)
	No	80 (88.9%)	70 (94.6%)	150 (91.5%)
Acute myelogenous/lymphocytic leukaemia or multiple myeloma	Yes	16 (17.8%)	8 (10.8%)	24 (14.6%)
	No	74 (82.2%)	66 (89.2%)	140 (85.4%)
Chronic myelogenous/lymphocytic leukaemia	Yes	4 (4.4%)	7 (9.5%)	11 (6.7%)
	No	86 (95.6%)	67 (90.5%)	153 (93.3%)
Lymphoma	Yes	10 (11.1%)	12 (16.2%)	22 (13.4%)
	No	80 (88.9%)	62 (83.8%)	142 (86.6%)
Congenital immunohumoral or cellular immune deficiency state	Yes	2 (2.2%)	4 (5.4%)	6 (3.7%)
	No	88 (97.8%)	70 (94.6%)	158 (96.3%)

AIDS, acquired immunodeficiency syndrome.

TABLE 32 APACHE II scores

Measure	Conventional ventilation	HFOV	Total
Mean	21.7	21.8	21.8
n	383	382	765
SD	6.1	6.0	6.1
Median	21.0	22.0	22.0

Daily data in intensive care unit

There are 792 patients with ICU data – of the 795 patients randomised, three patients died on the same day as the randomisation day and therefore have no ICU data. *Tables 33–37* provide details of the daily data collected by group.

TABLE 33 Daily data (support/organ monitoring)

Organ support	Measure	Conventional ventilation	HFOV	Total
Ventilation-free (days) up to 30 days post randomisation	Mean	2.3	2.6	2.5
	n	397	395	792
	SD	3.5	3.5	3.5
	Median	0	1	1
	Range	0–21	0–20	0–21
Advanced respiratory support-free days	Mean	3.1	3.8	3.8
	n	397	395	792
	SD	4.7	5.9	5.3
	Median	2	2	2
	Range	0–32	0–57	0–57
Days on advanced cardiovascular support	Mean	2.8	2.9	2.9
	n	397	395	792
	SD	5.6	4.5	5.1
	Median	1	1	1
	Range	0–75	0–35	0–75
Days on basic cardiovascular support	Mean	11.8	12.5	12.1
	n	397	395	792
	SD	10.7	11.5	11.1
	Median	10	10	10
	Range	0–73	0–85	0–85
Days on renal support	Mean	2.6	4.5	3.5
	n	397	395	792
	SD	5.1	7.7	6.6
	Median	0	0	0
	Range	0–34	0–52	0–52

TABLE 33 Daily data (support/organ monitoring) (*continued*)

Organ support	Measure	Conventional ventilation	HFOV	Total
Days on gastrointestinal support	Mean	16.0	17.4	16.7
	n	397	395	792
	SD	15.1	16.7	15.9
	Median	12	13	12
	Range	0–113	0–114	0–114
Days on dermatological support	Mean	1.0	0.9	1.0
	n	397	395	792
	SD	5.3	4.6	5.0
	Median	0	0	0
	Range	0–59	0–47	0–59
Days on liver support	Mean	0.04	0.03	0.03
	n	397	395	792
	SD	0.4	0.2	0.3
	Median	0	0	0
	Range	0–5	0–2	0–5

TABLE 34 Daily data (antimicrobial use)

Antimicrobial use	Measure	Conventional ventilation	HFOV	Total
Number of days free from antimicrobial use	Mean	4.9	5.9	5.4
	n	397	395	792
	SD	8.2	9.2	8.7
	Median	1	2	2
	Range	0–60	0–63	0–63
Number of days antimicrobial used	Mean	12.4	12.8	12.6
	n	397	395	792
	SD	10.3	12.0	11.2
	Median	10	10	10
	Range	0–68	0–111	0–111
Number of days antimicrobial used to treat pulmonary infection	Mean	9.8	9.9	9.8
	n	397	395	792
	SD	9.3	9.7	9.5
	Median	8	8	8
	Range	0–54	0–68	0–68
Number of days antimicrobial given intravenously	Mean	11.7	11.9	11.8
	n	397	395	792
	SD	9.6	10.7	10.1
	Median	9	10	10
	Range	0–60	0–86	0–86

TABLE 35 Daily data (sedative use)

Sedative use	Measure	Conventional ventilation	HFOV	Total
Number of days free from sedative received primarily for sedation	Mean	8.8	9.4	9.1
	n	397	395	792
	SD	12.6	14.6	13.6
	Median	5	4	4
	Range	0–108	0–97	0–108
Number of days sedative received primarily for sedation	Mean	8.5	9.4	8.9
	n	397	395	792
	SD	6.9	7.2	7.0
	Median	7	8	7
	Range	0–39	0–50	0–50
Number of days an intravenous bolus dose used	Mean	0.5	0.4	0.5
	n	397	395	792
	SD	2.1	1.4	1.8
	Median	0	0	0
	Range	0–30	0–13	0–30
Number of days sedative given by infusion	Mean	8.3	9.1	8.7
	n	397	395	792
	SD	6.8	7.0	6.9
	Median	7	8	7
	Range	0–39	0–50	0–50
Number of days patient on **more than one** class of sedative	Mean	6.6	7.3	7.0
	n	397	395	792
	SD	5.9	5.7	5.8
	Median	5	6	6
	Range	0–36	0–44	0–44
Number of days patient on **more than two** classes of sedative	Mean	1.4	1.4	1.4
	n	397	395	792
	SD	3.2	3.0	3.1
	Median	0	0	0
	Range	0–28	0–26	0–28
Number of days patient on **more than three** classes of sedative	Mean	0.1	0.2	0.2
	n	397	395	792
	SD	0.8	0.8	0.8
	Median	0	0	0
	Range	0–11	0–9	0–11

TABLE 36 Daily data (muscle relaxant use)

Muscle relaxant use	Measure	Conventional ventilation	HFOV	Total
Number of days patient received muscle relaxant drugs to aid artificial ventilation	Mean	2.1	2.5	2.3
	n	397	395	792
	SD	3.4	3.5	3.5
	Median	1	1	1
	Range	0–22	0–25	0–25
Number of days an intravenous bolus dose used	Mean	0.5	0.5	0.5
	n	397	395	792
	SD	1.0	0.9	1.0
	Median	0	0	0
	Range	0–6	0–5	0–6
Number of days an muscle relaxants given by infusion	Mean	1.7	2.0	1.9
	n	397	395	792
	SD	3.3	3.4	3.3
	Median	0	0	0
	Range	0–22	0–24	0–24

TABLE 37 Daily data (others)

Treatment	Measure	Conventional ventilation	HFOV	Total
Number of days patient ventilated prone	Mean	0.5	0.2	0.3
	n	397	395	792
	SD	1.3	0.7	1.1
	Median	0	0	0
	Range	0–12	0–8	0–12
Number of days patient received inhaled nitric oxide	Mean	0.4	0.2	0.3
	n	397	395	792
	SD	2.1	0.9	1.6
	Median	0	0	0
	Range	0–23	0–12	0–23

Table 38 details the statistical analysis in terms of model fitting.

Plots of daily percentage of patients on each type of support

The daily counts of number patients for all percentage plots are shown in *Table 39*.

TABLE 38 Statistical analysis of daily data in ICU data

Organ support	Means estimate	Conventional ventilation (95% CI)	HFOV (95% CI)	Difference (95% CI)	*p*-value[a]
Ventilation-free days (up to 30 days post randomisation)	Unadjusted	2.3 (2.0 to 2.6)	2.6 (2.3 to 3.0)	0.3 (–0.2 to 0.8)	0.1731
	Adjusted	2.3 (1.9 to 2.8)	2.6 (2.2 to 3.1)	0.3 (–0.2 to 0.7)	0.2483
Advanced respiratory support-free days (up to 30 days post randomisation)	Unadjusted	3.1 (2.7 to 3.6)	3.8 (3.2 to 4.4)	0.6 (–0.1 to 1.4)	0.0888
	Adjusted	3.1 (2.4 to 3.8)	3.7 (3.0 to 4.4)	0.6 (–0.1 to 1.4)	0.0962
Basic respiratory support-free days (up to 30 days post randomisation)	Unadjusted	14.7 (13.3 to 16.1)	15.6 (14.1 to 17.1)	0.9 (–1.1 to 2.9)	0.3780
	Adjusted	14.0 (12.1 to 15.9)	15.0 (13.0 to 16.9)	1.0 (–1.0 to 2.9)	0.3430
Days on advanced cardiovascular support	Unadjusted	2.8 (2.3 to 3.7)	2.9 (2.5 to 3.4)	0.1 (–0.6 to 0.8)	0.7446
	Adjusted	3.0 (2.3 to 3.6)	3.2 (2.5 to 3.9)	0.2 (–0.4 to 0.9)	0.4966
Days on basic cardiovascular support	Unadjusted	11.8 (10.7 to 12.9)	12.5 (11.4 to 13.6)	0.7 (–0.9 to 2.2)	0.3853
	Adjusted	11.5 (10.0 to 13.0)	12.2 (10.7 to 13.7)	0.7 (–0.9 to 2.3)	0.3802
Days on renal support	Unadjusted	2.6 (2.1 to 3.1)	4.5 (3.7 to 5.2)	1.8 (0.9 to 2.7)	0.0001
	Adjusted	2.5 (1.6 to 3.4)	4.3 (3.4 to 5.2)	1.8 (0.9 to 2.7)	0.0001
Days on gastrointestinal support	Unadjusted	16.0 (14.5 to 17.5)	17.4 (15.7 to 19.0)	1.3 (–0.9 to 3.6)	0.2382
	Adjusted	15.3 (13.2 to 17.5)	16.7 (14.6 to 18.9)	1.4 (–0.8 to 3.6)	0.2193
Dermatological support days	Unadjusted	1.0 (0.5 to 1.6)	0.9 (0.5 to 1.4)	–0.1 (–0.8 to 0.6)	0.7037
	Adjusted	0.9 (0.2 to 1.6)	0.8 (0.1 to 1.5)	–0.1 (–0.8 to 0.6)	0.7330
Liver support days	Unadjusted	0.040 (–0.001 to 0.100)	0.03 (0.01 to 0.10)	–0.002 (–0.040 to 0.040)	0.9127
	Adjusted	0.03 (–0.01 to 0.10)	0.03 (–0.01 to 0.10)	–0.001 (–0.040 to 0.040)	0.9501
Number of days free of antimicrobial use	Unadjusted	4.9 (4.1 to 5.7)	5.9 (5.0 to 6.8)	1.0 (–0.2 to 2.2)	0.1109
	Adjusted	4.5 (3.3 to 5.6)	5.5 (4.3 to 6.7)	1.0 (–0.2 to 2.2)	0.1030
Number of days free of drugs received primarily for sedation	Unadjusted	8.8 (7.6 to 10.0)	9.4 (7.9 to 10.8)	0.6 (–1.3 to 2.5)	0.5628
	Adjusted	7.7 (5.9 to 9.6)	8.3 (6.5 to 10.2)	0.6 (–1.3 to 2.5)	0.5435

a *p*-values: unadjusted analysis is based on comparison of the means only; the adjusted analysis is based on the analysis of covariance with adjustments made for centre, P : F ratio and sex of the patient.

TABLE 39 Number of patients available for each day for the categorical variables

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Conventional ventilation (*n*)	397	381	369	356	337	328	308	290	273	259	246	227	205	192	173	155	147	132	124	117
HFOV (*n*)	395	379	362	350	343	332	321	306	290	271	258	241	227	208	189	167	157	145	139	131
Total (*n*)	792	760	731	706	680	660	629	596	563	530	504	468	432	400	362	322	304	277	263	248
Day	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
Conventional ventilation (*n*)	110	102	96	89	82	79	77	69	44	60	55	54	52	48	45	41	38	38	36	34
HFOV (*n*)	122	117	107	99	91	88	86	77	69	65	64	60	58	54	48	44	42	40	38	35
Total (*n*)	232	219	203	188	173	167	163	146	113	125	119	114	110	102	93	85	80	78	74	69

Primary outcome

The primary outcome was all-cause mortality at 30 days following randomisation.

In the protocol, the original sample size of 1006 randomised patients was based on reducing mortality by 9% from 45% (on control group). In an early formal interim analysis, it was decided to change the effect size, in agreement with the HTA. At that point in the trial, the control group illustrated a higher proportion of mortality and difference of 10% required 802 patients.

Table 40 illustrates the results for mortality at 30 days post randomisation.

No statistically significant difference in mortality rates at 30 days post randomisation was found between the two interventions (chi-squared test: $p = 0.8523$). The absolute difference in mortality rates between the two interventions was 0.65% (95% CI –6.17% to 7.46%).

No statistically significant difference in mortality rates at 30 days post randomisation was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (logistic regression: *p*-value 0.8674). The odds of being alive (as opposed to dying) were 1.03 (95% CI 0.75 to 1.40) when on conventional ventilation compared with HFOV.

Figure 7 illustrates the Kaplan–Meier curve with the probability of survival up to 30 days post randomisation for each intervention. There is evidence from this plot that, on some days, HFOV did marginally worse than the conventional ventilator with respect to survival of patients over time.

TABLE 40 Patient status at 30 days (primary outcome)

Status	Conventional ventilation	HFOV	Total
Alive	234 (58.9%)	232 (58.3%)	466 (58.6%)
Died	163 (41.1%)	166 (41.7%)	329 (41.4%)
Total	397	398	795

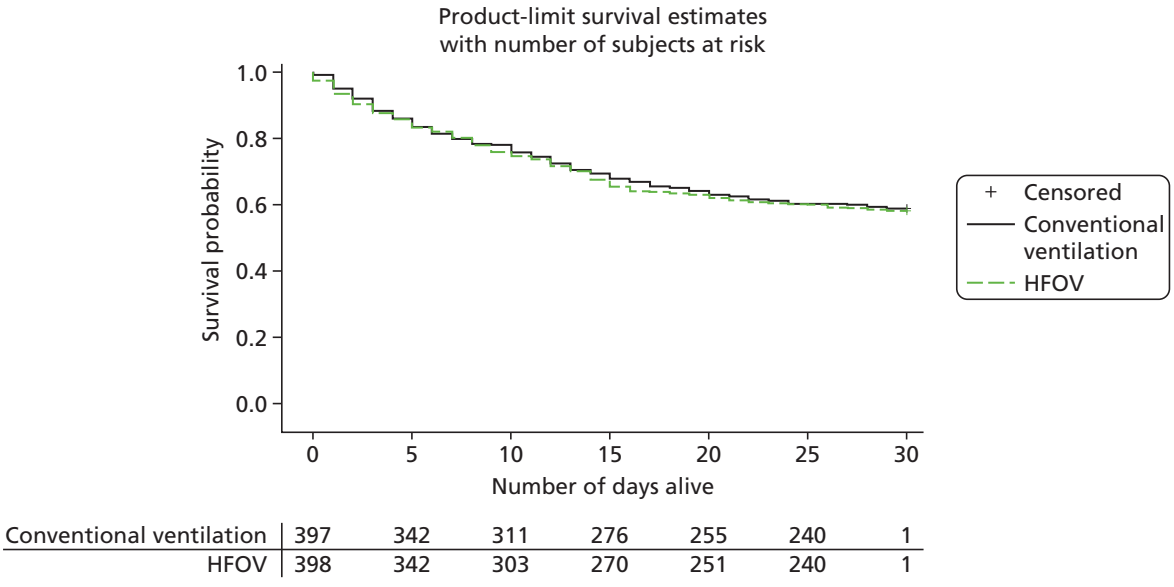


FIGURE 7 Kaplan–Meier curves for survival to day 30 post randomisation.

Secondary outcomes

Mortality rate at first discharge from intensive care unit/intensive care unit length of stay

The number (and percentage) of patients who died in ICU or were alive at discharge from ICU are summarised in *Table 41* by each intervention. Note that there are 794 patients in total with ICU data, as one patient was still in an ICU when the database was analysed.

No statistically significant difference in mortality rates at first discharge from ICU was found between the two interventions (chi-squared test: $p = 0.5664$). The difference in mortality rates between the two interventions was 2.02% (95% CI –4.85% to 8.86%).

For the survival analysis, patients who died up to first discharge from ICU were uncensored, and all others (including the one patient in ICU) were uncensored. No statistically significant difference in mortality rates at first discharge from ICU was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (logistic regression: *p*-value 0.5400). The odds of being alive (as opposed to dying) at first discharge from ICU were 1.102 (95% CI 0.807 to 1.505) when on conventional ventilation compared with HFOV.

Table 42 details the summary statistic for the length of stay in ICU (from randomisation to first discharge). No significant difference was found in the length of stay in ICU between the interventions. Using a linear regression model and adjusting for centre, sex, P : F ratio and APACHE II score, the mean [standard error (SE)] estimates were conventions: 15.8 (1.1) days; HFOV 17.5 (1.1) days and a difference of 1.8 (1.2) days: *p*-value for difference = 0.1314.

Figure 8 illustrates the Kaplan–Meier curve for the probability of survival in ICU against the number of days in ICU (with the number of patients at risk). The event here was mortality from randomisation to first discharge from ICU. Thus all patients who did not die in ICU and were discharged alive are censored (as their death date was beyond that of discharge from ICU date).

From *Table 42*, it is evident that the number of days in ICU range from 0 to 114 over both intervention groups. From *Figure 8*, we can see that the probability of survival in ICU appears to increase for patients on HFOV from day 50 (in ICU) to just beyond day 75. However, this is based on a small sample of patients at risk.

TABLE 41 Patient status at first discharge from ICU

Status	Conventional ventilation	HFOV	Total
Alive	230 (57.9%)	222 (55.9%)	452 (56.9%)
Died	167 (42.1%)	175 (44.1%)	324 (43.1%)
Total	397	397	794

TABLE 42 Summary statistics for the number of days from randomisation to first discharge from ICU

	Measure	Conventional ventilation	HFOV	Total
Time from ICU admission to ICU discharge (days)	Mean	16.2	17.6	16.9
	n	397	397	794
	SD	15.2	16.6	15.9
	Median	12	13	13
	Range	0–112	0–114	0–114

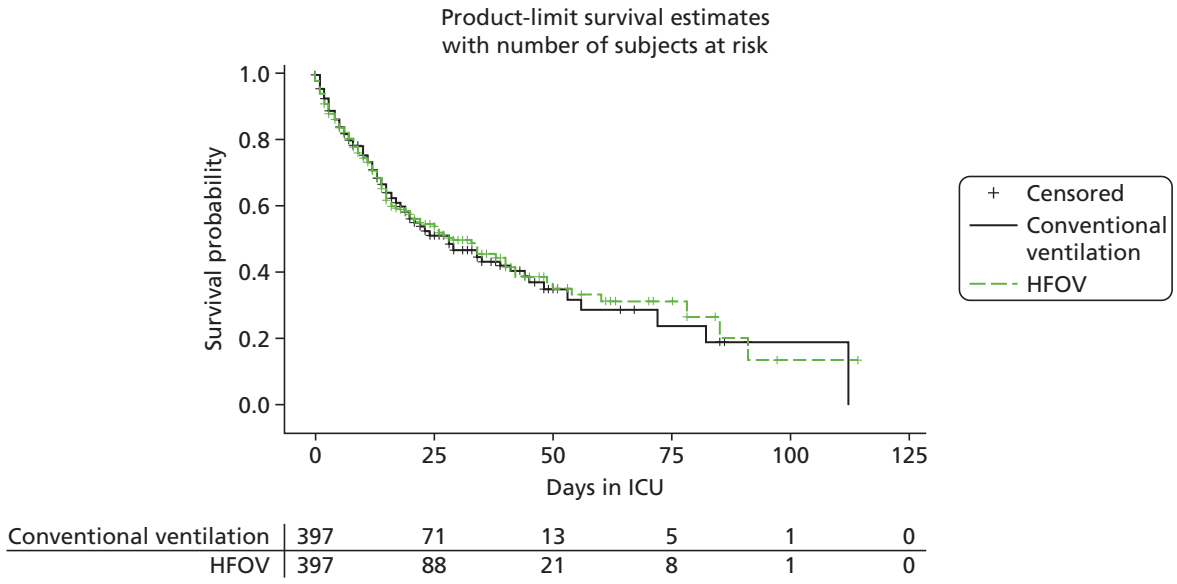


FIGURE 8 Kaplan–Meier curves displaying the probability of survival in ICU over the time in ICU for both interventions.

Mortality rate at first discharge from hospital/hospital length of stay

The number (and percentage) of patients who died prior to hospital discharge or were alive at hospital discharge are summarised in *Table 43* by each intervention. Note that there are 788 patients in total with hospital data – one patient was still in ICU and the other six patients were in hospital and had not been discharged.

No statistically significant difference in mortality rates at first discharge from hospital was found between the two interventions (chi-squared test: $p = 0.6187$). The difference in mortality rates between the two interventions was 1.77% (95% CI –5.19% to 8.71%).

No statistically significant difference in mortality rates at first discharge from hospital was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (logistic regression: *p*-value 0.5276). The odds of being alive (as opposed to dying) at first discharge from ICU were 1.104 (95% CI 0.812 to 1.501) when on conventional ventilation compared with HFOV.

Table 44 details the summary statistics for the length of stay in hospital (from randomisation to first discharge from hospital). No significant difference was found in the length of stay in hospital between the interventions. Using a linear regression model and adjusting for centre, sex, P : F ratio and the APACHE II score, the mean (SE) estimates were conventions: 31.0 (3.0) days; HFOV 32.8 (3.1) days and a difference of 1.9 (3.2) days: *p*-value for difference = 0.5426.

Figure 9 illustrates the Kaplan–Meier curve for the probability of survival in hospital against the number of days in hospital (with the number of patients at risk).

TABLE 43 Patient status at first discharge from hospital

Status	Conventional ventilation	HFOV	Total
Alive	204 (51.7%)	196 (49.9%)	400 (50.8%)
Died	191 (48.4%)	197 (50.1%)	388 (49.2%)
Total	395	393	788

TABLE 44 Number of days from randomisation to first discharge from hospital

	Measure	Conventional ventilation	HFOV	Total
Number of days from randomisation to first discharge from hospital	Mean	33.1	33.9	33.5
	n	395	393	788
	SD	44.3	41.6	43.0
	Median	21	21	21
	Range	0–584	0–280	0–584

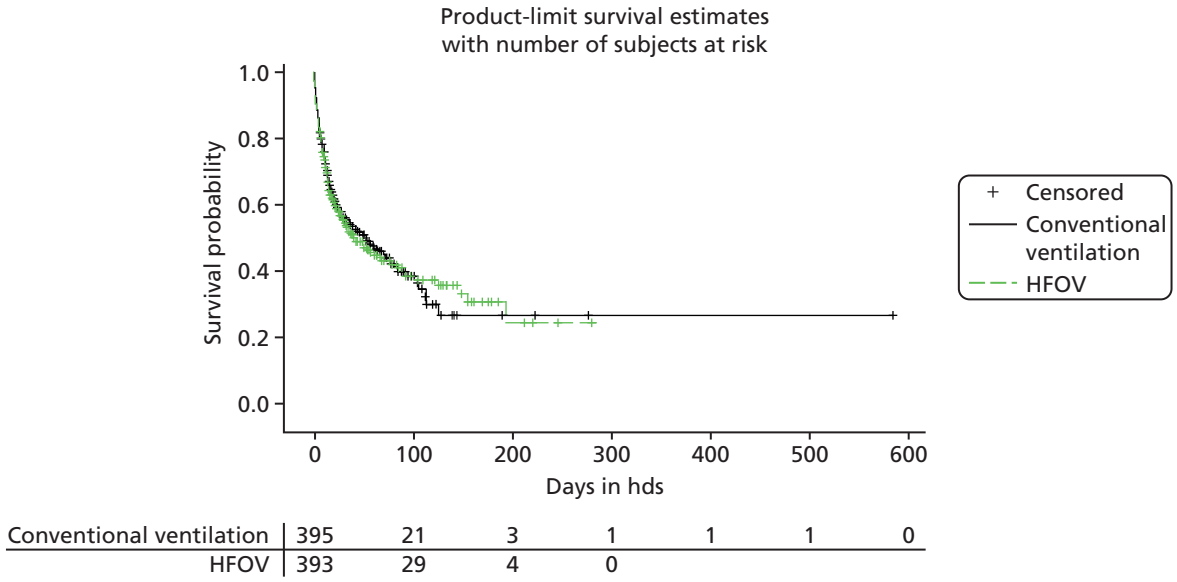


FIGURE 9 Kaplan–Meier curves displaying the probability of survival in hospital over the time in hospital for both interventions.

Mortality rate one year after randomisation

The number (and percentage) of patients who were alive/died on year after randomisation are summarised in *Table 45* by each intervention. An assumption that all of those who have not reached 12-month follow-up are alive has been made for the survival analysis. The uncensored observations are all of those who died prior to 12 months and the censored are all other subjects.

Allowing for the censoring, no statistically significant difference in mortality rates at 12 months post randomisation were found between the two interventions (log-rank test: $p = 0.2419$). The difference in mortality rates between the two interventions was 0.38% (95% CI –6.54% to 7.29%).

TABLE 45 Survival status 1 year after randomisation

Status	Conventional ventilation	HFOV	Total
Alive (or assumed alive)	194 (48.9%)	196 (49.2%)	390
Died	203 (51.1%)	202 (50.8%)	405
Total	397	398	795

No statistically significant difference in mortality rates at 12 months post randomisation from hospital was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (Cox's regression model: p-value = 0.1781). The odds of being alive (as opposed to dying) at 12 months post randomisation were 1.148 when on conventional ventilation compared with HFOV.

Figure 10 illustrates the Kaplan–Meier curve for the probability of survival up to 12 months post randomisation (with the number of patients at risk).

Follow-up

As the study recruitment period was extended, the longer-term follow-up for this study was not complete when this report was written. Data available up to 14 October 2012 are reported here. These results should be interpreted with considerable caution as they are not complete.

Six-month follow-up

From *Table 43*, there are 400 patients who are alive at hospital discharge.

From *Table 46*, there were 15 patients who died from hospital discharge to the 6-month follow-up time point and one patient withdrew from their 6 month follow-up. Also, there are 37 patients who are not due for their 6-month follow-up questionnaire. Thus, 53 patients will not have had their 6-month follow-up.

In total, 347 patients (86.8% of those discharged) were sent the 6-month questionnaire.

In total, we received back 221 questionnaires (63.6% of those sent). Thus, our follow-up rate at 6 months is currently 64%. Of these 221 questionnaires, 6 were returned blank and 215 were returned with data. There are 126 (36.3%) non-responders at 6 months. *Table 46* lists the numbers sent the questionnaires and followed up at 6 months by treatment group.

The statistical results from the linear regression models (unadjusted estimates and adjusted for centre, sex, APACHE II score and P : F ratio) are given in *Table 47*. The outcomes for the 6 months are in *Tables 48–50*.

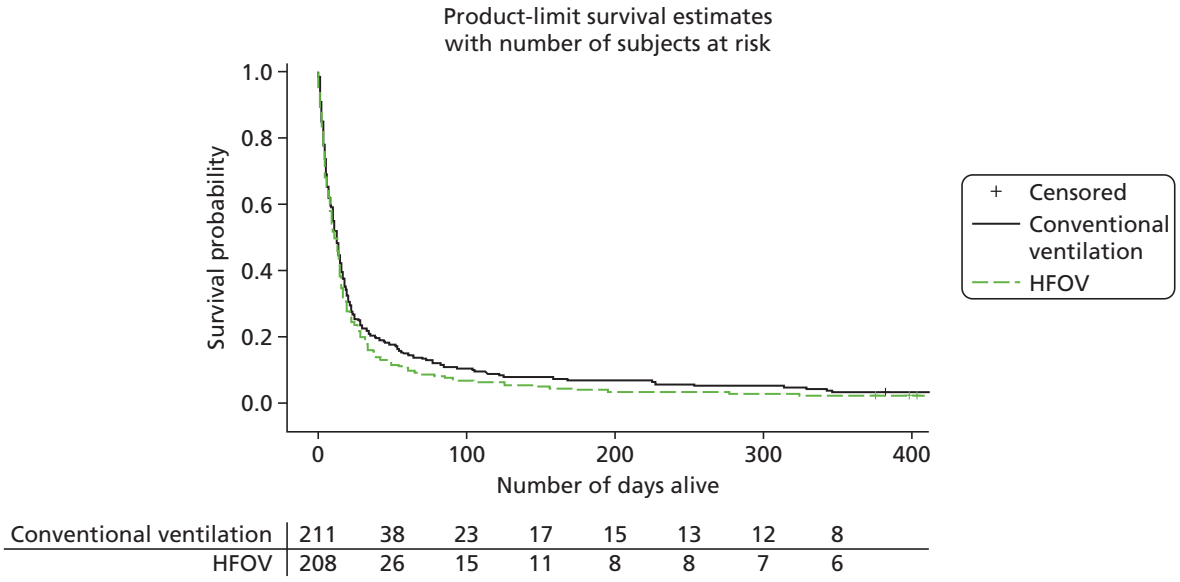


FIGURE 10 Kaplan–Meier curves displaying the probability of survival up to 12 months post randomisation for both interventions.

TABLE 46 Responders (during follow-up)

Time point	Status	Conventional ventilation	HFOV	Total
6-month follow-up	**Died prior to 6-month follow-up**	**196 (49.6%)**	**199 (50.4%)**	**395**
	Known to be alive at 6-month follow-up	**201 (50.3%)**	**199 (49.8%)**	**400**
	Not due their 6-month questionnaire	17 (45.9%)	20 (54.1%)	37
	Withdrawn from 6-month follow-up	1 (100.0%)	0 (0.0%)	1
	Not sent questionnaire[a]	1 (33.3%)	2 (66.7%)	3
	Follow-up questionnaire sent out	**176 (51.2%)**	**221 (64.2%)**	**344**
	Overdue their 6-month questionnaire (non-responders)	62 (50.4%)	61 (49.6%)	123
	Received completed follow-up questionnaire (on database)	110 (51.2%)	105 (48.8%)	215
	Received follow-up questionnaire, but blank	6 (100.0%)	0 (0.0%)	6
12-month follow-up	**Died prior to 12-month follow-up**	**203 (50.1%)**	**202 (49.9%)**	**405**
	Known to be alive at 12-month follow-up	**194 (49.7%)**	**196 (50.3%)**	**390**
	Not due their 12-month questionnaire	44 (53.0%)	39 (47.0%)	83
	Withdrawn from 12-month follow-up	2 (66.7%)	1 (33.3%)	3
	Not sent questionnaire	1 (50.0%)	1 (50.0%)	2
	Follow-up questionnaire sent out	**147 (48.8%)**	**155 (51.3%)**	**302**
	Overdue their 6-month questionnaire (non-responders)	62 (52.1%)	57 (47.9%)	119
	Received completed follow-up questionnaire (on database)	**84 (46.9%)**	**95 (53.1%)**	**179**
	Received follow-up questionnaire, but blank	1 (25.0%)	3 (75.0%)	4

a The centre has not notified the trial office that these patients had been discharged prior to 6-month follow-up.

TABLE 47 Statistical analysis of SF-12 and SGRQ follow-up (6 and 12 months)

Score and time	Means estimates	Conventional ventilation (95% CI)	HFOV (95% CI)	Difference (95% CI)	*p*-value[a]
SF-12 (mental) 6 months	Unadjusted	45.2 (42.6 to 47.8)	46.5 (43.8 to 49.2)	1.3 (–2.4 to 5.0)	0.4760
	Adjusted	44.8 (41.7 to 47.9)	46.5 (43.1 to 49.8)	1.7 (–2.1 to 5.4)	0.3890
SF-12 (mental) 12 months	Unadjusted	45.5 (42.6 to 48.3)	48.0 (45.3 to 50.7)	2.56 (–1.30 to 6.40)	0.1956
	Adjusted	45.3 (41.8 to 48.9)	46.8 (43.3 to 50.3)	1.5 (–2.9 to 5.8)	0.5089
SF-12 (physical) 6 months	Unadjusted	36.9 (34.5 to 39.3)	38.2 (35.4 to 40.9)	1.3 (–2.3 to 4.9)	0.4777
	Adjusted	36.3 (33.2 to 39.4)	38.5 (35.2 to 41.9)	2.2 (–1.6 to 6.1)	0.2470
SF-12 (physical) 12 months	Unadjusted	38.7 (35.8 to 41.6)	41.6 (38.6 to 44.5)	2.9 (–1.3 to 6.9)	0.1723
	Adjusted	38.0 (34.3 to 41.7)	41.5 (37.9 to 45.0)	3.5 (–1.0 to 7.9)	0.1309
SGRQ 6 months	Unadjusted	33.3 (28.1 to 38.6)	30.7 (25.3 to 36.1)	–2.6 (–10.1 to 4.9)	0.4874
	Adjusted	34.3 (27.3 to 41.3)	29.5 (22.6 to 36.5)	–4.8 (–12.9 to 3.4)	0.2499
SGRQ 12 months	Unadjusted	33.6 (27.2 to 40.0)	27.9 (21.8 to 34.1)	–5.7 (–14.4 to 3.1)	0.2037
	Adjusted	35.2 (27.0 to 43.4)	30.0 (22.5 to 37.6)	–5.2 (–14.8 to 4.5)	0.2918

a Linear regression models adjusted for centre, sex, APACHE II score and P : F ratio effects.

TABLE 48 European Quality of Life-5 Dimensions at follow-up (6 months: $n = 215$)

Domain	Level	Conventional ventilation	HFOV	Total
Mobility	I have no problems in walking about	44 (40.0%)	45 (42.9%)	89
	I have some problems in walking about	61 (55.5%)	57 (54.3%)	118
	I am confined to bed	2 (1.8%)	2 (1.9%)	4
	Missing	3 (2.7%)	1 (1.0%)	4
Self-care	I have no problems with self-care	69 (62.7%)	75 (71.4%)	144
	I have some problems with washing and dressing myself	29 (26.4%)	26 (24.8%)	55
	I am unable to wash and dress myself	6 (5.5%)	3 (2.9%)	9
	Missing	6 (5.5%)	1 (1.0%)	7
Usual activities	I have no problems with performing my usual activities	37 (33.6%)	43 (41.0%)	80
	I have some problems with my usual activities	55 (50.0%)	50 (47.6%)	105
	I am unable to perform by usual activities	17 (15.5%)	10 (9.5%)	27
	Missing	1 (0.9%)	2 (1.9%)	3
Pain/discomfort	I have no pain or discomfort	40 (36.4%)	54 (51.4%)	94
	I have moderate pain or discomfort	54 (49.1%)	40 (38.1%)	94
	I have extreme pain or discomfort	14 (12.7%)	10 (9.5%)	24
	Missing	2 (1.8%)	1 (1.0%)	3
Anxiety	I am not anxious or depressed	48 (43.6%)	58 (55.2%)	106
	I am moderately anxious or depressed	52 (47.3%)	34 (32.3%)	86
	I am extremely anxious or depressed	9 (8.2%)	13 (12.4%)	22
	Missing	1 (1.0%)	0 (0.0%)	1

TABLE 49 European Quality of Life-5 Dimensions at follow-up (12 months: $n = 179$)

Domain	Level	Conventional ventilation	HFOV	Total
Mobility	I have no problems in walking about	29 (34.5%)	45 (47.4%)	74
	I have some problems in walking about	49 (58.3%)	44 (46.3%)	93
	I am confined to bed	2 (2.4%)	2 (2.1%)	4
	Missing	4 (4.8%)	4 (4.2%)	8
Self-care	I have no problems with self-care	50 (59.5%)	65 (68.4%)	115
	I have some problems with washing and dressing myself	28 (33.3%)	26 (27.4%)	54
	I am unable to wash and dress myself	4 (4.8%)	1 (1.1%)	5
	Missing	2 (2.4%)	3 (3.2%)	5
Usual activities	I have no problems with performing my usual activities	30 (35.7%)	42 (44.2%)	72
	I have some problems with my usual activities	40 (47.6%)	44 (46.3%)	84
	I am unable to perform by usual activities	10 (11.9%)	7 (7.4%)	17
	Missing	4 (4.8%)	2 (2.1%)	6
Pain/discomfort	I have no pain or discomfort	31 (36.9%)	44 (46.3%)	75
	I have moderate pain or discomfort	44 (52.4%)	41 (43.2%)	85
	I have extreme pain or discomfort	6 (7.1%)	9 (9.5%)	15
	Missing	3 (3.6%)	1 (1.0%)	4
Anxiety	I am not anxious or depressed	32 (38.1%)	48 (50.5%)	80
	I am moderately anxious or depressed	43 (51.2%)	34 (35.8%)	77
	I am extremely anxious or depressed	8 (9.5%)	11 (11.6%)	19
	Missing	1 (1.2%)	2 (2.1%)	3

TABLE 50 St. George's Respiratory Questionnaire scores (6 and 12 months)

Assessment point	Summary measure	Conventional ventilation	HFOV	Total
6 months	Mean	33.3	30.7	32.0
	n	86	80	163
	SD	24.5	23.9	24.2
	Median	28.4	26.2	27.2
	Range	0.0–88.9	0.0–90.3	0.0–90.3
12 months	Mean	32.6	27.9	30.6
	n	59	67	126
	SD	24.4	25.1	24.9
	Median	30.3	22.2	28.4
	Range	0.0–79.8	0.0–89.4	0.0–89.4

Twelve-month follow-up

- Similar to the 6-month flow of patients, the 12-month rates are displayed in *Table 51*.
- The follow-up rate at 12 months is currently 60%.

TABLE 51 Short-Form questionnaire-12 items and SGRQ scores at follow-up (6 and 12 months)

Score	Time	Measure	Conventional ventilation	HFOV	Total
SF-12 (mental)	6 months	Mean	45.2	46.5	45.8
		n	98	94	192
		SD	12.7	13.2	13.0
		Median	44.9	50.7	47.1
		Range	18.4–72.0	15.8–67.1	15.8–72.0
	12 months	Mean	45.5	48.0	46.8
		n	73	80	153
		SD	12.1	12.2	12.2
		Median	44.3	51.1	47.7
		Range	19.7–68.3	15.6–64.9	15.6–68.3
SF-12 (physical)	6 months	Mean	36.9	38.2	37.5
		n	98	94	192
		SD	11.9	13.4	12.6
		Median	35.8	39.4	36.8
		Range	11.1–61.9	8.2–66.1	8.2–66.1
	12 months	Mean	38.7	41.6	40.2
		n	73	80	153
		SD	12.5	13.2	12.9
		Median	37.4	40.8	39.0
		Range	12.2–63.9	18.9–65.5	11.9–65.5
SGRQ	6 months	Mean	33.30	30.68	32.10
		n	86	77	163
		SD	24.5	23.9	24.2
		Median	28.4	26.2	27.2
		Range	0.0–88.9	0.0–90.3	0.0–90.3
	12 months	Mean	33.6	27.9	30.6
		n	59	67	126
		SD	24.4	25.1	24.9
		Median	30.3	22.2	28.4
		Range	0.0–79.7	0.0–89.4	0.0–89.4

Subgroup analysis

Severity of illness

The APACHE II score was used to compute the risk of dying and thus the severity of illness. For the calculation, the diagnostic coefficient was set to 0 (i.e. all the patients were given a respiratory infection diagnosis). A logistic regression model was set up to assess the risk of dying, with the APACHE II score as the independent variable. The cut-off point of a score of 26 for the APACHE II score was chosen, as this divided patients into equal risk groups [patients with a score of < 26 ($N = 607$) had more than 50% risk of survival, whereas those with a score of ≥ 26 ($N = 188$) had less than 50% risk of survival]. Thus, those in the latter category were more severely ill. The 50% risk cut off was selected during study design.

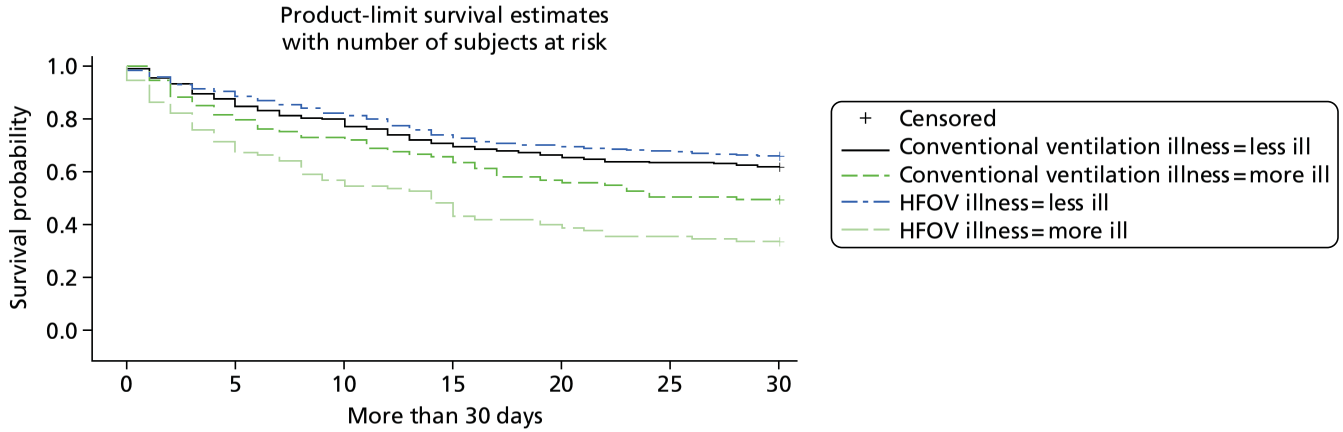
There is an indication that the interaction term for the subgroupings of illness and intervention is significant, with patients who are more ill likely to survive (up to 30 days) on the conventional ventilation group and patients who are less ill likely to survive (up to 30 days) on the intervention group (*Table 52* and *Figure 11*).

The statistical significance of the interaction term ($p = 0.0104$) indicates the need for caution in interpreting these findings.

The interaction of intervention and the two groups of illness for the number of days in ICU (*Table 53* and *Figure 12*) and number of days in hospital (*Table 54* and *Figure 13*) were not significant.

TABLE 52 Subgroup analysis: Cox proportional hazards model estimates for number of days survived (up to 30 days) with subgroups of severity of illness ($N = 795$)

Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
Less	Conventional ventilation	30 (12–30)	304	116	1.2 (0.9 to 1.5)	0.0104
Less	HFOV	30 (14–30)	303	103		
More	Conventional ventilation	28 (8–30)	93	47	0.6 (0.4 to 0.9)	
More	HFOV	30 (4–30)	95	63		

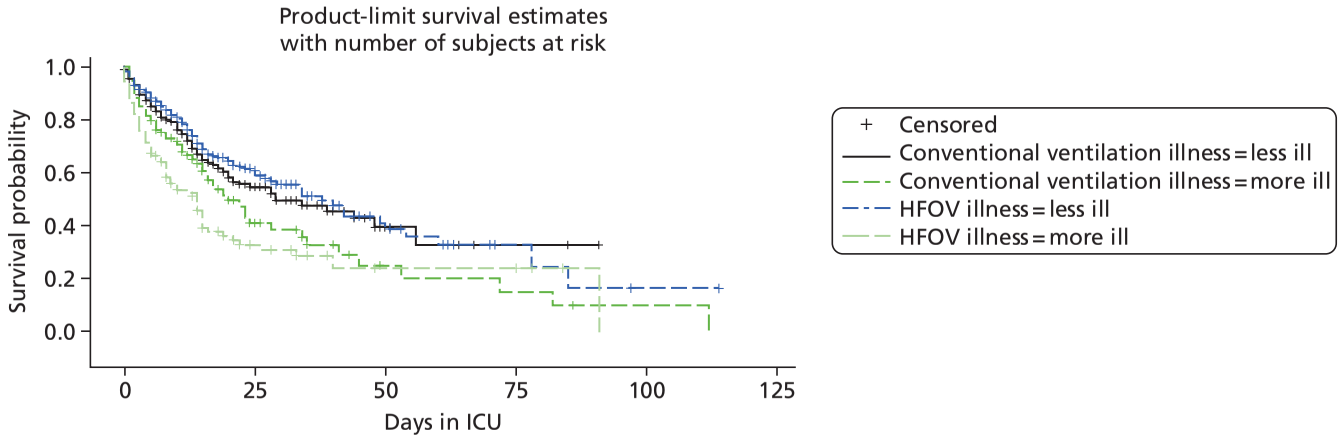


Conventional ventilation illness=less ill	304	290	272	258	247	243	232	219	211	207	202	197	194	193	192	1
Conventional ventilation illness=more ill	93	88	79	74	70	68	64	62	59	54	53	52	49	47	47	1
HFOV illness=less ill	303	290	277	268	259	249	242	230	220	215	213	209	207	205	202	1
HFOV illness=more ill	95	82	72	64	61	54	52	50	41	40	38	36	34	34	33	1

FIGURE 11 Subgroup analysis: Kaplan–Meier curve for number of days survived (up to 30 days) with subgroups of severity of illness ($n = 795$).

TABLE 53 Subgroup analysis: Cox proportional hazards estimates for number of days in ICU with subgroups of severity of illness ($N = 794$)

Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
Less	Conventional ventilation	12 (6.5–20.0)	304	114	0.7 (0.5 to 1.1)	0.0637
Less	HFOV	14 (8–23)	302	113		
More	Conventional ventilation	12 (6–40)	93	53	1.4 (0.9 to 1.5)	
More	HFOV	9 (4–19)	95	95		

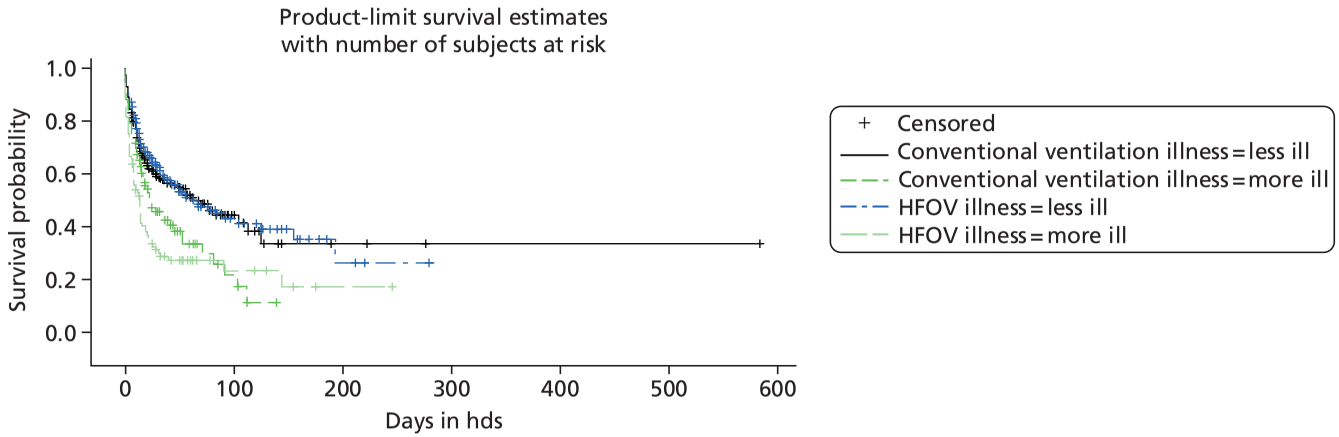


Conventional ventilation illness = less ill	304	54	8	2	0	
Conventional ventilation illness = more ill	93	18	5	3	1	0
HFOV illness = less ill	302	71	17	4	1	0
HFOV illness = more ill	95	17	4	4	0	

FIGURE 12 Subgroup analysis: Kaplan–Meier curve for number of days in ICU with subgroups of severity of illness ($n = 794$).

TABLE 54 Subgroup analysis: Cox proportional hazards estimates for number of days up to hospital discharge with subgroups of severity of illness ($N = 788$)

Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
Less	Conventional ventilation	21 (10–44)	303	133	1.1 (0.8 to 1.4)	0.1085
Less	HFOV	23 (12–42)	299	129		
More	Conventional ventilation	18 (7.5–40.0)	92	58	0.75 (0.50 to 1.10)	
More	HFOV	13 (4–13)	94	68		



Conventional ventilation illness = less ill	303	16	3	1	1	1	0
Conventional ventilation illness = more ill	92	5	0				
HFOV illness = less ill	299	23	3	0			
HFOV illness = more ill	94	6	1	0			

FIGURE 13 Subgroup analysis: Kaplan–Meier curve for number of days up to hospital discharge with subgroups of severity of illness ($n = 788$).

P : F ratio

The cut-off point for the P : F ratio was based on the median value of 15 kPa (i.e. the value where 50% of the data fall above and below 15 kPa).

There was no indication of an interaction between intervention and the categories of P : F ratio for any of the outcomes (*Tables 55–57* and *Figures 14–16*).

TABLE 55 Subgroup analysis: Cox proportional hazards estimates for number of days survived (up to 30 days) with subgroups based on the P : F ratio ($N = 795$)

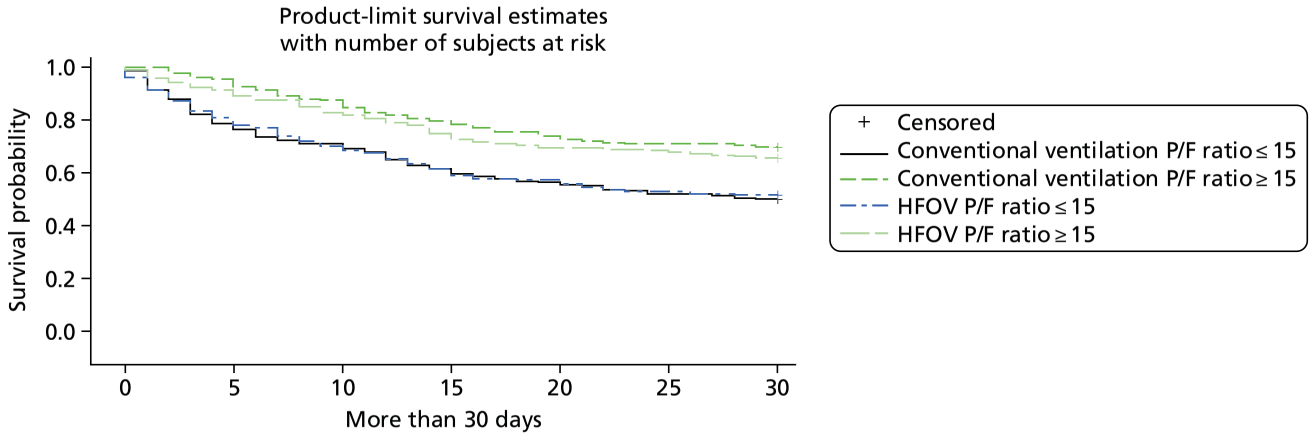
Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
< 15 kPa	Conventional ventilation	30 (6–30)	221	110	0.8 (0.6 to 1.2)	0.3906
< 15 kPa	HFOV	30 (7–30)	211	102		
≥ 15 kPa	Conventional ventilation	30 (19–30)	176	53	1.0 (0.8 to 1.4)	
≥ 15 kPa	HFOV	30 (14–30)	187	64		

TABLE 56 Subgroup analysis: Cox proportional hazards estimates for number of days in ICU with subgroups based on the P : F ratio ($N = 794$)

Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
< 15 kPa	Conventional ventilation	12 (5–18)	221	109	0.9 (0.6 to 1.3)	0.4863
< 15 kPa	HFOV	13 (6–22)	210	109		
≥ 15 kPa	Conventional ventilation	13 (7–22)	176	58	1.1 (0.8 to 1.4)	
≥ 15 kPa	HFOV	14 (9–23)	187	66		

TABLE 57 Subgroup analysis: Cox proportional hazards estimates for number of days up to hospital discharge with subgroups based on the P : F ratio ($N = 788$)

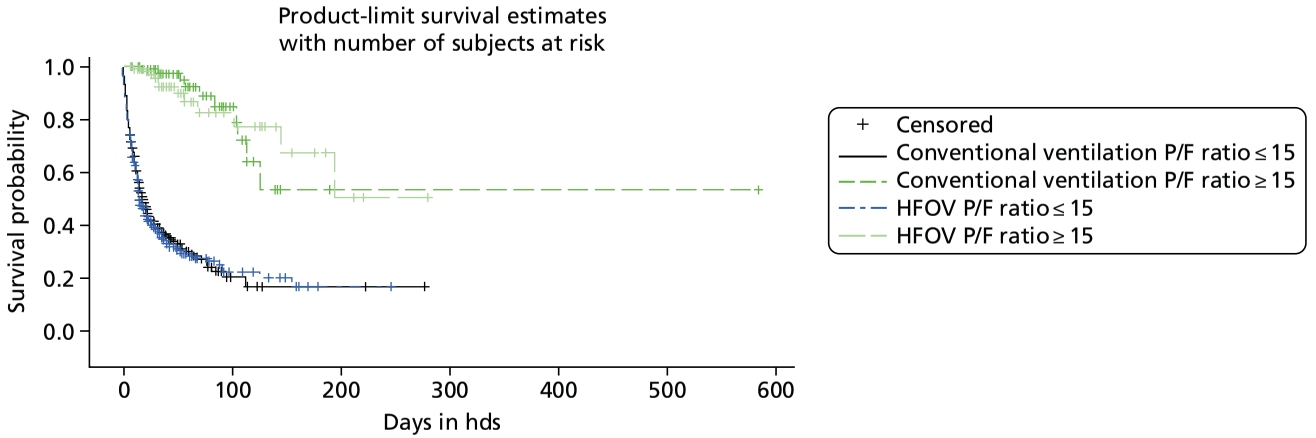
Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
< 15 kPa	Conventional ventilation	15 (6–33)	280	181	1.0 (0.8 to 1.2)	0.7739
< 15 kPa	HFOV	14 (6–33)	276	185		
≥ 15 kPa	Conventional ventilation	33 (21–65)	115	10	0.9 (0.4 to 2.0)	
≥ 15 kPa	HFOV	32 (22–52)	117	12		



Conventional ventilation P/F ratio ≤ 15	221 202 182 169 160 157 150 139 132 128 125 122 118 115 114	1
Conventional ventilation P/F ratio ≥ 15	176 176 169 163 157 154 146 142 138 133 130 127 125 125 125	1
HFOV P/F ratio ≤ 15	211 193 176 165 156 148 143 134 125 122 121 115 112 112 110	1
HFOV P/F ratio ≥ 15	187 179 173 167 164 155 151 146 136 133 130 130 129 127 125	1

FIGURE 14 Subgroup analysis: Kaplan–Meier curve for number of days survived (up to 30 days) with subgroups based on P : F ratio ($n = 795$).

FIGURE 15 Subgroup analysis: Kaplan–Meier curve for number of days in ICU with subgroups based on P : F ratio ($n = 795$).



Conventional ventilation P/F ratio ≤ 15	280	6	2	0			
Conventional ventilation P/F ratio ≥ 15	115	15	1	1	1	1	0
HFOV P/F ratio ≤ 15	276	14	1	0			
HFOV P/F ratio ≥ 15	117	15	3	0			

FIGURE 16 Subgroup analysis: Kaplan–Meier curve for number of days in hospital with subgroups based on P : F ratio ($n = 788$).

Causes of hypoxaemic respiratory failure

The two categories for the cause of hypoxaemic respiratory failure were pulmonary and extrapulmonary.

There was no indication of an interaction between intervention and the categories of hypoxaemic respiratory failure for any of the outcomes (*Tables 58–60* and *Figures 17–19*).

TABLE 58 Subgroup analysis: Cox proportional hazards estimates for number of days survived (up to 30 days) with subgroups of hypoxaemic respiratory failure ($N = 795$)

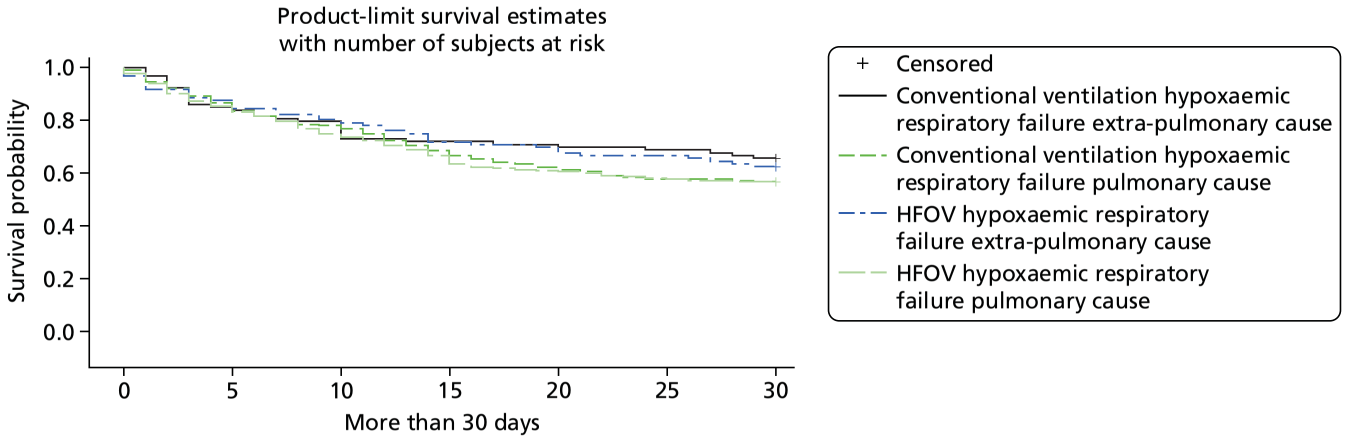
Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio (risk of dying)	*p*-value (interaction)
Pulmonary	Conventional ventilation	30 (11.5–30.0)	304	131	0.9 (0.6 to 1.5)	0.8096
Pulmonary	HFOV	30 (9–30)	302	130		
Extrapulmonary	Conventional ventilation	30 (10–30)	93	32	1.0 (0.8 to 1.3)	
Extrapulmonary	HFOV	30 (13.5–30.0)	96	36		

TABLE 59 Subgroup analysis: Cox proportional hazards estimates for number of days in ICU with subgroups based on the cause of hypoxaemic respiratory failure ($N = 794$)

Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio	*p*-value (interaction)
Pulmonary	Conventional ventilation	13 (6–21)	304	134	1.0 (0.6 to 1.3)	0.8293
Pulmonary	HFOV	13 (7–23)	301	137		
Extrapulmonary	Conventional ventilation	11 (7–20)	93	33	1.0 (0.8 to 1.3)	
Extrapulmonary	HFOV	13 (8.5–22.0)	96	38		

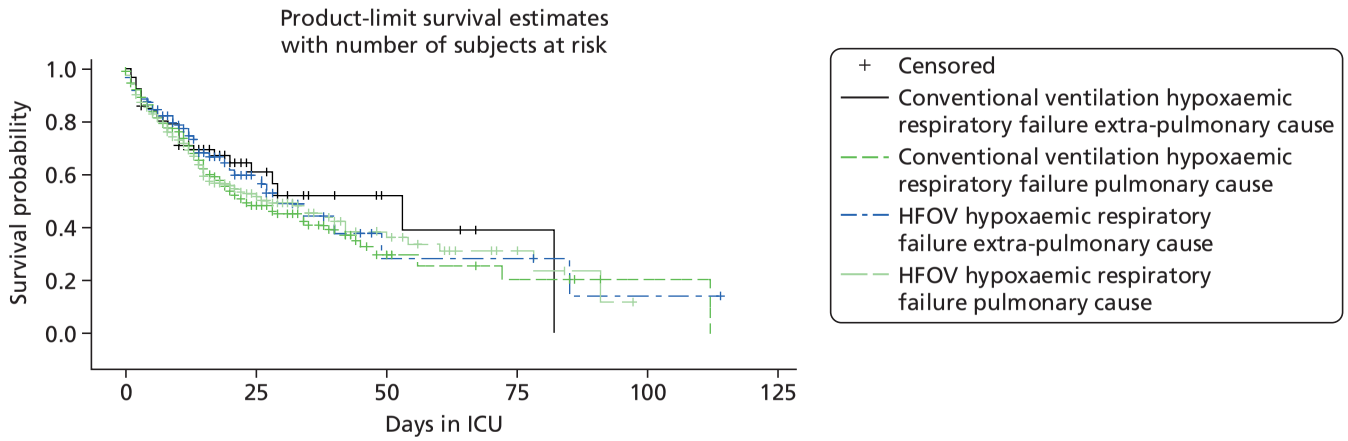
TABLE 60 Subgroup analysis: Cox proportional hazards estimates for number of days up to hospital discharge with subgroups based on the cause of hypoxaemic respiratory failure ($N = 788$)

Illness	Treatment	Median (quartile range)	*n*	Died	Hazard ratio	*p*-value (interaction)
Pulmonary	Conventional ventilation	19 (9–41)	303	155	0.9 (0.6 to 1.4)	0.6678
Pulmonary	HFOV	18 (9–37)	298	153		
Extrapulmonary	Conventional ventilation	23.5 (10.0–51.0)	92	36	1.0 (0.8 to 1.2)	
Extrapulmonary	HFOV	28 (2–52)	95	44		



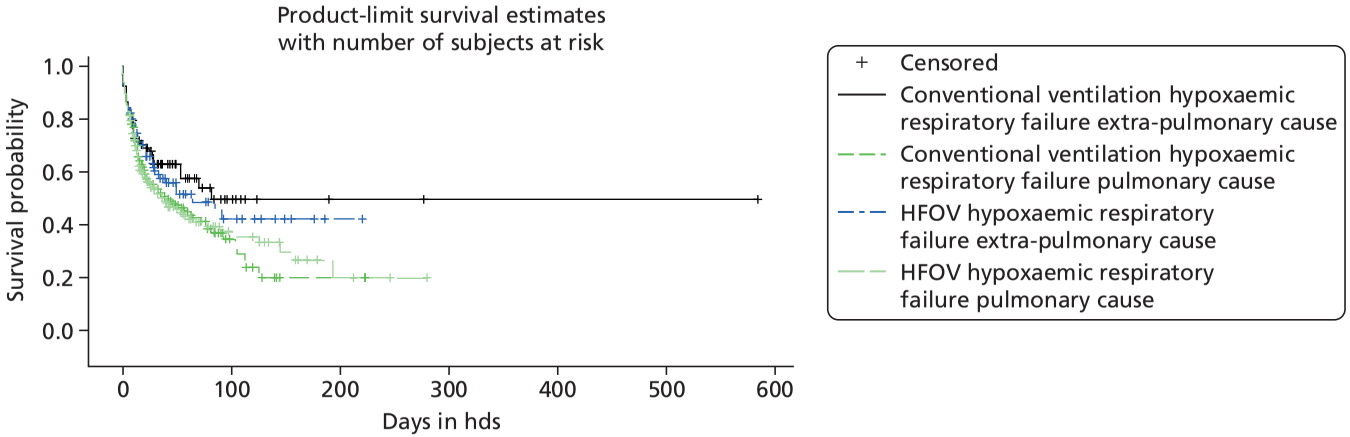
Conventional ventilation hypoxaemic respiratory failure extra-pulmonary cause	93	90	80	78	75	74	68	67	67	66	66	65	65	64	63	1
Conventional ventilation hypoxaemic respiratory failure pulmonary cause	304	288	271	254	242	237	228	214	203	195	189	184	178	176	176	1
HFOV hypoxaemic respiratory failure extra-pulmonary cause	96	88	85	81	79	77	75	72	69	68	67	64	64	64	62	1
HFOV hypoxaemic respiratory failure pulmonary cause	302	284	264	251	241	226	219	208	192	187	184	181	177	175	173	1

FIGURE 17 Subgroup analysis: Kaplan–Meier curve for number of days survived (up to 30 days) with subgroups based on the cause of hypoxaemic respiratory failure ($n = 795$).



Conventional ventilation hypoxaemic respiratory failure extra-pulmonary cause	93	16	4	1	0	
Conventional ventilation hypoxaemic respiratory failure pulmonary cause	304	55	9	4	1	0
HFOV hypoxaemic respiratory failure extra-pulmonary cause	96	19	3	3	1	0
HFOV hypoxaemic respiratory failure pulmonary cause	301	69	18	5	0	

FIGURE 18 Subgroup analysis: Kaplan–Meier curve for number of days in ICU with subgroups based on the cause of hypoxaemic respiratory failure ($n = 794$).



Conventional ventilation hypoxaemic respiratory failure extra-pulmonary cause	92	8	2	1	1	1	0
Conventional ventilation hypoxaemic respiratory failure pulmonary cause	303	13	1	0			
HFOV hypoxaemic respiratory failure extra-pulmonary cause	95	11	1	0			
HFOV hypoxaemic respiratory failure pulmonary cause	298	18	3	0			

FIGURE 19 Subgroup analysis: Kaplan–Meier curve for number of days in hospital with subgroups based on the cause of hypoxaemic respiratory failure ($n = 794$).

Per-protocol analysis

There are 84 patients who had a protocol violation (as detailed in *Table 17*). These patients were as follows:

- Randomised to HFOV but did not receive it: 8.
- Randomised to HFOV but received < 12 hours of HFOV: 25.
- Randomised to HFOV but did not receive it and received < 12 hours of HFOV: 2.
- Randomised to HFOV but received < 12 hours of HFOV and classified as protocol violator: 3.
- Randomised to HFOV but received < 12 hours of HFOV and recorded as ventilator problems on HFOV weaning: 3.
- Randomised to conventional ventilation but received HFOV: 11.
- Classified as protocol violator: 15.
- Classified as protocol violator and recorded as ventilator problems: 1.
- Recorded as ventilator problems on HFOV weaning: 16.

Table 61 illustrates the distribution of patients who violated the protocol and the randomised treatment allocations.

The following tables contain patients who complied with the protocol ($n = 711$, *Tables 62–81*).

TABLE 61 Distribution of protocol violations over the two treatment groups

Compliance	Conventional ventilation	HFOV	Total
Violation of the protocol	11 (2.8%)	73 (18.3%)	84 (10.6%)
Complied with the protocol	386 (97.2%)	325 (81.7%)	711 (89.4%)
Total	397	398	795

% based on the number of patients within each treatment group and the total.

TABLE 62 Pre randomisation clinical variables

Ventilation	Summary measure	Exhaled minute volume (l/minute)	Total respiratory rate (breaths/minute)	PEEP (cmH_2O)	Plateau pressure (cmH_2O)	Arterial blood gas			
						PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	FiO_2
Conventional ventilation	Mean	10.20	21.20	11.33	22.33	10.47	6.88	7.32	0.74
	n	385	386	380	370	386	386	381	386
	SD	3.47	8.23	3.31	9.17	2.52	1.84	0.10	0.18
	Median	9.90	20.00	10.00	24.00	10.00	6.70	7.32	0.70
	Minimum	0.30	8.00	5.00	0.00	5.00	3.50	7.00	0.35
	Maximum	33.40	70.00	36.00	48.00	24.20	16.30	7.53	1.00
	Missing	1	0	6	16	0	0	5	0
HFOV	Mean	10.38	20.96	11.28	21.58	10.23	6.87	7.32	0.72
	n	325	325	320	315	325	325	319	325
	SD	3.34	8.22	3.29	9.08	2.19	1.81	0.11	0.18
	Median	10.10	20.00	10.00	22.00	9.90	6.70	7.33	0.70
	Minimum	3.04	0.00	5.00	0.00	5.90	3.60	6.86	0.35
	Maximum	30.8	69.0	33.0	43.0	23.6	15.9	7.7	1.0
	Missing	0	0	5	10	0	0	6	0
Total	Mean	10.28	21.09	11.31	21.00	10.36	6.90	7.32	0.73
	n	710	711	700	685	711	711	700	711
	SD	3.41	8.22	3.30	9.13	2.37	1.82	0.10	0.18
	Median	9.93	20.00	10.00	23.00	10.00	6.70	7.32	0.70
	Minimum	0.30	0.00	5.00	0.00	5.00	3.50	6.86	0.35
	Maximum	33.4	70.0	36.0	48.0	24.2	16.3	7.7	1.0
	Missing	1	0	11	26	0	0	11	0

TABLE 63 Number of patients (%) for each support/organ monitoring categories pre randomisation

Treatment or organ support		Response	Conventional ventilation	HFOV	Total
Support organ monitoring	Advanced respiratory support	No	1 (0.3%)	1 (0.3%)	2 (0.3%)
		Yes	385 (99.7%)	324 (99.7%)	709 (99.7%)
	Basic respiratory support	No	325 (84.2%)	282 (86.8%)	607 (85.4%)
		Yes	61 (15.8%)	43 (13.2%)	104 (14.6%)
	Advanced cardiovascular support	No	205 (53.1%)	201 (61.8%)	406 (57.1%)
		Yes	181 (46.9%)	124 (38.2%)	305 (42.9%)
	Basic cardiovascular support	No	142 (36.8%)	104 (32.0%)	246 (34.6%)
		Yes	244 (63.2%)	221 (68.0%)	465 (65.4%)
	Renal support	No	316 (81.9%)	261 (80.3%)	577 (81.2%)
		Yes	70 (18.1%)	64 (19.7%)	134 (18.8%)

TABLE 63 Number of patients (%) for each support/organ monitoring categories pre randomisation (*continued*)

Treatment or organ support		Response	Conventional ventilation	HFOV	Total
	Gastrointestinal support	No	84 (21.8%)	65 (20.0%)	149 (21.0%)
		Yes	302 (78.2%)	260 (80.0%)	562 (79.0%)
	Dermatological support	No	373 (96.6%)	312 (96.0%)	685 (96.3%)
		Yes	13 (3.4%)	13 (4.0%)	26 (3.7%)
	Liver support	No	381 (98.7%)	325 (100.0%)	706 (99.3%)
		Yes	5 (1.3%)	0 (0.0%)	5 (0.7%)
Antimicrobial use	Antimicrobial drug received	No	12 (3.1%)	13 (4.0%)	25 (3.5%)
		Yes	374 (96.9%)	312 (96.0%)	686 (96.5%)
	Antimicrobial for pulmonary infection	No	59 (15.8%)	54 (17.3%)	113 (16.5%)
		Yes	315 (84.2%)	258 (82.7%)	573 (83.5%)
	Antimicrobial intravenous	No	3 (0.8%)	2 (0.6%)	5 (0.7%)
		Yes	371 (99.2%)	310 (99.4%)	681 (99.3%)
Sedation use	Sedation received	No	7 (1.8%)	7 (2.2%)	14 (2.0%)
		Yes	379 (98.2%)	318 (97.8%)	697 (98.0%)
	Sedation intravenous	No	342 (90.2%)	278 (87.4%)	620 (89.0%)
		Yes	37 (9.8%)	40 (12.6%)	77 (11.0%)
	Sedation infusion	No	2 (0.5%)	2 (0.6%)	4 (0.6%)
		Yes	377 (99.5%)	316 (99.4%)	693 (99.4%)
	Sedation one class	No	45 (11.9%)	41 (12.9%)	86 (12.3%)
		Yes	334 (88.1%)	277 (87.1%)	611 (87.7%)
	Sedation two classes	No	329 (86.8%)	283 (89.0%)	612 (87.8%)
		Yes	50 (13.2%)	35 (11.0%)	85 (12.2%)
	Sedation three or more classes	No	376 (99.2%)	315 (99.1%)	691 (99.1%)
		Yes	3 (0.8%)	3 (0.9%)	6 (0.9%)
Muscle relaxants	Muscle relaxants received	No	218 (56.5%)	180 (55.4%)	398 (56.0%)
		Yes	168 (43.5%)	145 (44.6%)	313 (44.0%)
	Muscle relaxants intravenous	No	87 (51.8%)	66 (45.5%)	153 (48.9%)
		Yes	81 (48.2%)	79 (54.5%)	160 (51.1%)
	Muscle relaxants infusion	No	68 (40.5%)	58 (40.0%)	126 (40.3%)
		Yes	100 (59.5%)	87 (60.0%)	187 (59.7%)
Others	Prone position ventilated	No	153 (91.1%)	130 (89.7%)	283 (90.4%)
		Yes	15 (8.9%)	15 (10.3%)	30 (9.6%)
	Nitric oxide received	No	378 (97.9%)	316 (97.2%)	694 (97.6%)
		Yes	8 (2.1%)	9 (2.8%)	17 (2.4%)

TABLE 64 Time to randomisation and time to ICU

Interval	Summary measure	Conventional ventilation	HFOV	Total
Time from hospital admission to ICU admission (days)	Mean	3.86	4.19	4.01
	n	386	325	711
	SD	7.57	10.31	8.92
	Median	1	1	1
	Minimum	0	0	0
	Maximum	80	108	108
Time from hospital admission to randomisation (days)	Mean	8.38	7.07	7.78
	n	386	325	711
	SD	37.78	11.18	28.83
	Median	4	4	4
	Minimum	0	0	0
	Maximum	732	130	732
Time from ICU to randomisation (days)	Mean	4.53	2.88	3.77
	n	386	325	711
	SD	37.20	2.61	27.46
	Median	2	2	2
	Minimum	0	0	0
	Maximum	732	22	732

TABLE 65 Demographic details of randomised patients

Demographic	Summary measure	Conventional ventilation	HFOV	Total
Age group (years)	≤ 55	168 (43.5%)	148 (45.5%)	316 (44.4%)
	> 55	218 (56.5%)	177 (54.5%)	395 (55.6%)
Sex	Male	230 (59.6%)	207 (63.7%)	437 (61.5%)
	Female	156 (40.4%)	118 (36.3%)	274 (38.5%)
P : F ratio	≤ 15	227 (58.8%)	188 (57.8%)	415 (58.4%)
	> 15	159 (41.2%)	137 (42.2%)	296 (41.6%)
Weight (kg)	Mean	78.70	81.23	79.86
	n	386	325	711
	SD	20.98	21.91	21.43
	Median	76	80	78
	Minimum	37	40	37
	Maximum	215	186	215
PaO_2 (kPa)	Mean	10.47	10.23	10.36
	n	386	325	711
	SD	2.52	2.18	2.37
	Median	10.0	9.9	10.0
	Minimum	5.0	5.9	5.0
	Maximum	24.2	23.6	24.2
Associated FiO_2	Mean	0.74	0.73	0.73
	n	386	325	711
	SD	0.18	0.18	0.18
	Median	0.70	0.70	0.70
	Minimum	0.35	0.35	0.35
	Maximum	1.00	1.00	1.00

TABLE 66 Hypoxaemic respiratory failure

Cause of respiratory failure	Conventional ventilation	HFOV	Total
Pulmonary	298 (77.2%)	248 (76.3%)	546 (76.8%)
Extrapulmonary	88 (22.8%)	77 (23.7%)	165 (23.2%)

TABLE 67 Initial ventilation data

Ventilation start	Conventional ventilation	HFOV	Total
Before hospital admission	20 (5.2%)	11 (3.4%)	31 (4.4%)
Prior to ICU admission	116 (30.0%)	96 (29.5%)	212 (29.8%)
During ICU stay	249 (64.5%)	218 (67.1%)	467 (65.7%)
Where first ventilated not known	1 (0.3%)	0 (0.0%)	1 (0.1%)
Patient height or heel/crown (m/cm)	**Conventional ventilation**	**HFOV**	**Total**
Mean	1.68	1.69	1.69
n	376	316	692
SD	0.11	0.11	0.11
Median	1.68	1.70	1.69
Minimum	1.40	1.21	1.21
Maximum	2.01	1.97	2.01

TABLE 68 APACHE II scores

Summary measure	Conventional ventilation	HFOV	Total
Mean	21.9	21.6	21.8
n	372	313	685
SD	6.07	5.87	5.97
Median	22	22	22
Minimum	5	7	5
Maximum	45	39	45

TABLE 69 Admission to ICU

Surgical status	NCEPOD classification	Conventional ventilation	HFOV	Total
Was the patient admitted to your ICU directly from the operating theatre/recovery area in your hospital?	No	338 (87.6%)	282 (88.8%)	620 (87.2%)
	Yes	48 (12.4%)	43 (13.2%)	91 (12.8%)
If 'yes'	Emergency	19 (39.6%)	19 (44.2%)	38 (41.8%)
	Urgent	17 (35.4%)	17 (39.5%)	34 (37.4%)
	Scheduled	2 (4.2%)	1 (2.3%)	3 (3.3%)
	Elective	10 (20.8%)	6 (14.0%)	16 (17.6%)

NCEPOD, National Confidential Enquiry into Peri-Operative Deaths.

TABLE 70 Daily data (support/organ monitoring)

Support	Summary measure	Conventional ventilation	HFOV	Total
Ventilation-free days up to 30 days post randomisation	Mean	2.3	2.8	2.6
	n	386	325	711
	SD	3.5	3.5	3.5
	Median	1	2	1
	Range	0–21	0–20	0–21
Advanced respiratory support-free days	Mean	3.2	3.9	3.5
	n	386	325	711
	SD	4.7	6.1	5.4
	Median	2	2	2
	Range	0–32	0–57	0–57
Basic respiratory support-free days	Mean	14.5	16.0	15.2
	n	386	325	711
	SD	13.8	15.5	14.4
	Median	11	12	11
	Range	0–91	0–106	0–106
Days on advanced cardiovascular support	Mean	2.8	2.7	2.8
	n	386	325	711
	SD	5.7	4.1	5.0
	Median	1	1	1
	Range	0–75	0–28	0–75
Days on basic cardiovascular support	Mean	11.6	13.1	12.3
	n	386	325	711
	SD	10.6	11.8	11.2
	Median	10	11	10
	Range	0–73	0–85	0–85
Days on renal support	Mean	2.57	4.5	3.5
	n	386	325	711
	SD	5.0	8.1	6.7
	Median	0	0	0
	Range	0–34	0–52	0–52
Days on gastrointestinal support	Mean	15.9	17.7	16.7
	n	386	325	711
	SD	15.1	16.6	15.8
	Median	12	13	13
	Range	0–113	0–114	0–114

continued

TABLE 70 Daily data (support/organ monitoring) (*continued*)

Support	Summary measure	Conventional ventilation	HFOV	Total
Days on dermatological support	Mean	1.1	0.9	1.0
	n	386	325	711
	SD	5.4	4.2	4.9
	Median	0	0	0
	Range	0–59	0–31	0–59
Days on liver support	Mean	0.04	0.02	0.03
	n	386	325	711
	SD	0.37	0.15	0.29
	Median	0	0	0
	Range	0–5	0–2	0–5

TABLE 71 Daily data (antimicrobial use)

Antimicrobial use	Summary measure	Conventional ventilation	HFOV	Total
Number of days free from antimicrobial used	Mean	4.9	5.8	5.3
	n	386	325	711
	SD	8.2	8.9	8.5
	Median	1	2	2
	Range	0–60	0–63	0–63
Number of days antimicrobial used	Mean	12.2	13.3	12.7
	n	386	325	711
	SD	10.3	12.5	11.4
	Median	10	10	10
	Range	0–68	0–111	0–111
Number of days antimicrobial used to treat pulmonary infection	Mean	9.7	10.4	10.0
	n	39	325	711
	SD	9.3	10.2	9.7
	Median	8	8	8
	Range	0–54	0–68	0–68
Number of days antimicrobial given intravenously	Mean	11.5	12.4	11.9
	n	386	325	711
	SD	9.5	11.1	10.3
	Median	9	10	10
	Range	0–60	0–86	0–86

TABLE 72 Daily data (sedative use)

Sedative use	Summary measure	Conventional ventilation	HFOV	Total
Number of days free from sedative received primarily for sedation	Mean	8.9	9.5	9.2
	n	386	325	711
	SD	12.7	14.7	13.6
	Median	5	5	5
	Range	0–108	0–97	0–97
Number of days sedative received primarily for sedation	Mean	8.2	9.7	8.9
	n	386	325	711
	SD	6.4	7.4	6.9
	Median	7	8	7
	Range	0–38	0–50	0–50
Number of days an intravenous bolus dose used	Mean	0.5	0.4	0.4
	n	386	325	711
	SD	2.1	1.2	1.7
	Median	0	0	0
	Range	0–30	0–13	0–30
Number of days sedative given by infusion	Mean	8.1	9.4	8.7
	n	386	325	711
	SD	6.4	7.2	6.8
	Median	6.5	8.0	7.0
	Range	0–38	0–50	0–50
Number of days patient on more than one class of sedative	Mean	6.4	7.6	7.0
	n	386	325	711
	SD	5.6	5.9	5.8
	Median	5	6	6
	Range	0–36	0–44	0–44
Number of days patient on more than two classes of sedative	Mean	1.3	1.4	1.4
	n	386	325	711
	SD	2.9	3.0	3.0
	Median	0	0	0
	Range	0–28	0–26	0–28
Number of days patient on more than three classes of sedative	Mean	0.1	0.2	0.1
	n	386	325	711
	SD	0.8	0.9	0.8
	Median	0	0	0
	Range	0–11	0–9	0–11

TABLE 73 Daily data (muscle relaxant use)

Muscle relaxant	Summary measure	Conventional ventilation	HFOV	Total
Number of days patient received muscle relaxant drugs to aid artificial ventilation	Mean	2.0	2.5	2.2
	n	386	325	711
	SD	3.0	3.6	3.3
	Median	1	1	1
	Range	0–22	0–25	0–25
Number of days an intravenous bolus dose use	Mean	0.5	0.6	0.5
	n	386	325	711
	SD	1.0	0.9	1.0
	Median	0	0	0
	Range	0–6	0–5	0–6
Number of days muscle relaxants given by infusion	Mean	1.6	2.0	1.8
	n	386	325	711
	SD	2.8	3.4	3.1
	Median	0	0	0
	Range	0–20	0–24	0–24

TABLE 74 Daily data (others)

Treatment	Summary measure	Conventional ventilation	HFOV	Total
Number of days patient been placed prone	Mean	0.5	0.2	0.3
	n	386	325	711
	SD	1.3	0.7	1.0
	Median	0	0	0
	Range	0–12	0–8	0–12
Number of days patient received inhaled nitric oxide	Mean	0.30	0.20	0.26
	n	386	325	711
	SD	1.9	0.9	1.5
	Median	0	0	0
	Range	0–23	0–12	0–23

TABLE 75 Statistical analysis of daily data in ICU data

Variable	Means estimates	Conventional ventilation (95% CI)	HFOV (95% CI)	Difference (95% CI)	*p*-value[a]
Ventilation-free days up to 30 days post randomisation	Unadjusted	2.30 (2.00 to 2.69)	2.80 (2.44 to 3.21)	0.50 (–0.04 to 1.00)	0.0696
	Adjusted	2.40 (1.91 to 2.86)	2.70 (2.23 to 3.24)	0.40 (–0.16 to 0.86)	0.1757
Advanced respiratory support-free days	Unadjusted	3.20 (2.71 to 3.65)	3.90 (2.25 to 4.57)	0.70 (–0.07 to 1.52)	0.0735
	Adjusted	3.10 (2.38 to 3.87)	3.80 (2.96 to 4.55)	0.60 (–0.17 to 1.43)	0.1226
Basic respiratory support-free days	Unadjusted	14.50 (13.15 to 15.91)	16.00 (14.40 to 17.67)	1.50 (–0.62 to 3.63)	0.1646
	Adjusted	13.60 (11.66 to 15.58)	15.00 (12.92 to 17.12)	1.40 (–0.71 to 3.52)	0.1937
Days on advanced cardiovascular support	Unadjusted	2.80 (2.25 to 3.39)	2.70 (2.40 to 3.14)	–0.10 (–0.85 to 0.63)	0.7635
	Adjusted	3.00 (2.31 to 3.62)	3.00 (2.33 to 3.73)	0.10 (–0.63 to 0.78)	0.8417
Days on basic cardiovascular support	Unadjusted	11.60 (10.58 to 12.70)	13.10 (11.78 to 13.11)	1.40 (–0.22 to 3.07)	0.0903
	Adjusted	11.20 (9.62 to 12.71)	12.40 (10.77 to 14.08)	1.30 (–0.41 to 2.93)	0.1378
Days on renal support	Unadjusted	2.60 (2.07 to 3.08)	4.50 (3.63 to 5.40)	1.90 (0.97 to 2.92)	0.0001
	Adjusted	2.20 (1.32 to 3.15)	4.20 (3.19 to 5.15)	1.90 (0.95 to 2.92)	0.0001
Days on gastrointestinal support	Unadjusted	15.90 (14.41 to 17.43)	17.70 (15.91 to 19.55)	1.80 (–0.53 to 4.14)	0.1286
	Adjusted	15.00 (12.86 to 17.21)	16.70 (14.40 to 19.06)	1.70 (–0.66 to 4.04)	0.1577
Days on dermatological support	Unadjusted	1.10 (0.53 to 1.61)	0.90 (0.42 to 1.34)	–0.20 (–0.91 to 0.53)	0.6054
	Adjusted	0.90 (0.24 to 1.58)	0.70 (–0.01 to 1.44)	–0.20 (–0.92 to 0.53)	0.5963
Days on liver support	Unadjusted	0.040 (–0.001–0.070)	0.020 (–0.001 to 0.030)	–0.02 (–0.06 to 0.02)	0.3423
	Adjusted	0.03 (–0.01 to 07)	0.01 (–0.03 to 0.05)	–0.02 (–0.06 to 0.02)	0.3562
Number of days free of antimicrobial use	Unadjusted	4.90 (4.06 to 5.70)	5.80 (4.86 to 6.81)	1.00 (–0.31 to 2.21)	0.1398
	Adjusted	4.40 (3.20 to 5.57)	5.40 (4.09 to 6.63)	1.00 (–0.29 to 2.26)	0.1314
Number of days free of drugs used primarily for sedation	Unadjusted	8.90 (7.68 to 10.22)	9.50 (7.86 to 11.08)	0.50 (–1.49 to 2.54)	0.6111
	Adjusted	7.80 (5.90 to 9.69)	8.20 (6.21 to 10.25)	0.40 (–1.60 to 2.47)	0.6737

a *p*-values: unadjusted analysis is based on comparison of the means only; the adjusted analysis is based on the analysis of covariance with adjustments made for centre, P : F ratio and sex of the patient.

Primary outcome

Table 76 illustrates the results for mortality at 30 days post randomisation. No statistically significant difference in mortality rates at 30 days post randomisation was found between the two interventions (chi-squared test: $p = 0.6053$). The absolute difference in mortality rates between the two interventions was 1.90% (95% CI –5.35% to 9.05%). No statistically significant difference in mortality rates at 30 days post randomisation was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (logistic regression: p-value = 0.8536). The odds of being alive (as opposed to dying) were 0.97 (95% CI 0.69 to 1.36) when on conventional ventilation compared with HFOV. *Figure 20* illustrates the Kaplan–Meier curve with the probability of survival up to 30 days post randomisation for each intervention. There is essentially no separation between the curves.

Secondary outcomes

Mortality rate at first discharge from intensive care unit/intensive care unit length of stay

The number (and percentage) of patients who died in ICU or were alive at discharge from ICU are summarised in *Table 77* by each intervention. Note that there are 710 patients in total with ICU data, as one patient was still in an ICU when the database was analysed. No statistically significant difference in mortality rates at first discharge from ICU was found between the two interventions (chi-squared test: $p = 0.9801$). The difference in mortality rates between the two interventions was 0.1% (95% CI –7.2% to 7.3%). For the survival analysis, patients who died up to first discharge from ICU were uncensored and all others (including the one patient in ICU) were uncensored. No statistically significant difference in mortality rates at first discharge from ICU was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (logistic regression: p-value = 0.7126). The odds of being alive (as opposed to dying) at first discharge from ICU were 1.07 (95% CI 0.76 to 1.49) when on conventional ventilation compared with HFOV.

Table 78 details the summary statistic for the length of stay in ICU (from randomisation to first discharge). No significant difference was found in the length of stay in ICU between the interventions. Using a linear regression model, and adjusting for centre, sex, P : F ratio and APACHE II score, the mean (SE) estimates were conventions: 15.4 (1.4) days; HFOV 17.4 (1.4) days and a difference of 2.3 (1.2) days: p-value for difference = 0.0643.

Figure 21 illustrates the Kaplan–Meier curve for the probability of survival in ICU against the number of days in ICU (with the number of patients at risk). The event here was mortality from randomisation to first discharge from ICU. Thus all patients who did not die in ICU and were discharged alive are censored (as their death date was beyond that of discharge from ICU date).

TABLE 76 Patient status at 30 days (primary outcome)

Status	Conventional ventilation	HFOV	Total
Alive	229 (59.3%)	199 (61.2%)	428 (60.2%)
Died	157 (40.7%)	126 (38.8%)	283 (39.8%)
Total	386	325	711

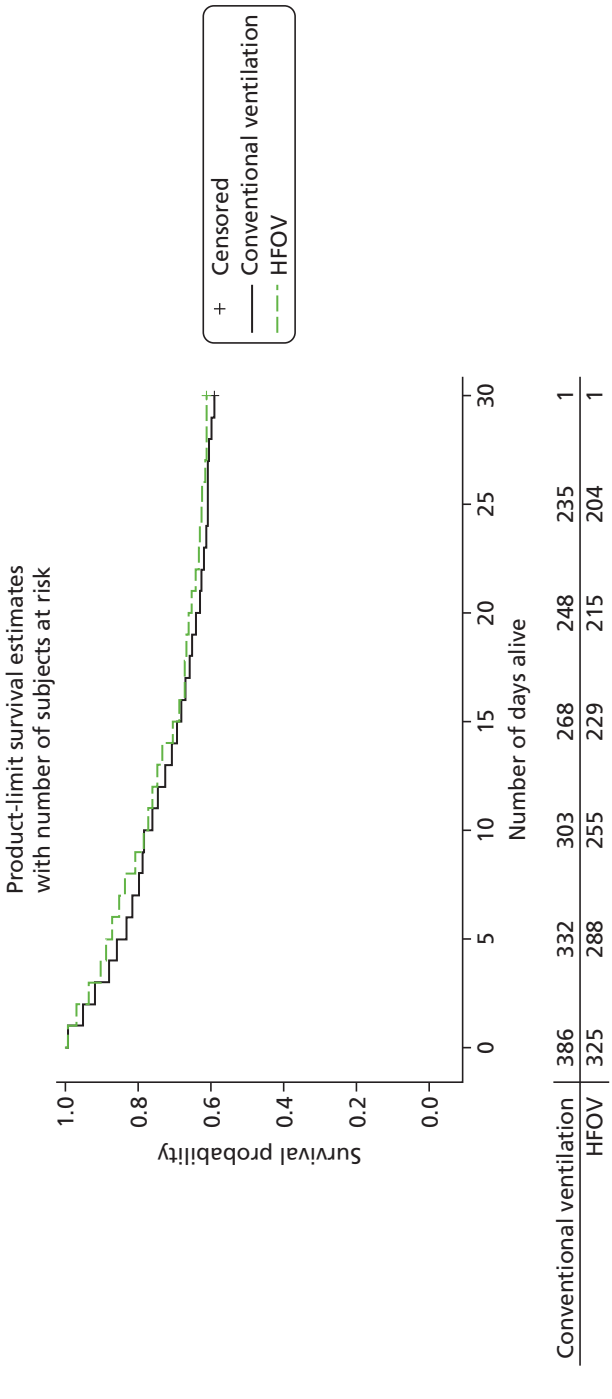


FIGURE 20 Kaplan–Meier curves for survival to day 30 post randomisation.

TABLE 77 Patient status at first discharge from ICU

Status	Conventional ventilation	HFOV	Total
Alive	226 (58.6%)	190 (58.6%)	416 (58.6%)
Died	160 (41.5%)	134 (41.4%)	294 (41.1%)
Total	386	324	710

TABLE 78 Summary statistics for the number of days from randomisation to first discharge from ICU

Summary measure	Conventional ventilation	HFOV	Total
Mean	16.0	18.1	16.9
n	386	324	710
SD	15.1	16.5	15.8
Median	12.0	13.5	13.0
Range	0–112	0–114	0–114

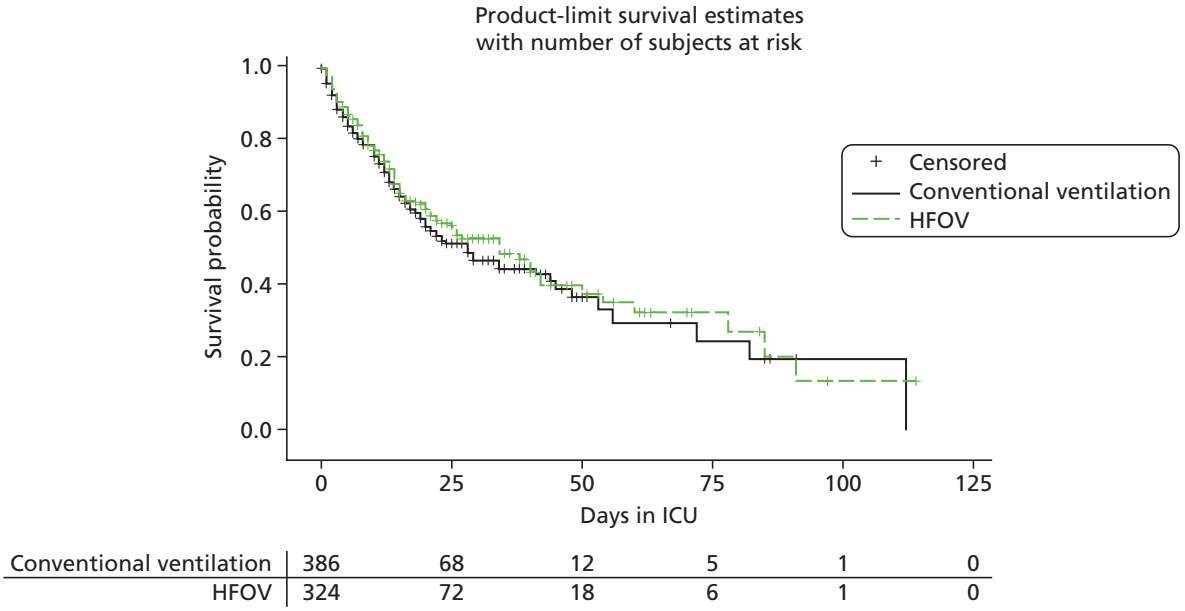


FIGURE 21 Kaplan–Meier curves for survival to first discharge from ICU mortality rate at first discharge from hospital/hospital length of stay.

The numbers (and percentage) of patients who died prior to hospital discharge or were alive at hospital discharge are summarised in *Table 79* by each intervention. Note that there are 706 patients in total with hospital data for the per protocol analysis. This is because, of the 795 randomised patients, two patients were in hospital and are also protocol violators. Thus, of the 711 patients, only five (not seven patients) would be excluded from the hospital stay data as these five have not reached end of hospital discharge.

No statistically significant difference in mortality rates at first discharge from hospital was found between the two interventions (chi-squared test: $p = 0.9641$). The difference in mortality rates between the two interventions was 0.2% (95% CI –7.2% to 7.5%). No statistically significant difference in mortality rates at first discharge from hospital was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (logistic regression: p-value = 0.5872). The odds of being alive (as opposed

TABLE 79 Patient status at first discharge from hospital

Status	Conventional ventilation	HFOV	Total
Alive	204 (51.7%)	196 (49.9%)	400 (50.8%)
Died	191 (48.4%)	197 (50.1%)	388 (49.2%)
Total	395	393	788

to dying) at first discharge from ICU were 1.10 (95% CI 0.79 to 1.53) when on conventional ventilation compared with HFOV.

Table 80 details the summary statistic for the length of stay in hospital (from randomisation to first discharge from hospital). No significant difference was found in the length of stay in hospital between the interventions. Using a linear regression model and adjusting for centre, sex, P : F ratio and the APACHE II score, the mean (SE) estimates were conventions: 31.1 (3.1) days; HFOV 33.6 (3.4) days and a difference of 2.5 (3.6) days: *p*-value for difference = 0.4563.

Figure 22 illustrates the Kaplan–Meier curve for the probability of survival in hospital against the number of days in hospital (with the number of patients at risk).

Mortality rate one year after randomisation

The number (and percentage) of patients who were alive/died 1 year after randomisation are summarised in *Table 81* by each intervention. An assumption that all those who have not reached 12-month follow-up are alive has been made for the survival analysis. The uncensored observations are all those who died prior to 12 months and the censored are all other subjects.

Allowing for the censoring, no statistically significant difference in mortality rates at 12 months post randomisation were found between the two interventions (log-rank test: $p = 0.5702$). The difference in mortality rates between the two interventions was 1.90% (95% CI –5.45% to 9.22%).

No statistically significant difference in mortality rates at 12 months post randomisation from hospital was found between the two interventions when adjusting for centre, sex, P : F ratio and APACHE II score (Cox's regression model: *p*-value = 0.6539). The odds of being alive (as opposed to dying) at 12 months post randomisation is 1.051 when on conventional ventilation compared with HFOV.

Figure 23 illustrates the Kaplan–Meier curve for the probability of survival up to 12 months post randomisation (with the number of patients at risk).

The results for the health economics analysis are given in *Chapter 5*.

TABLE 80 Number of days from randomisation to first discharge from hospital

Summary measure	Conventional ventilation	HFOV	Total
Mean	33.1	33.9	33.5
n	395	393	788
SD	44.3	41.6	43.0
Median	21	21	21
Range	0–584	0–280	0–584

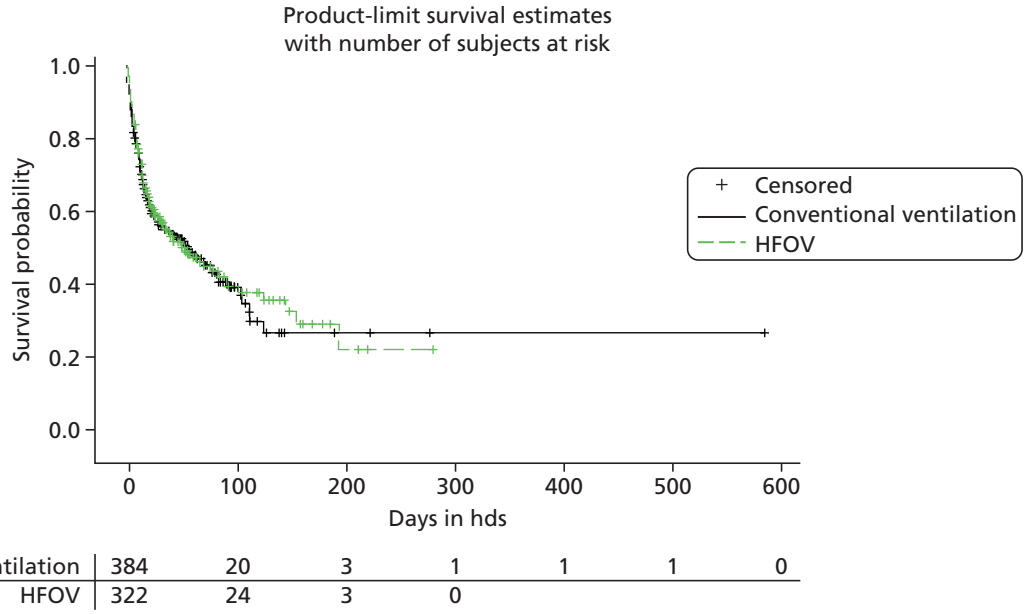


FIGURE 22 Kaplan–Meier curves displaying the probability of survival in hospital over the time in hospital for both interventions.

TABLE 81 Survival status 1 year after randomisation

Status	Conventional ventilation	HFOV	Total
Alive (or assumed alive)	191 (49.5%)	167 (51.4%)	358
Died	195 (50.2%)	158 (48.6%)	353
Total	386	325	711

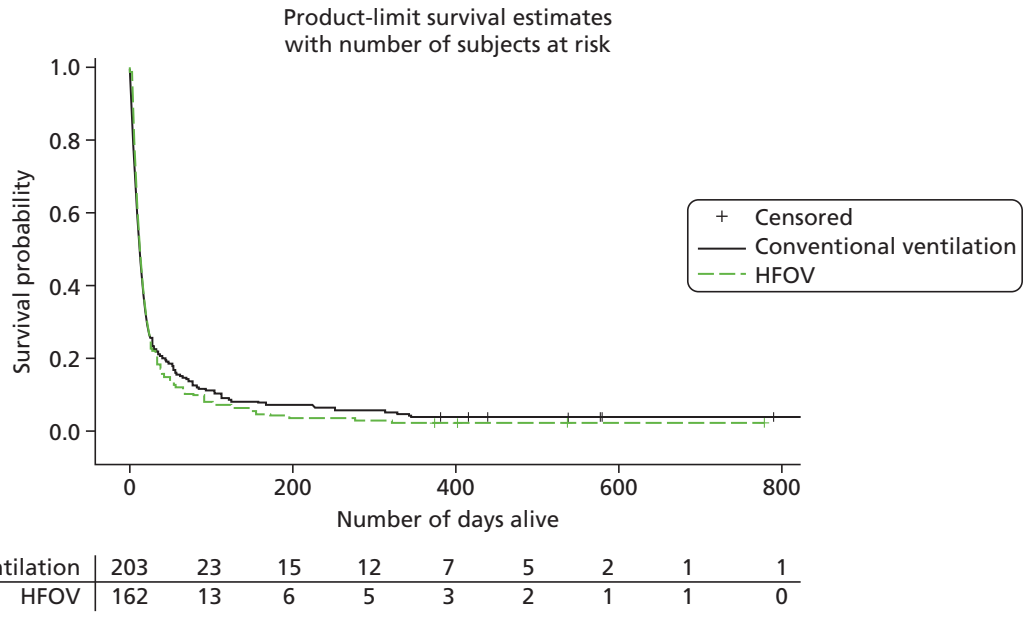


FIGURE 23 Kaplan–Meier curves displaying the probability of survival up to 12 months post randomisation for both interventions.

Chapter 5 OSCillation in ARDS trial economic analysis

Methods

The economic evaluation was carried out alongside the trial using recommended methods.[90] An additional model-based analysis was used to extrapolate the results over the expected lifetime of the trial participants. The perspective of the NHS and personal social services was undertaken for the main analysis with an additional analysis from a societal perspective. Other methods were in line with NICE Technology Appraisal Guidelines.[91]

The primary health economic outcome is the cost per QALY gained 1 year after randomisation. The primary outcome for the clinical analysis was mortality at 30 days and the economic analysis therefore also used cost per life saved at 30 days and cost per LY gained at 30 days. Cost analysis was undertaken to present costs at 30 days, costs at ICU discharge, costs at hospital discharge and costs over 1 year from randomisation.

Cost estimation

Resource use was collected during the trial and unit costs were assigned at the time of analysis. Patients were randomised after up to 7 days on ventilation and only resources used from the date of randomisation were included. These included the resources used on the initial ICU admission; the costs of subsequent ICU admissions were based solely on the number of days admitted to ICU (a per day cost). The cost post CU was based on the number of days on the step down ward until death or hospital discharge. If a patient was discharged to another hospital after ICU, the cost of transport was taken as that of an emergency transfer. SAEs were costed on an individual basis. After discharge, the resources used included the use of aids and devices, use of medical services including residential care, cost of travel for the patient and carers, loss of earnings and patient out of pocket expenses. *Tables 82–84* list the costs of resources used.

Measuring resources

During the patients' initial ICU stay, daily CRFs were completed by the medical and nursing staff. These included data on the organs supported and for the use of antibiotics, sedatives and muscle relaxants. The CRF was also used to collect data on discharge from the ICU and from hospital; death was recorded in the same CRF. The data collected at this stage included date and time of discharge from the ICU or death, where the patient was discharged to and whether or not discharge was to the same hospital. It contained information on readmissions to ICU, whether or not the patient required a chest drain or if there was any radiological evidence of barotrauma while on ICU.

Once discharged, questionnaires were sent to surviving patients and their carers at 6 and 12 months with follow-up questionnaires 1 month later if there was no response. The patient questionnaires contained questions relating to the cost for the patients themselves, and to the NHS, of aids and devices. Patients were asked about their use of medical services including residential inpatient stays, major expenses and their gross loss of earnings. The questionnaires also included the EQ-5D. The carers' questionnaires included questions regarding the cost of travel to and from medical services, major expenses and loss of earnings.

Estimating unit costs

Total costs per patient while in ICU were calculated on a daily basis using the individual unit costs per resource used and the sum per patient was calculated. The costs of medicines used were taken from the *British National Formulary* (BNF) 64.[93] The CRFs provided information on whether the patient had oral or

TABLE 82 Hospital inpatient costs

Resource used	Cost (£)	Reference
Number of organs supported in ICU		NHS Reference Costs 2011–12[92]
0	631.00	
1	868.00	
2	1223.00	
3	1401.00	
4	1586.00	
5	1745.00	
Renal replacement therapy	156.00	NHS Reference Costs 2011–12[92]
Chest X-ray (evidence for barotrauma)	30.00	NHS Reference Costs 2011–12[92]
Cost of pneumothorax	1773.00	NHS Reference Costs 2011–12[92]
Intravenous antibiotics (per dose)		BNF 2012[93]
Tazocin	42.63	
Ciprofloxacin	44.00	
Levofloxacin	50.20	
Antibiotics in renal failure (per dose)		BNF 2012[93]
Tazocin	28.42	
Ciprofloxacin	22.00	
Levofloxacin	12.60	
Oral antibiotics (per dose)		BNF 2012[93]
Augmentin	1.14	
Ciprofloxacin	0.14	
Levofloxacin	5.18	
Sedation (per dose)		BNF 2012[93]
Propofol (bolus)	0.73	
Propofol (infusion)	65.18	
Alfentanyl	25.00	
Midazolam	8.40	
Haloperidol	0.07	
Muscle relaxants (per dose)		BNF 2012[93]
Atracurium (infusion)	63.12	
Atracurium (bolus)	1.51	
Palliative care (per day)	113.00	NHS Reference Costs 2011–12[92]
Level 3 care (per day)	1476.07	NICE – Critical illness rehabilitation (CG83)[91]
Level 2 care (per day)	1476.07	NICE – Critical illness rehabilitation (CG83)[91]
Level 1 care (per day)	297.00	NHS Reference Costs 2011–12[92]
Emergency transport	261.35	PSSRU – Unit Costs of Health and Social Care 2011[94]
Rehabilitation (per day)	297.00	NHS Reference Costs 2011–12[92]
Nursing home (per day)	106.10	PSSRU – Unit Costs of Health and Social Care 2011[94]

All costs adjusted to base year 2012.

TABLE 83 Community-based resource costs

Resource used	Unit of measure	Cost (£)	Reference
Primary and community-based health and social services			
GP			PSSRU – Unit Costs of Health and Social Care 2011[94]
Surgery visit		37.19	
Telephone consultation		22.73	
Home visit		125.00	
Practice nurse	Per appointment	52.68	
District nurse			NHS Reference Costs 2011–12[92]
Face to face		38.00	
Telephone consultation		14.00	
Health visitor			NHS Reference Costs 2011–12[92]
Face to face		46.00	
Telephone consultation		21.00	
Social worker			PSSRU – Unit Costs of Health and Social Care 2011[94]
Face to face		219.00	
Telephone consultation		76.44	
Support worker			PSSRU – Unit Costs of Health and Social Care 2011[94]
Face to face		29.96	
Telephone consultation		24.79	
Addiction services			PSSRU – Unit Costs of Health and Social Care 2011[94]
Face to face		141.52	
Telephone consultation		48.55	
Physiotherapy	Per session	46.00	NHS Reference Costs 2011–12[92]
Occupational therapy	Per session	71.00	NHS Reference Costs 2011–12[92]
Dietitian	Per session	71.00	NHS Reference Costs 2011–12[92]
Phlebotomy	Per visit	3.00	NHS Reference Costs 2011–12[92]
Home help	Per session	22.73	PSSRU – Unit Costs of Health and Social Care 2011[94]
NHS walk-in centre	Per visit	42.35	PSSRU – Unit Costs of Health and Social Care 2011[94]
NHS Direct	Per call	8.00	NHS Reference Costs 2011–12[92]
Meals on wheels	Per day	25.83	PSSRU – Unit Costs of Health and Social Care 2011[94]
Family support	Per session	27.89	PSSRU – Unit Costs of Health and Social Care 2011[94]
Respite care	Per day	68.00	NHS Reference Costs 2011–12[92]
Tuberculosis specialist nurse	Per appointment	60.00	NHS Reference Costs 2011–12[92]
Palliative care specialist nurse	Per appointment	86.00	NHS Reference Costs 2011–12[92]
Stoma care nurse	Per appointment	43.00	NHS Reference Costs 2011–12[92]
Critical care nurse	Per appointment	86.00	NHS Reference Costs 2011–12[92]

continued

TABLE 83 Community-based resource costs (*continued*)

Resource used	Unit of measure	Cost (£)	Reference
Upper GI specialist nurse	Per appointment	86.00	NHS Reference Costs 2011–12[92]
Rapid response team	Per appointment	36.16	NHS Reference Costs 2011–12[92]
Cardiology nurse specialist	Per appointment	73.00	NHS Reference Costs 2011–12[92]
Macmillan nurse specialist	Per appointment	66.00	NHS Reference Costs 2011–12[92]
Magnetic resonance imaging	Per scan	145.00	NHS Reference Costs 2011–12[92]
Hospital and residential care services			
Hospital inpatient stay	Per day	297.00	NHS Reference Costs 2011–12[92]
Hospital day centre	Per day	148.00	NHS Reference Costs 2011–12[92]
Hospital outpatient clinic	Per appointment	150.00	NHS Reference Costs 2011–12[92]
Psychiatry	Per appointment	136.36	NHS Reference Costs 2011–12[92]
Respiratory outpatients clinic	Per appointment	143.00	NHS Reference Costs 2011–12[92]
Nephrology outpatients clinic	Per appointment	164.00	NHS Reference Costs 2011–12[92]
Diabetic outpatients clinic	Per appointment	130.00	NHS Reference Costs 2011–12[92]
Stoma outpatients clinic	Per appointment	105.00	NHS Reference Costs 2011–12[92]
Pain management	Per appointment	125.00	NHS Reference Costs 2011–12[92]
Hospital A&E visit	Per visit	151.85	PSSRU – Unit Costs of Health and Social Care 2011[94]
Local authority day centre	Per day	37.19	PSSRU – Unit Costs of Health and Social Care 2011[94]
Residential care home	Per day	148.31	PSSRU – Unit Costs of Health and Social Care 2011[94]
Rehabilitation centre	Per day	98.87	PSSRU – Unit Costs of Health and Social Care 2011[94]
Warden controlled residence	Per day	61.68	PSSRU – Unit Costs of Health and Social Care 2011[94]

A&E, accident and emergency; GI, gastrointestinal; GP, general practitioner.
All costs adjusted to base year 2012.

TABLE 84 Aids, equipment and travel resource costs

Resource used	Cost (£)	Reference
Commode	81.70	NHS supply chain[95]
Mowbray frame	21.49	
Combiframe	27.37	
Free-standing toilet frame	27.37	
Raised toilet seat	27.81	
Urine bottle	14.79	
Bed pan	27.11	
Chair raisers	83.21	
Bed sitting support	144.74	
Bed leaver/grab rail	94.00	
Transfer board	190.00	
Banana board	58.72	
Slide sheet	3.96	
Walking frame	17.34	
Mobilator	91.67	
Walking frame with wheels	70.79	
Walking stick	4.02	
Quad stick	11.82	
Perching stool	28.80	
Leg lifter	5.81	
Bottom wipers	25.28	
Buckingham caddy	24.71	
Hospital bed	348.15	
Petrol	0.45	HMRC[96]

All costs adjusted to base year 2012.

intravenous antibiotics and whether these were for sepsis relating to the lung or another source. The choice of antibiotic was not standardised across centres and therefore the costs had to be estimated, and for this we took those antibiotics that are recommended by the British Thoracic Society guidelines for the treatment of community-acquired pneumonia[97] and the Scottish Intercollegiate Guidelines Network guidelines for the management of suspected bacterial urinary tract infections in adults.[98] For sepsis secondary to a pulmonary source we used co-amoxiclav orally, with piperacillin and tazobactam if given intravenously. Despite pneumonia being both the leading cause of sepsis leading to ICU admission[99] and sepsis causing ARDS,[100] urinary tract infection (UTI) remains the most prevalent bacterial infection in hospitals and in the community with a high incidence in the critically ill.[101–104] We therefore assumed that the majority of patients requiring antibiotics for an extrapulmonary cause would be due to a UTI and used the cost for ciprofloxacin either orally or intravenously (based on the CRF) in this cohort.

In the case of penicillin allergy we were not provided with patient-specific information. Patient self-reported rates for penicillin allergy can be as high as 15% with 10% a generally accepted figure,[105–108] with true rates of penicillin allergy likely to be much lower.[105,106,109] We therefore used the cost of levofloxacin either orally or intravenously for 10% of patients who required antibiotics. The unit costs per

medication are provided in *Table 83*. For patients on dialysis, we adjusted the costs accordingly in those antibiotics which are renally excreted. The costs of ICU resources including radiology and the cost of pneumothorax were taken from the National Schedule of Reference Costs.[92]

The added cost of the HFOV machine was calculated based on the cost of the Novalung Vision Alpha High-frequency Oscillator. The difference in price between the HFOV and conventional ventilation machines was calculated based on the machines being used for 5 years with annual maintenance. The costs of single-use circuits for were also included for each patient. The purchase cost of the Novalung Vision Alpha High-frequency Oscillator was £45,000, with an annual maintenance cost of £840. A single-use circuit was £400. The price for conventional ventilation was a Covidien (Puritan Bennett/Tyco) Ventilator (Covidien plc, Mansfield, MA) at £23,000 with an annual maintenance cost of £1300 and a single-use circuit per patient of £100. Once patients were discharged from ICU, the cost of step down was calculated using the number of days until death or discharge multiplied by the cost of the level of care required. The costs for the step down care were taken from various nationally available references.[92,94,110]

Once discharged from hospital, the costs of attendance at medical services were calculated using national reference costs multiplied by the number of times a patient attended. Inpatient stays were based on the number of days admitted multiplied by the cost for each resource taken from the unit costs of health and social care.[94] The questionnaire sent to each patient at 6 and 12 months provided a list of individual aids or devices available to them. If a patient used one of these but did not pay for it, the cost was taken from the NHS supply chain cost for each individual item.[95] If a patient bought an item themselves, then the actual cost provided by the patient in the questionnaire was used. The cost of travel for both carers and patients was based on the distance in miles provided in the questionnaires multiplied by the cost per petrol mile as provided by Her Majesty's Revenue and Customs (HMRC).[96] Patients and carers were asked to give the gross amount lost in earnings in the 6 months covered by each questionnaire. Patients who had died at the 6- and 12-month time points were considered to have incurred no costs and were included in all calculations.

All costs were adjusted to 2012 prices using the Hospital and Community Healthcare Services (HCHS) Index published by Personal Social Services Research Unit (PSSRU).[94]

Quality of life

The quality-adjusted survival was estimated from the Kaplan–Meier survival function to 1 year from randomisation and the questionnaires sent to patients at 6 and 12 months, which contained the EQ-5D questionnaire. For the time that patients were intubated until extubation, their scores were taken as those for an unconscious patient (–0.40) reported in the EQ-5D scoring manual.[65] From the day following successful weaning from ventilation to day 240, the QoL score was measured using the mean EQ-5D score from the patient questionnaires sent out at the 6 month period. As patients only fill in the EQ-5D questionnaires at 6-monthly intervals, we used the 6-month questionnaires to day 240 in order to reflect the fact that patients QoL is unlikely to change immediately after completing the 6-month questionnaire to the score on the 12-month questionnaire. From day 241 to 1 year, the score was taken as the mean EQ-5D from the 12-month questionnaires. The mean QALYs per patient were estimated by multiplying the EQ-5D score by the area under the survival curve to 1 year from randomisation.[65,111]

Analysis and reporting

The cost for each patient was calculated using the unit cost of each resource used as described above. The costs and QALYs are presented as means with 95% CIs calculated by bootstrapping.[112] All costs are presented as the mean cost per patient. The cost-effectiveness acceptability curve (CEAC) and the cost-effectiveness acceptability plane were generated following the recommendations of Briggs and Fenn.[113] Mean costs from the 6- and 12-month questionnaires were calculated separately with the means from each time point being summed to provide an estimate of mean costs to 1 year post discharge.

Cost-effectiveness outcome measures are:

1. 30-day cost per life saved (NHS perspective)
2. 30-day cost per LY (NHS perspective)
3. 1-year cost per QALY (NHS and societal perspectives).

To assess cost-effectiveness over the lifetime horizon a Markov model was constructed[114] (*Figure 24*). The parameters for the model, and their sources, are listed in *Table 85*. The long-term survival of patients following discharge from ICU has been shown to be lower than that of the general population.[115] For years 2 to 9 post randomisation, we therefore used the relative survival rates from an observational study of long-term survival following ICU discharge in an Australian population.[115] This study presented relative survival data for four subsets: hospitalised patients with either sepsis or not and ICU patients with sepsis or no evidence of sepsis; each of these was presented separately by sex. Only the data for the ICU patient subsets were used. If an OSCAR patient required antibiotics at any point during their ICU stay, they were included in the septic cohort of ICU survivors. The relative survival effects from this study, weighted by the proportion of each subgroup in OSCAR were then applied to age and sex matched UK population reference mortality published by the ONS.[116] From year 10 onwards, as there are no data available for the

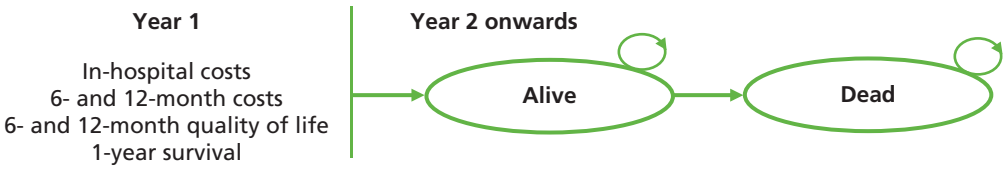


FIGURE 24 Markov model. Year 1 – data from study.

TABLE 85 Markov model parameters

Parameters		Conventional ventilation	HFOV	Reference
Year 0–1				
Mean LYs saved		0.5578547	0.5232611	Trial data
Mean QALY		0.2456425	0.3021253	Trial data
Mortality		0.5113	0.5101	Trial data
Cost (£)		40,129.87	44,550.26	Trial data
Year 2 onwards				
Mortality rate	*Year*	*Age- and sex-matched norms*		ONS[116]
Relative survival	2	0.864665	0.864665	Ghelani *et al.*[115] and ONS[116]
	3	0.950213	0.950213	
	4	0.981684	0.981684	
	5	0.993262	0.993262	
	6	0.997521	0.997521	
	7	0.999088	0.999088	
	8	0.999665	0.999665	
	9	0.999877	0.999877	
	> 9	Unadjusted		
Utility		Age- and sex-matched norms		

survival of patients post ICU, unadjusted age- and sex-matched mortality rates were therefore used. With limited data on the long-term effects on EQ-5D scores following ARDS, the age and sex matched EQ-5D norms for the UK general population for the QoL weight were used from 1 year post randomisation onwards[117] (see *Table 88*).

Missing data

Analysis of the 6- and 12-month questionnaires used complete case analysis for costs and QoL. Mean values for QoL and cost were calculated separately from returned questionnaires at the 6- and 12-month time points. A sensitivity analysis was conducted using multiple imputations (chained equation method) for missing questionnaire-derived costs and utility values at 6 and 12 months.[118]

Results

There were 795 patients randomised, although 3 died prior to initiation of treatment and were excluded from the analysis (*Table 86*). Data for inpatient resources were therefore collected on 792 patients: 397 in the conventional ventilation group and 398 in the HFOV group. Once discharged, a total of 226 patients completed the 6-month questionnaires: 116 in the conventional ventilation group and 110 in the HFOV group. One hundred and eighty-six patients completed the 12-month questionnaires; 89 in the conventional ventilation group and 97 in the HFOV group. One hundred and fifty-six patients completed both the 6- and the 12-month questionnaires, with 78 in each group. One hundred and fifty-four carers completed the 6-month questionnaires with 79 in the conventional ventilation group and 75 in the HFOV group. At 12 months, 108 carers had completed the questionnaires with 53 in the conventional ventilation group versus 55 in the HFOV group. A total of 76 carers completed both the 6- and 12-month questionnaires with 38 in each group.

Cost analysis 1 – NHS and personal social services perspective

Thirty-day costs

The primary end point for costs was 30-day costs (*Table 87*). The total cost for patients in the HFOV group at 30 days is more expensive at £30,889.30 compared with £29,064.00 in the conventional ventilation group with an incremental cost of £1825.30. At 30 days, the cost of the initial ICU admission was more expensive for those patients on HFOV at £27,769.47 versus £25,279.65 giving an incremental cost of £2489.83. Even without accounting for the higher cost of the HFOV machine compared with conventional ventilation, it was more expensive in the HFOV group. Total cost for the first 30 days without the cost of

TABLE 86 Number of data sets completed

Data source	Number of complete data sets	Number of complete data sets	Number of complete data sets
Inpatient data sheets	795[a]	397	398
Patient questionnaire at 6 months	226	116	110
Patient questionnaire at 12 months	186	89	97
Patient questionnaire at both 6 and 12 months	156	78	78
Carer questionnaire at 6 months	154	79	75
Carer questionnaire at 12 months	108	53	55
Carer questionnaire at both 6 and 12 months	76	38	38

a Three patients died prior to treatment.

TABLE 87 30-day costs

Arm	Mean (£)	Lower CI 95% (£)	Upper CI 95% (£)
Total cost to day 30			
Conventional ventilation	29,064.00	27,280.62	30,780.85
HFOV	30,889.30	29,069.11	33,999.24
Incremental cost	1825.30	–1006.24	4818.91
Cost of initial ICU admission to day 30			
Conventional ventilation	25,279.65	23,183.81	27,490.50
HFOV	27,769.47	25,412.51	30,228.39
Incremental cost	2489.82	–749.90	5728.20
Cost of initial ICU admission excluding the cost of HFOV equipment to day 30			
Conventional ventilation	25,279.65	23,183.23	27,491.39
HFOV	27,327.58	24,957.11	29,809.61
Incremental cost	2047.92	–1197.91	5288.84
Cost of ICU readmissions to day 30			
Conventional ventilation	6642.33	738.04	14,760.74
HFOV	6425.26	2604.84	10,766.66
Incremental cost	–217.07	–8639.38	7380.37
Post-ICU costs to day 30			
Conventional ventilation	3784.35	3216.28	4203.94
HFOV	3119.83	2641.66	3588.74
Incremental cost	–664.51	–1246.51	–251.42

the HFOV machines was £27,327.58 versus £25,279.65 in the conventional ventilation group with an incremental cost of £2047.92.

The cost of readmission to ICU was marginally more expensive in the conventional ventilation group, but patients in the HFOV were more than twice as likely to be readmitted to the ICU. In total there were 22 patients readmitted once (7 in the conventional ventilation group and 15 in the HFOV group), and 3 patients readmitted twice (1 in the conventional ventilation group compared with 2 in the HFOV group). The cost of readmission to ICU up to day 30 in the conventional ventilation group was £6642.33 compared with £6425.26 giving an incremental cost of –£217.07.

The cost post ICU was also marginally more expensive in the conventional ventilation group at a cost of £3784.35 versus £3119.83 in the HFOV group. This gives an incremental cost of –£664.51.

Total NHS and Personal Social Services costs to 1 year following discharge

The total NHS and Personal Social Services (PSS) costs to 1 year were dominated by the NHS cost during the patients ICU stay.

Total cost to the NHS over 1 year

At 1 year following randomisation, the total cost to the NHS including inpatient stay and resources used following discharge was higher in the HFOV group at £44,550.26 compared with £40,129.87 in those patients on conventional ventilation. This gives an incremental cost of £4420.39 (*Table 88*).

TABLE 88 Costs to the NHS and PSS at 1 year post randomisation

Arm	Mean (£)	Lower CI 95% (£)	Upper CI 95% (£)
Total cost to the NHS over 1 year			
Conventional ventilation	40,129.87	36,489.31	43,960.34
HFOV	44,550.26	40,375.16	48,989.02
Incremental cost	4420.39	–2044.65	9239.74
Total cost of inpatient stay			
Conventional ventilation	36,101.77	32,913.81	39,919.86
HFOV	38,997.20	34,742.45	43,620.86
Incremental cost	2895.43	–2732.54	8508.93
Cost of initial ICU admission			
Conventional ventilation	25,279.65	23,183.81	27,490.50
HFOV	27,769.47	25,412.51	30,228.39
Incremental cost	2489.82	–749.90	5728.20
Total cost of initial ICU admission excluding the cost of HFOV equipment			
Conventional ventilation	25,279.65	23,183.23	27,491.39
HFOV	27,327.58	24,957.11	29,809.61
Incremental cost	2047.92	–1197.91	5288.84
Cost of readmission to ICU			
Conventional ventilation	19,557.99	5904.30	36,901.86
HFOV	17,018.27	10,766.66	23,790.85
Incremental cost	–2539.72	–21,186.01	12,893.94
Total cost post ICU			
Conventional ventilation	10,822.12	8798.29	13,250.11
HFOV	11,227.73	8504.71	14,347.87
Incremental cost	405.61	–3076.64	4141.05

Total cost of inpatient stay

When looking at the total cost of a patient's inpatient stay, similar results are found. With all inpatient resources considered, the total cost for patients in the HFOV group comes to £38,997.20 compared with £36,101.77 for patients in the conventional ventilation group with an incremental cost of £2895.43. The initial ICU admission was more expensive for patients in the HFOV group at £27,769.47 versus £25,279.65 in the conventional ventilation group, with an incremental cost of £2489.82. If the added cost of HFOV is removed, the initial ICU admission still remains more expensive for those patients in the HFOV group of the trial at £27,327.58 compared with £25,279.58 in the conventional ventilation group, with an incremental cost of £2047.92. If a patient required readmission to ICU (numbers are the same as in the 30 day analysis) then the cost in the conventional ventilation group was markedly higher than those patients in the HFOV group at £19,557.99 and £17,018.72, respectively, with an incremental cost of –£2539.72. Even with the increased cost of readmission to ICU in the HFOV group, when the total cost for a patient post ICU is considered, it is still marginally more expensive in the HFOV group at £11,227.73 compared with £10,822.12 giving an incremental cost of £405.61.

Cost analysis 2 – societal perspective

Total cost to society over 1 year

Taking into consideration the cost to the NHS, patient and carers out-of-pocket expenses and the loss of earnings over 1 year post randomisation, the total cost to society was higher in the HFOV group at £50,583.31 compared with £45,568.12 with an incremental cost of £5015.19 (*Table 89*).

Patient out-of-pocket expenses

Once patients were discharged, we estimated the cost to the patient over the first year post randomisation based on the questionnaires. In the conventional ventilation group, patients on average had to spend £183.64 of their own money; this included travel to and from medical services and the cost of aids and devices that they paid for themselves. In the HFOV group, this was lower at £54.83 giving an incremental cost of –£128.81.

Total cost for carers 1 year post randomisation

At 1 year post randomisation there was a slightly higher cost to the carers of patients in the HFOV group at £1100.25 compared with £926.71 with an incremental cost of £173.54.

TABLE 89 Cost analysis 2 – cost to society at 1 year post randomisation

Arm	Mean (£)	Lower CI 95% (£)	Upper CI 95% (£)
Total cost to society over 12 months			
Conventional ventilation	45,568.12	41,610.63	49,805.00
HFOV	50,583.31	44,427.88	54,057.85
Incremental cost	5015.19	–2985.68	9817.05
Patient out-of-pocket expenses			
Conventional ventilation	183.64	64.57	356.52
HFOV	54.83	19.39	104.63
Incremental	–128.81	–306.39	0.87
Total cost for carers to 1 year post randomisation			
Conventional ventilation	926.71	500.76	1454.80
HFOV	1100.25	596.43	1705.79
Incremental	173.54	–561.09	924.85
Loss of earnings for patients			
Conventional ventilation	4576.81	3500.92	5730.82
HFOV	2993.74	1981.37	4143.27
Incremental	–1583.08	–3117.80	–8.30
Loss of earnings for carers			
Conventional ventilation	516.68	310.18	768.28
HFOV	758.64	460.97	1108.09
Incremental	241.96	–148.20	648.29
Total loss of earnings for patients and carers			
Conventional ventilation	5093.49	3988.15	6278.49
HFOV	3752.37	2689.52	4937.84
Incremental	–1341.12	–2926.31	282.55

Loss of earnings

Following discharge, patients in the conventional ventilation group have a higher loss of earnings at 1 year post randomisation at £4576.81 compared with £2993.74 in the HFOV group with an incremental cost of –£1583.08.

For carers, there was a slightly higher loss of earnings in the HFOV group; in this group the carers lost £758.64 over the course of the year compared with £516.68 in the conventional ventilation group, giving an incremental cost of £241.96. The total loss of earnings over the first year following randomisation is therefore £5093.49 in the conventional ventilation group and £3752.37 in the HFOV group with an incremental cost of –£1341.12.

Cost-effectiveness

30-day cost-effectiveness

At 30 days, the incremental lives saved is –0.0041 (*Table 90*) and with an incremental cost of £1825.30, the incremental cost-effectiveness ratio (ICER) is –£445,195.12 (see *Table 94*). The incremental cost per life saved at 1 year for HFOV is therefore –£47,487,837.

Figure 25 is a scatterplot of incremental costs versus number of lives saved at 30 days showing a right and left upper quadrant distribution, indicating that HFOV is more expensive than conventional ventilation.

TABLE 90 Incremental lives-saved at 30 days

Arm	Lives saved at day 30	Cost (£)	ICER
Conventional ventilation	0.4106	28,923.87	
HFOV	0.4065	30,613.80	
Incremental	–0.0041	1825.30	Conventional ventilation dominates HFOV

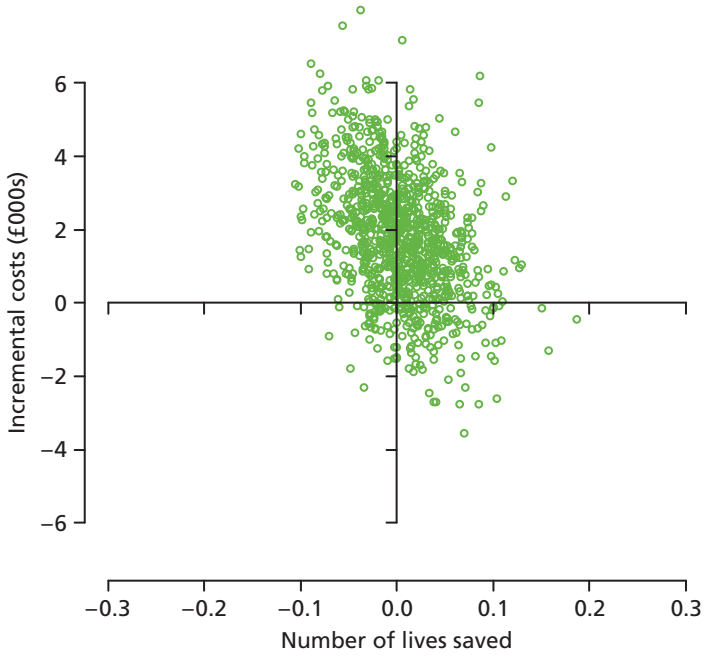


FIGURE 25 Incremental costs vs. lives saved at 30 days.

Cost-effectiveness at 1 year

At 1 year, the cost to both the NHS and to society is more in the HFOV group of the trial at £40,129.87 and £45,568.12, respectively, with an incremental cost of £4420.39 and £5015.14, respectively. There was however a higher QALY at 1 year in the HFOV group at 0.302 compared with those patients in the conventional ventilation group at 0.246 with an incremental QALY of 0.056. This gives an ICER for the cost to society per QALY of £88,790.57 and an ICER for the cost to the NHS per QALY of £78,260.82.

Figures 26 and *27* show scatterplot diagrams for the incremental cost to the NHS and to society per QALY respectively, with the diagonal at the threshold of £20,000 per QALY. Both show a right upper quadrant dominant pattern with the majority above the diagonal.

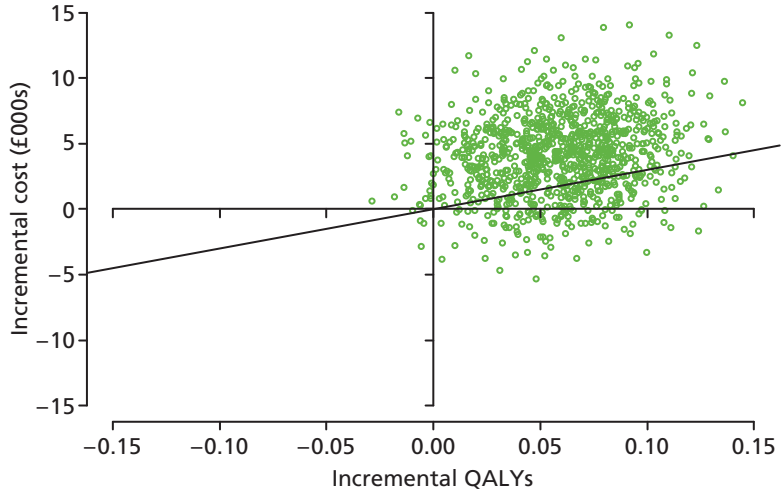


FIGURE 26 Cost-effectiveness plane for the incremental cost to the NHS per QALY with the diagonal at the threshold of £20,000 per QALY. Right upper quadrant dominant pattern.

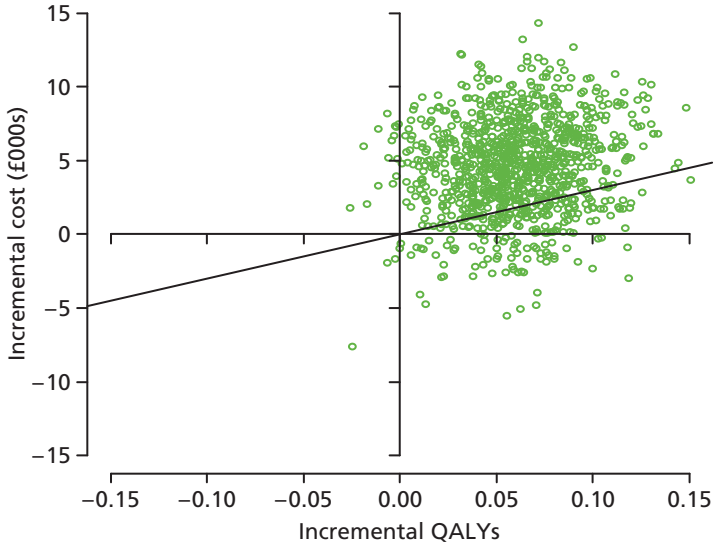


FIGURE 27 Cost-effectiveness plane for the incremental cost to society per QALY, again with the diagonal at the threshold of £20,000 per QALY. Right upper quadrant dominant pattern.

Figures 28 and *29* show the CEAC for the cost to the NHS and to society, respectively.

There were 0.558 LYs saved in the conventional ventilation group compared with the 0.523 in the HFOV group of the trial. This gives an incremental LYs saved of –0.035. The cost to society per LY saved is therefore –£144,973.06 and the cost to the NHS per LY saved is –£127,780.57 (*Table 91*).

Lifetime cost-effectiveness

The cost-effectiveness extrapolated to the lifetime time horizon using the Markov model gives the mean LYs per patient for the conventional ventilation group as 8.27 compared with the HFOV group whose mean LYs per patient was 8.39. The mean QALY is slightly higher in the HFOV group at 6.60 compared with 6.21 and it remains more expensive at £44,550.26 versus £40,129.87 in the conventional ventilation group. This results in an ICER of £11,334 per QALY (*Table 92*).

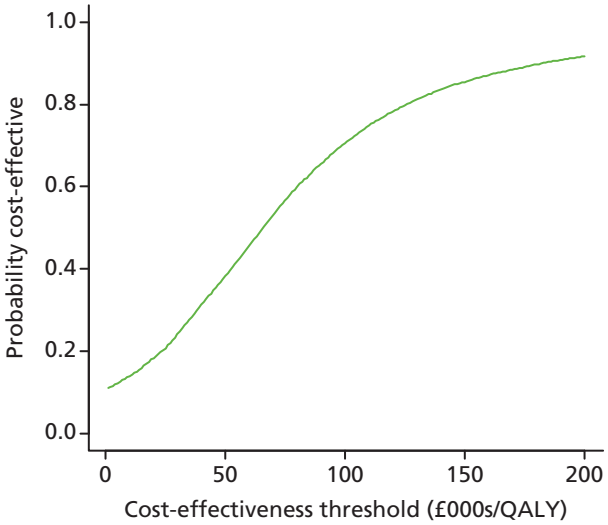


FIGURE 28 Cost-effectiveness acceptability curve for the cost to the NHS.

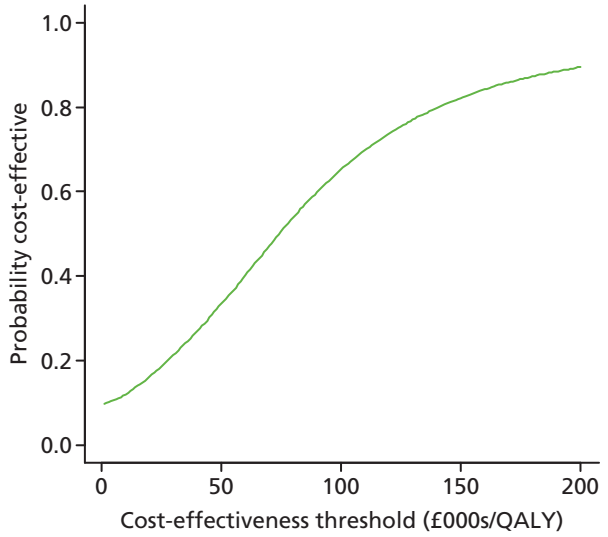


FIGURE 29 Cost-effectiveness acceptability curve for the cost to society.

TABLE 91 Cost to society and the NHS at 1 year, cost per LY, QALYs, ICERs and imputation results

Costs	Conventional ventilation	HFOV	Incremental
Societal costs (95% CI)	£45,568.12 (£41,811.72 to £49,805.00)	£50,583.31 (£44,427.88 to £54,057.85)	£5015.14 (–£2985.68 to £9817.05)
Cost to NHS (95% CI)	£40,129.87 (£36,679.95 to £43,869.53)	£44,550.26 (£40,375.16 to £48,989.02)	£4420.39 (–£2044.65 to £9239.74)
LYs (95% CI)	0.5578547 (0.5253814 to 0.5861216)	0.5232611 (0.4849942 to 0.5481074)	–0.0345936 (–0.0403872 to –0.0380142)
QALYs (95% CI)	0.2456425 (0.2242694 to 0.2668142)	0.3021253 (0.2819215 to 0.3184306)	0.0564828 (0.0576521 to 0.0516164)
ICER			
Cost to society/LY	–	–	Conventional ventilation dominates HFOV
Cost to society/QALY	–	–	£88,790.57
Probability of cost-effectiveness at £20,000/QALY			0.1632
Probability of cost-effectiveness at £30,000/QALY			0.2130
Cost to NHS/LY	–	–	Conventional ventilation dominates HFOV
Cost to NHS/QALY	–	–	£78,260.82
Probability of cost-effectiveness at £20,000/QALY			0.1837
Probability of cost-effectiveness at £30,000/QALY			0.2415
Imputation			
Societal costs (95% CI)	£39,553.67 (£35,964.98 to £43,419.66)	£43,445.121 (£38,832.11 to £48,317.78)	£3878.31 (–£2360.46 to £9713.41)
LYs (95% CI)	0.5508081 (0.5050072 to 0.5988424)	0.5472963 (0.5003348 to 0.5944412)	–0.0035118 (–0.0691065 to 0.0608372)
QALYs (95% CI)	0.1874296 (0.1609454 to 0.2190520)	0.2010838 (0.1723002 to 0.2334543)	0.0136542 (–0.0295872 to 0.0515767)
Cost to society/LY	–	–	Conventional ventilation dominates HFOV
Cost to society/QALY	–	–	£284,037.88
Probability of cost-effectiveness at £20,000/QALY			0.2357
Probability of cost-effectiveness at £30,000/QALY			0.2605

TABLE 92 Lifetime mean LYs saved, mean QALYs and mean costs from the Markov model

Arm	Mean LYs saved	Mean QALY	Mean cost (£)	ICER (£)
Conventional ventilation	8.27	6.21	40,129.87	–
HFOV	8.39	6.60	44,550.26	–
Incremental	–	0.39	4420.39	11,334.33

Sensitivity analysis

Thirty-day sensitivity analysis

The sensitivity analysis for the cost to the NHS by day is shown in *Table 93* and graphically in *Figures 30* and *31* as tornado charts.

TABLE 93 Sensitivity analysis for the cost to the NHS at day 30. Mean incremental cost is £1825.30. Incremental lives saved –0.0041. Mean ICER –£445,195.12

	Cost to NHS at day 30 (£)		ICER (£)	
Variable	25th centile	75th centile	25th centile	75th centile
Cost of initial ICU stay (IQR)	–10,232.04	11,748.69	2,495,619.51	–2,865,534.15[a]
Cost of renal replacement therapy (IQR)	–4200.15	6132.37	1,024,426.10	–1,495,700.73[a]
Cost of readmission to ICU (IQR)	–3696.57	6635.95	901,602.44	–1,618,524.63[a]
Cost of hospital stay following discharge from ICU (IQR)	488.80	3161.80	–119,220.10[a]	–771,171.22[a]
Cost of number of organs supported (2–3)	23.21	2399.53	–5659.87[a]	–585,250.73[a]
Cost of HFOV (no extra cost – +£1000 per patient)	1270.71	2270.71	–309,929.49[a]	–553,831.93[a]

IQR, interquartile range.
a Conventional ventilation dominates HFOV.

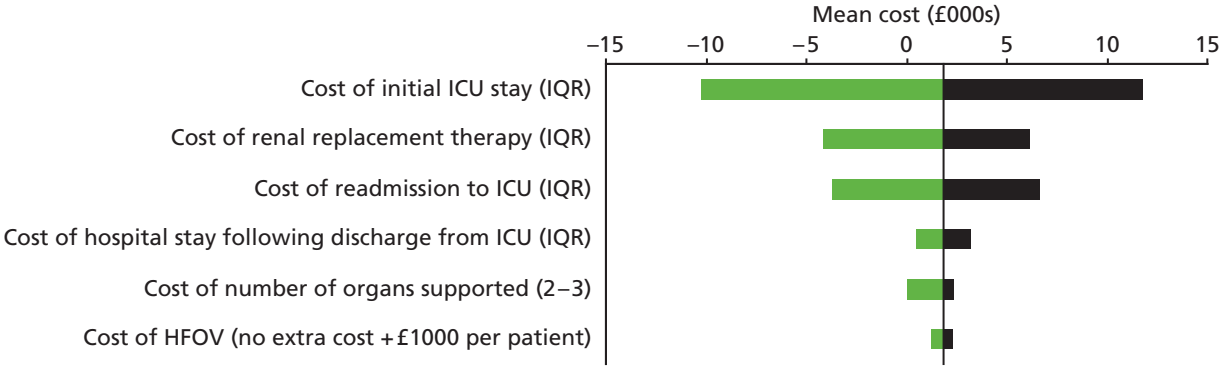


FIGURE 30 Tornado chart for sensitivity analysis of cost to the NHS to day 30: mean cost.

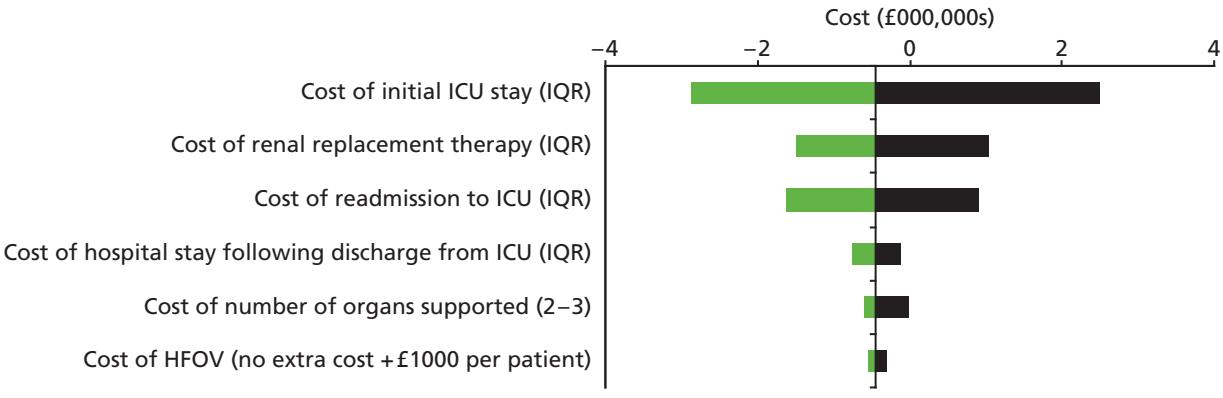


FIGURE 31 Tornado chart for sensitivity analysis of cost to the NHS to day 30: ICER.

One-year sensitivity analysis

Table 94 shows the sensitivity analysis for the cost per patient to the NHS out to 1 year. *Figure 32* shows the associated tornado chart for mean cost and *Figure 33* shows the tornado plot for the ICER.

TABLE 94 Sensitivity analysis for the cost to the NHS at 1 year. Mean incremental cost is £4420.39. Mean incremental QALY is 0.0564828. Mean incremental cost per QALY is £78,260.82

	Cost to NHS at 1 year (£)		ICER (£)	
Variable	25th centile	75th centile	25th centile	75th centile
Cost of hospital stay (IQR)	–11,254.40	20,095.07	199,253.58	355,773.26
Cost following discharge from hospital (IQR)	2281.73	6558.94	40,396.81	116,122.82
Use of primary- and community-based health and social services (IQR)	4063.24	5416.56	71,937.72	95,897.55
Use of hospital and residential care services (IQR)	3279.90	5404.35	58,068.95	95,681.41
Use of equipment and aids (IQR)	4578.40	4657.40	81,058.27	82,456.92

IQR, interquartile range.

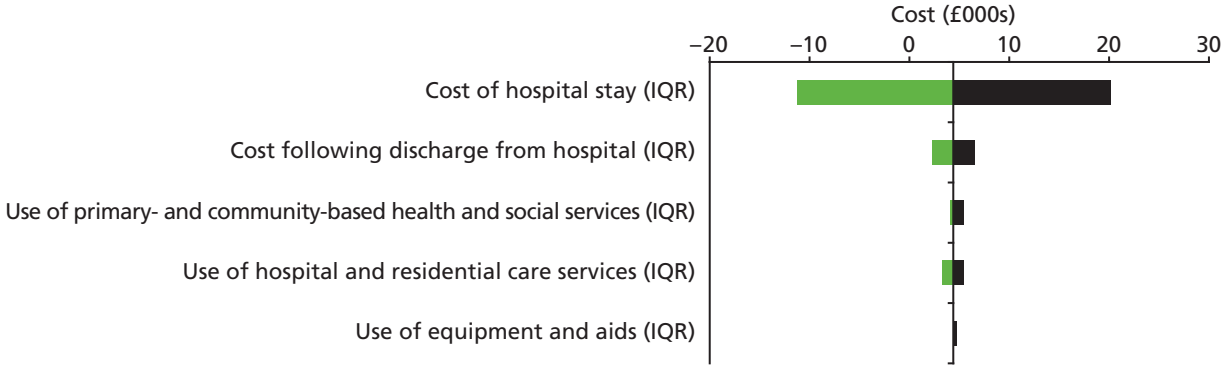


FIGURE 32 Tornado chart for sensitivity analysis of cost to the NHS to 1 year – mean cost.

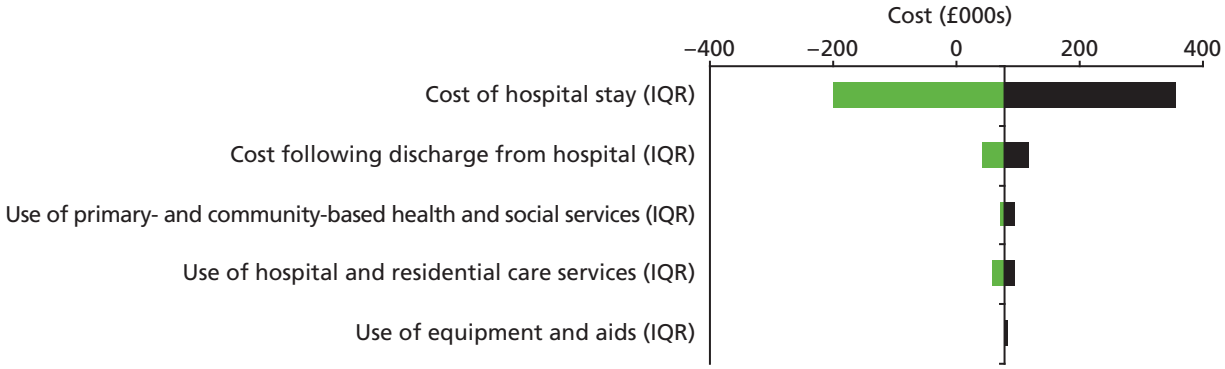


FIGURE 33 Tornado chart for sensitivity analysis of cost to the NHS to 1 year – ICER.

Discussion

The clinical results for the OSCAR trial shows that there was no significant difference between the two groups for the primary end point of mortality at 30 days and found no benefit or harm to patient outcomes in using HFOV in adults with ARDS.[119] The economic analysis shows that the mean cost of HFOV is overall more expensive than conventional ventilation. Given this, there would be no economic justification for recommending HFOV over conventional ventilation in the treatment of ARDS. Perhaps of more importance is the certainty with which this statement can be made. *Figure 26* shows a large overlap with both the *x*- and *y*-axes on the cost-effectiveness plane, implying substantial uncertainty about the true balance of costs and benefits, with the difference between the two trial groups likely to be small.

Breaking down the costs that comprise the overall 30-day totals: the costs of initial ICU admission, and of the initial ICU admission accounting for the increased cost of the HFOV machine, are both more expensive in the HFOV group. The cost per ICU readmissions are slightly cheaper in the conventional ventilation group but in the HFOV group, patients are more than twice as likely to be readmitted in the first place and more likely to be readmitted for a second time. The cost of the post-ICU stay to 30 days was also more expensive in the conventional ventilation group. The ICER shows that conventional ventilation dominates HFOV, implying that HFOV is more expensive and less effective up to the 30-day point.

More relevant to reimbursement decision-making is the 1-year cost and QALY differences. At 1 year the costs to the NHS and to society remain more expensive in the HFOV group and the cost of the post-ICU stay has reverted to being more expensive in the HFOV group. For carers, it appears that the cost in the HFOV group is also more expensive but the patients themselves have more out-of-pocket expenses and loss of earnings in the conventional ventilation group. Their QoL is also slightly better in the HFOV at both 6 and 12 months. At 1 year, the cost to society and to the NHS per LYs saved still shows conventional ventilation dominating HFOV and the ICER for the cost per QALY does not fall below the established range for cost-effectiveness in the UK.

Perhaps the most important message to be gleaned from the 1-year cost-effectiveness results is the level of uncertainty around these. With a probability of being cost-effective at a threshold of £20,000 per QALY of 0.18 the chance of HFOV ever being cost-effective must be considered low, although the uncertainty about this grows as the threshold increases.

The imputed results for the missing data show that there is a smaller incremental QALY and a smaller incremental cost to society for the HFOV at 1 year but the conventional ventilation still dominates the HFOV in the ICER. The imputation is most likely alluding to the likelihood for missing QoL data to be due to poor questionnaire return in patients experiencing a worse QoL. Extrapolation based on the sensitivity analysis at both 30 days and 1 year the most important consideration for the cost of intervention is the cost of the initial ICU admission and the cost of the total hospital stay, respectively.

There are a number of limitations in this study brought about by the inevitable shortfall in information retrieval in a clinical trial setting. For example, patients were separated into those requiring antibiotics based on whether they experienced pulmonary symptoms or non-pulmonary symptoms. We therefore had to assume that those in the non-pulmonary group were using them for a UTI as this is the most common cause of sepsis in hospital and the community.[101–105] We also had no information about which antibiotics were in use or patient allergies and therefore based our costing on antibiotics in common use and assumed a similar rate of allergy to penicillin as the normal population. We had to assume which types of muscle relaxants and sedation were in use as there was no standard protocol in place. It should be noted that the QoL data were based on incomplete follow-up for some patients. We therefore used complete-case analysis followed by a second analysis using imputation for missing values. A subsequent analysis will update the 1-year cost-effectiveness.

Markov modelling shows that over a lifetime horizon the cost of HFOV remains higher than conventional ventilation and with a continuation of the small improvement in QALYs. The ICER reported from the model suggests that HFOV is cost-effective, which is a surprise given the within-trial analysis results. This appears to be driven by the slightly greater proportion of patients surviving at the end of 1-year follow-up in the HFOV group of the trial. More complete trial follow-up is required in order to make reliable inference from this analysis. It should also be noted that we have not adjusted for baseline characteristics or stratification factors. We did not have evidence that this increased mortality continues past 9 years but it is unlikely to revert to that of the normal population and more data would be required to make this a robust analysis. However, as there was no evidence available we used the mortality rate for the normal population after this. The evidence for the increased mortality up to 9 years post-ICU discharge was based on an Australian population and we assumed there would be a high correlation with that of our UK population. Another limitation was the lack of long-term data for utility values associated with ARDS and ICU admission available and we therefore assumed that once patients were 1 year post randomisation, their utility value reverted back to that of the normal population.

Conclusion

A number of uncertainties in the evidence for cost-effectiveness remain but at present there is no economic justification for the use of HFOV over conventional ventilation in the setting of ARDS.

Chapter 6 Discussion

The design of the OSCAR study

The OSCAR study was a randomised, open, effectiveness study of HFOV in patients with ARDS. It was primarily designed to answer the question 'what would be the effect of introducing high-frequency oscillatory ventilation into the NHS?'. It was a largely pragmatic study, meeting 7 of the 10 criteria of the Pragmatic–Explanatory Continuum Indicator Summary (PRECIS).[120] The study was not totally pragmatic because of the tight protocol-specified restrictions on the use of HFOV, protocol-compliance monitoring and follow-up beyond that required clinically.

The patients we recruited all had ARDS as determined by the internationally agreed definitions current when the study was planned,[20] and by the revised definitions published as the study was finishing.[21,121] However, these definitions alone are insufficient as study entry criteria, largely because they do not specify a duration during which the P : F ratio needs to be below a threshold value. As the P : F ratio has a non–linear relationship with inspired oxygen, PEEP, patient position and ventilation mode, a patient may be eligible on one blood gas estimation but with a change in treatment but no real change in the severity of their ARDS be ineligible on the next. In addition, for HFOV to have any effect, it would have to be in use long enough to avoid lung damage caused by the alternative conventional ventilation. This is not a problem unique to OSCAR, it applies to all other studies of lung-protective ventilation. Thus, we additionally specified that the patient should be expected to be ventilated for a further 48 hours. During the study we were asked by collaborators for guidelines on how to predict expected duration of ventilation other than with clinical skills. We systematically searched the literature to find a prediction tool that was useable during the first 7 days of artificial ventilation, which had been validated, which was applicable to a wide range of causes of ARDS, and was sufficiently sensitive and specific to be used on individual patients. We were unable to find such a tool. To try to ensure the maximum benefit from HFOV we used it as long as possible, up to the point at which the mechanics of the HFOV ventilator hindered weaning.

We recruited patients with moderate-to-severe ARDS, with an average P : F ratio of 15.1 kPa. The study entry criterion was a P : F ratio of < 26.7 kPa, which was in line with the agreed definitions of ARDS but the additional requirement of a further 48 hours or more of mechanical ventilation may have excluded milder cases of ARDS. The average P : F ratio is nearly identical to the mean of 14.9 kPa reported in the recent systematic review of HFOV[18] and is similar to the mean values reported in studies of other treatments for ARDS.[122–124]

To deliver HFOV in our study, we used the Novalung (Metran) R100 ventilator, a device that had not been used before in clinical trials. To date, all other studies of HFOV in adults have used the SensorMedics 3100B ventilator. The differences in the techniques used to generate HFOV between the machines were not believed to be important when the study was designed, as both were CE marked and reported to improve oxygenation. No additional data emerged during the study to suggest one device was superior to the other. As the SensorMedics 3100B ventilator has a diaphragm that is electrically driven it is possible to vary the inspiratory to expiratory time ratio, an adjustment not possible on the pneumatically driven diaphragm in the R100. This probably had little effect, as in studies on model lungs using both ventilators the 1 : 1 ratio that the R100 uses caused greatest gas movement.[125] However, the R100 did have the facility to perform conventional ventilation, which made protocol design and training considerably easier, and it was this that largely determined our choice of ventilator.

Our study specified a higher starting frequency than most other studies. Most studies used 5 Hz as the starting frequency,[17,51] with only the OSCILLATE[56] study allowing high starting frequencies. We chose the 10 Hz starting frequency because higher frequencies are thought to offer more lung protection, although carbon dioxide clearance becomes less efficient at higher frequencies. As noted in *Chapter 3*, this choice of starting frequency did cause problems with hypercarbia in some patients, including one patient in whom the local investigator raised a SAE, and the algorithms required a modification to deal with this. Other than the higher starting frequency, our algorithms were similar to those used in other studies and were based on algorithms used clinically in Addenbrooke's Hospital (Cambridge), the University of Wales Hospital (Cardiff) and Queen Elizabeth Hospital (Birmingham).

Early in the study design process we had to decide whether to use centres 'experienced' in HFOV or HFOV-naïve centres. The advantages of using experienced centres include reduced training requirements, the possibility of using their own equipment thereby reducing study costs, and the availability of experienced clinicians for advice on trial design and execution. However, centres with HFOV already in use as part of their clinical management of ARDS were unlikely to have equipoise, and when asked were not willing to undertake conventional ventilation in half the patients they would previously have treated with HFOV. In addition, there were simply not enough experienced centres in the UK to run the study. We therefore chose to base the study on HFOV-naïve centres and put a comprehensive training package in place.

However, the need for experienced clinicians remained. Three of the applicants on the grant (Shah, Tunnecliffe and MacKenzie) had experience with HFOV, and convinced their centres (Queen Elizabeth Hospital, Birmingham and University Hospital of Wales, Cardiff) to take part. As they had SensorMedics 3100B ventilators, the study supplied leased R100 ventilators. In addition, two hospitals who bought R100 ventilators as the study started [Ysbyty (Wrexham) Maelor Hospital and Queen Elizabeth Hospital, Gateshead] agreed to join the study using their own ventilators. The ventilator suppliers kept us appraised of all new orders so we could approach centres buying R100 ventilators to join the study. The hospitals who agreed to join the study using their own new ventilators were Southend Hospital, Royal Victoria Hospital (Newcastle), James Cook University Hospital (Middlesbrough) and the James Paget Hospital (Great Yarmouth). Later in the study the Leeds hospitals, also experienced in HFOV, joined the study. Thus though the majority of recruited patients came from HFOV-naïve centres, three major centres with HFOV experience also took part.

The original recruitment rate estimate was 2 patients per centre per month. The final figure was less than half of this (0.82 patients per centre per month), and as a result the recruitment period had to be extended and took 56 months rather than the planned 36 months. Overall, we recruited for 80.7 centre-years. The usual checks and inducements were used to monitor and increase the recruitment rate, including a formal review of barriers to recruitment, 'Not in trial' log reviews, publicity at professional meetings, site visits, newsletters, recruitment prizes, a study nurses' network, and repeated training sessions. With one ventilator per site recruitment could only take place when the ventilator was not in use, but the 'Not in trial' logs suggested this was not a practical problem. In some trials, in-critical-care patients are lost when they present out-of-hours, but in OSCAR the study recruitment window allowed office hours recruitment. We believe part of the problem was the original recruitment estimates were too optimistic. The estimates were largely based on epidemiological studies, which record the incidence of ARDS in ICUs. As noted above, this incidence could be based on patients with only one blood gas estimation in the required range, and so the epidemiological studies took no account of the duration of illness. In addition, we were unable to estimate the number of ineligible patients. In hindsight, there were indications that recruitment might be difficult. The discrepancy between the number of patients in Oxford with abnormal blood gas readings on at least one occasion and the clinically recorded incidence of ARDS might have alerted us. The problem of recruitment to studies of ARDS in the UK was not limited to the OSCAR study. The BALTI-2 study[122] which ran simultaneously with the OSCAR study and had similar entry criteria recruited at about 0.2 patients per centre per month.

The limitations of the OSCillation in ARDS study

The study was powered on the primary outcome, 30-day all-cause mortality. Although planned subgroup analyses were performed, the study was not powered for these analyses and so the results should be interpreted with caution. The study group allocation was necessarily open to study staff, clinical staff, patients and their relatives, and so there is a risk of bias in reported subjective secondary outcomes. We believe that this may be one explanation for the modestly improved QoL reported to date (full follow-up is not complete) in the patients who received HFOV. Similarly, treatments other than ventilation may have differed between groups, either as a result of different effects of HFOV and conventional ventilation or differing decision making in the presence of unblinded allocation. The generous page count for this report enabled us to report all the analyses in our predefined analysis plan, which minimises the chance of reporting bias, but even so we cannot report every nuance of the study

The validity of the OSCillation in ARDS study

The study has good internal and external validity. Bias was minimised by using centres with equipoise (see above), by concealing treatment assignments before randomisation by using random block sizes, by concealing interim analysis results from all study investigators except for the DMEC, and by using an analysis plan that was agreed on before study closure and before any results were available. There was no loss to follow-up, crossovers were minimal, and the study recruited 99.1% of the planned sample size.

External validity was maintained by using a large number of different-sized ICUs spread across the UK. Most of the centres in this trial were inexperienced with the intervention at the start, but this was unavoidable, since few centres in the United Kingdom had experience with the use of HFOV. We invested heavily in training at each study centre. The consent refusal rate was low, as was the dropout rate.

The study showed no survival benefit from HFOV in a group of adult patients with moderate to severe ARDS. The 95% confidence limits for the risk ratio were –6.1% to 7.5%, indicating that the effect size, if any, was less than the 10% absolute reduction in 30-day mortality the study was powered to detect, and less than the 9% that the study was originally powered for. The two Kaplan–Meier survival probability curves essentially overlay each other to 30 days, indicating both the number and timing of deaths were similar in both groups. Thus, this study does not show a short-term survival benefit for HFOV seen in the systematic review,[18] where patients randomised to high-frequency oscillation, mortality was significantly reduced (risk ratio 0.77, 95% CI 0.61 to 0.98; $p = 0.03$; six trials, 365 patients, 160 deaths).

The CCCTG were running a similar study in Canada during the period OSCAR was recruiting. The OSCILLATE study (ISRCTN42992782 and ISRCTN87124254) took place from July 2007 to August 2012 in 39 ICUs in five countries, but was primarily run in Canada. The entry criteria were similar, using standard definitions of ARDS. The HFOV was delivered using the SensorMedics 3100B ventilator, and most centres were already experienced in HFOV and had their own ventilators. The design was closer to an efficacy study than OSCAR, with a tightly protocolised ventilation strategy for the control group. The study was stopped by the DMEC at 500 recruited patients, when the treatment (HFOV) group mortality was 47% and the control group mortality was 35% (RR 1.33, 95% CI 1.09 to 1.64). The Kaplan–Meier survival curves suggest the excess mortality occurred in the first 20–25 days after randomisation. The primary study results were published alongside the headline clinical result of the OSCAR study in the same edition of the *New England Journal of Medicine*.[56,119]

The OSCILLATE investigators suggested some mechanisms which may have contributed to the increased mortality with HFOV seen in their study. Higher mean airway (and hence intrathoracic) pressures in the HFOV group may have resulted in haemodynamic compromise by decreasing venous return or directly affecting right ventricular function and thereby reducing cardiac output. Increased use of vasodilating

sedative agents in the HFOV group may also have contributed to haemodynamic compromise. The study could not exclude the possibility of increased barotrauma in association with HFOV.

There was little evidence of harm caused by haemodynamic compromise in the OSCAR study. There was increased use of renal support in the HFOV group. We do not know the reason for this, it may represent a true effect of HFOV on renal function, possibly mediated via haemodynamic changes, or it may be that the respiratory acidosis seen early in the HFOV group altered clinicians' decision making about the timing of renal replacement.

The OSCILLATE HFOV group, and both the OSCAR groups had broadly similar hospital mortality (47% in the OSCILLATE HFOV group, 50.1% in the OSCAR HFOV group and 48.4% in the OSCAR control group). In the OSCILLATE paper, the authors suggest that one possible explanation for the discordant results in the two studies relates to the control group treatment. In OSCILLATE, tidal volumes were lower and PEEP greater in the control groups. It is possible that 'better' treatment of the control group in the OSCILLATE study 'unmasked' the harm the HFOV was causing, an effect not seen in OSCAR because of the higher control group mortality.

While superficially attractive, this theory really only applies if both studies had similar populations. When compared with the OSCAR study, the patients in OSCILLATE had a much higher APACHE II score (29 compared with OSCAR 22, though the OSCILLATE patients had the APACHE II score calculated at enrolment not ICU admission). OSCILLATE patients were treated earlier in their illness. To try and understand the differences in the studies the results are being pooled in a meta-analysis, which may reveal results in subgroups too small to be analysed if only one set of patients were available. This work is ongoing at the time of writing.

Conclusions

The major conclusion is that, in the NHS in England, Wales, Scotland and Northern Ireland, the introduction of HFOV as a treatment for ARDS would not result in an improved survival for patients or a reduction in resource use as measured by treatment duration in acute health-care facilities.

The study was not powered for equivalence, and the result should not be interpreted as indicating that HFOV does not cause harm, especially in light of the results from the OSCILLATE study.

The OSCAR and OSCILLATE studies were expensive and took a long time to complete. Unless the meta-analysis of OSCAR and OSCILLATE suggests a subset of patients in whom HFOV has a major benefit, we suggest further large studies of HFOV in patients for ARDS should not be a priority for health-care research.

The control group treatment in OSCAR suggests that 'best practice' of low tidal volume ventilation is not occurring in ICUs in the UK. The reasons for this require further investigation, as to date low tidal volume ventilation is the only commonly available intervention with proven efficacy in patients with ARDS.

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Dr Ranjit Lall (Senior Statistician, Warwick Clinical Trials Unit, Warwick, UK) participated in the design and running of the study, performed all statistical analyses except the health economics, and prepared this report.

Dr Patrick Hamilton (Clinical Researcher, Academic Unit of Health Economics, University of Leeds, Leeds, UK) participated in analysing the health economics data and writing the chapter on health economics.

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The OSCAR collaborators are listed in *Appendix 5*. They were the principal investigators who ran the study at their local hospitals.

Publication

Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, *et al.* High-Frequency Oscillation for Acute Respiratory Distress Syndrome. *N Engl J Med* 2013;**368**:806–13.

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Appendix 1 Substantial and non-substantial amendments to the OSCAR protocol

List 1: non-substantial amendments

Date of amendment	Non-substantial amendment
12 June 2007	Ensuring all inclusion criteria in box Expanding ventilator criteria Updating 'consent refused' in line with Mental Capacity Act 2005[76] (and broken down into who is refusing Professional or Personal consultee)
17 October 2007	Page 21: Eligibility of patients A) Clinician is 'substantially uncertain' as to the utility of HFOV in this patient Remains the same just a re-ordering of points: point 'v' moved down to become point 'vii' keeping all clinical points together B) Predicted by the attending clinician **likely** to require at least 48 hours of artificial ventilation from the time of randomisation Word 'likely' added to reinforce this is a prediction not exact C) Have been mechanically ventilated for LESS than 7 **consecutive** days **(≤ 168 hours)** at the point of randomisation 7 days clarified by 'consecutive' being included and the number of hours indicated to ease calculating time frame Page 21: Patients excluded D) Patients in whom HFOV might be hazardous: patients with **moderate or severe** airway disease expected to cause expiratory airflow limitation. 'Moderate or severe' added to aid definition of patient group E) Addition to exclusion criteria: 'Patients with any other condition the clinician believes would make receiving HFOV hazardous.' We had seen this as obvious but some clinicians asked for clarification hence now including it Page 22: Screening and recruitment flow chart F) Eligibility box has been updated in line with (A) to (C) above G) Consent box wording changed to match England/Scotland Acts re. incapacity wording in other parts of Protocol Now: 'Agreement from Consultee (Scotland: Consent from Welfare Guardian/Nearest Relative)' Continue over/. . . H) 'Trial Entry form' box wording changed to match name of form used Now: 'OSCAR Form 1: Pre-trial Entry Booklet completed' I) 'ICU/30 DAY/HOSPITAL DATA COLLECTED' box wording changed to match name of form used to collect data. Now: 'Daily: complete OSCAR Form 2: Post-Randomisation Patient Data Booklet'

Date of amendment	Non-substantial amendment
	Page 25: Figure 3: The algorithm for managing HFOV J) This flow chart is used for training clinicians in the use of the oscillator and has been expanded to aid training in the use of the Vision Alpha ventilator The adjustments have been made to match the controls on the Vision Alpha machine which were not available until the new machine was delivered New page 27 (was page 26): 4.9.2. Clinical management of patients in the control arm (conventional ventilation) K) Update to 4.9.2 text and accompanying chart More recent data have become available so minor changes have been made that is a synthesis of all available data 4.9.3 Proposed duration of treatment and weaning L) Typo – 0.5 should have been 0.4. This has now been changed Page 28: Figure 4: Patient treatment and weaning flow chart M) *Fi*O_2 chart box removed as duplicate of what on page 27 and is unnecessary in flow chart
17 October 2007	Page 2: Changes to wording (bold below) in numbers v and vi. Non-substantial amendment to Protocol led to this Summary Protocol being amended to ensure consistency: v Predicted by the attending clinician **likely** to require at least 48 hours of artificial ventilation from the time of randomisation vi Have been mechanically ventilated for LESS than 7 **consecutive** days **(≤ 168 hours)** at the point of randomisation
7 March 2008	A minor clarification of the protocol has been made The wording of one of the inclusion criteria has changed from: Patient: v Predicted by the attending clinician likely to require at least 48 hours of artificial ventilation from the time of randomisation. To: Patient: Will not be extubated by tomorrow evening (predicted by attending clinician) The justification for this clarification is based on feedback from sites who find the 48 hours of ventilation prediction difficult. Therefore this has been turned into a practical question they can relate to Patients are generally screened for suitability for the trial on the morning ward rounds once a day therefore the time frame still applies. Pages affected: 5, 21, 22 (Appendices: 107, 110)
25 April 2008	A minor clarification of admission criteria has been made relating to the hypoxaemia criterion. The new criterion is: 'Lowest recorded PaO_2/FiO_2 ratio measured between onset of artificial ventilation and time of screening of ≤ 26.7 kPa with a positive end expiratory pressure (PEEP) ≥5 cmH_20' The requirement for a specific cause and a second test are removed

Date of amendment	Non-substantial amendment
1 October 2008	A more manageable size of protocol is required. Therefore the full protocol that is currently approved (Version 5.1, 4 March 2008) has been split into two documents – Working Protocol (Version 1 – 1 October 2008) and Background Information (Version 1 – 1 October 2008) The working protocol has been slimmed down from the original full protocol by removing the background information and copies of other trial documentation (already approved by MREC in their own right). The background information document (Version 1 – 1 October 2008) has been created from the information removed from the protocol A full protocol will still be maintained for the trial, the approved version 5.1, 4 March 2008, has been updated in section 5.8.2 and 5.13, as initially units collaborating the trial would receive a ventilator from the trial group and have the opportunity to potentially purchase it at the end of the trial, now however units are collaborating who already have their own ventilator and therefore they will not receive a ventilator from the trial group and have the opportunity to potentially purchase it As these changes do not alter the studies design, methodology, background or its scientific value, the Chief Investigator considers these are not significant changes to the protocol, nor do they alter any of the procedures undertaken by participants or alter the documentation participants receive, and these changes do not include a new site or a new Principal Investigator at an existing site, and this is therefore thought to be an non-substantial amendment
12 February 2009	Page 26 of current protocol: additional detail added to carbon dioxide algorithm We know that some patients experience a significant rise in carbon dioxide levels on initiation of HFOV, this has always been known. However, as we have received enquiries about such cases, we felt the advice we give should be incorporated into the algorithm. Hence, we have added more detail. This is a minor clarification of the protocol
22 January 2010	The 24-month questionnaires are sent out to patients recruited in the first year of the study only. Due to an administrative oversight, the questionnaires were printed with questions relating to the previous 6 months. In order to calculate QALYs, we need information for the previous 12 months not 6 as in the questionnaire. We have therefore amended the questionnaires we send to patients or carers as appropriate. The changes are almost entirely simple substitution of '12' for '6' months. Each questionnaire is accompanied by a covering letter which has also been changed as appropriate. Copies showing the changes using the Track Changes facility in Microsoft Word (Microsoft Corporation, Redmond, WA, USA) is attached. In addition, the questionnaire we sent to the patients recruited in the first year of the study at 24 months contained a section on the burden of illness and, specifically, respiratory morbidity. It became apparent during the preparation of the analysis plan that these data would not produce useful results. Therefore, to reduce the burden on the patients we have removed this section. These changes are judged as non-substantial amendments by the Chief Investigator as: as these changes do not alter the study design, methodology, background or its scientific value, the Chief Investigator considers these are not significant changes to the protocol, nor do they alter any of the procedures undertaken by participants and these changes do not include a new site or a new Principal Investigator at an existing site. They consist of simple changes to questions which do not significantly alter the content and a change that reduces the data burden to the patient
6 May 2011	Creation of a pre-questionnaire warning letter for participants. This letter will be sent out 2 weeks ahead of the first questionnaire at 6 months and the second questionnaire at 12 months following randomisation. It does not alter any of the previously approved documentation that participants receive as it will be sent solely as a reminder to participants that they are taking part in the study and are due to receive a questionnaire and will prepare them for the types of questions we are asking them to answer

List 2: substantial amendment 1, OSCAR trial – substantial amendment no. 1, 4 March 2008 summary of changes

Document name	No.	Page number	Subsection	Changed from	Updated to
Full Protocol		Front sheet		Version 4 – 12 June 2007	Version 5 – 4 March 2008
	1	20	4.3.1 Centres		First bullet point: we have amended the first criteria as the number of ICU admissions alone does not always reflect the case mix of the unit. It may therefore be necessary to take on sites with a lower admission rate (< 650 per year), but who have more ARDS cases
	2	30	4.12 Secondary outcome measures	N/A	Addition of ventilator-free, antimicrobial-free and sedative-free days to Secondary outcome measures. These should have been included in the protocol from the outset. This information is required for both economic analysis (to ensure we can calculate the true cost of either treatment), and is required by clinicians for an all round knowledge of the effect of HFOV vs. conventional ventilation
	3	31	4.13 Data collection	N/A	Final paragraph: the added text indicates the use of the SF-12 version 2 questionnaire and questions concerning social and health service use (see *Patient Questionnaire Section* below, 2 & 3)
	4	31	4.14 Health economics	N/A	Final paragraph: added text indicates use of questions concerning social and health service use
	5	39	5.13.2 Vision Alpha HFOV training	N/A	Second paragraph: this has been amended to reflect the way training has evolved during the initial phases of the trial. It was not possible for groups of individuals from busy ICUs to attend training in the Netherlands
FOLLOW-UP QUESTIONNAIRES TO PATIENTS	6	Front page			Identifying when another individual has completed the questionnaire for the patient. The front page of the questionnaire has a small change in the box (in bold), identifying when another individual has completed the questionnaire on the patient's behalf
	7	Page 8/9	Questions 25–31		Adding questions to the questionnaire: SF-12 Validated Questionnaire. In the original protocol we had proposed and justified using a 36-item questionnaire to measure quality of life – called the Short Form 36 (SF-36). This is a well-validated questionnaire, which is widely used. It has proven efficacy in the intensive care population. However, over the last 5 years, it has been recognised that the instrument is long, and newer version have been developed which retain all of the original features, but with less items [known as the Short Form 12 (SF-12)]. We are now proposing to utilise the SF-12 (version 2) as the respondent burden is considerably less. The SF-12 is currently being used in other ARDS trials, which will facilitate pooling of results in meta-analyses. It has proved a good measure of the quality of life for patients who have suffered from ARDS

Document name	No.	Page number	Subsection	Changed from	Updated to
	8	Pages 10–21	Questions 32–47		Adding questions to the questionnaire: Health Economic questions. The health economic questions have now been added. This is to establish an unbiased estimate of the long-term cost-effectiveness of HFOV vs. conventional ventilation. It is important to collect data on the patients' long-term health and social care utilisation and their expenditure as a result of their stay in the ICU. It is important that the study does not just provide information about the short-term health benefits and that any increased burden on the NHS and on the patients themselves is identified so that the overall value of this technology can be assessed
CARERS QUESTIONNAIRE	9				We have created a questionnaire for carers which will be sent with the patients follow-up questionnaires. Informal carers are estimated to save the NHS billions of pounds and although informal carers are not typically paid for their work, in some instances they are entitled to benefits from the state. In this study we are interested in learning about the impact on the resources of these informal carers as a result of providing care to someone who has been in the ICU. Collecting this information from carers allows us to gain a complete picture of the cost of the interventions not just to the NHS but to wider society

N/A, not applicable.

List 3: substantial amendment 2

Summary of changes

We would like the committee to approve the content of a follow-up reminder letter to participants. Our proposed letter is attached and is based on the wording in the initial follow-up letter sent to participants (approved by MREC).

The process:

Surviving patients are sent a follow-up letter/questionnaire, etc. (process and content already approved by MREC).

Non-responders 1 month later: status checked via ONS re: alive/deceased (process approved by MREC).

Those surviving are sent a reminder letter/questionnaire, etc. (process and questionnaire, etc. already approved by MREC, content of reminder letter not yet approved).

For your information, the relevant section of our approved protocol (page 30, section 4.13) is detailed below. This remains unchanged. 'The trial office will send self-administered questionnaires to determine health-related quality of life (EQ-5D and SF-12 version 2) and specifically respiratory function (St George's Respiratory Questionnaire) to all survivors at 6 months and 1 year after hospital discharge, with follow-up letters one month after the original mailing. These questionnaires also include questions on social and health service use. Freepost envelopes will be provided. Patients who have died after hospital discharge but prior to the mailing will be identified from the ONS returns and removed from the mailing list.'

List 4: substantial amendment 3

Document name	Page number	Subsection	Changed from	Updated to
Full Protocol	Front sheet		Version 6.1 – 1 October 2008	Version 7 – 19 October 2009
	5		Sample size: 1006 and 3-year recruitment period	Sample size: 802
	29	Outcome measures	Cognitive function 1 year after randomisation	Removal of cognitive function from outcome measures
	30	Sample size	1006	802 – plus explanation of change
	31	Sample size/justification for sample size	N/A	Inserted note to see update in section 4.15
	33	Planned recruitment rate	N/A	Inserted note to see update in section 4.15
Working Protocol	Front sheet		Version 1 – 1 October 2008	Version 2 – 19 October 2009
	2	Outcome measures	Cognitive function 1 year after randomisation	Removal of cognitive function from outcome measures
		Sample size	1006	802
		Planned recruitment period	November 2010	August 2011
Background Information	Front sheet		Version 1 – 1 October 2008	Version 2 – 19 October 2009
	17	Sample size	1006	802 – plus explanation of change (as in full protocol)
	18	Sample size/justification for sample size	N/A	Inserted note to see update in section 5
		Planned recruitment rate	N/A	Inserted note to see update in section 5
Summary Protocol	1	Outcome measures	Cognitive function 1 year after randomisation	Removal of cognitive function from outcome measures
	2	Sample size	1006	802
	2	Planned recruitment period	November 2010	August 2011

N/A, not applicable.

List 5: substantial amendment 4

Creation of a pre-questionnaire warning letter for participants. This letter may be sent out 2 weeks ahead of the first questionnaire at 6 months and the second questionnaire at 12 months following randomisation.

It does not alter any of the previously approved documentation that participants receive as it will be sent solely as a reminder to participants that they are taking part in the study and are due to receive a questionnaire and will prepare them for the types of questions we are asking them to answer.

The letter has been modified as suggested by the Sub Committee (letter dated 27 June 2011) to avoid anxiety in participants who may not have realised they were in the study.

List 6: substantial amendment 5

In order to maximise recruitment, it has been proposed that a subset of centres will continue to randomise patients to the OSCAR trial until such time that follow-up to 30 days (the primary outcome) is no longer possible. We anticipate that the last patients will be recruited to the trial in July 2012. To maintain the current end of trial date, the final follow-up for any patient will be October 2012; therefore additional follow-up will be limited based on individual randomisation dates. This will be explained in an addendum to both the protocol and informed consent documents.

Appendix 2 Consent process for the OSCAR trial by country

1. England and Wales OSCAR trial agreement processes

England and Wales – Mental Capacity Act 2005[76] (relates to collaborating hospitals in England and Wales)

Multicentre Research Ethics Committee: 07/H0502/98/version 2 – 3 September 2007

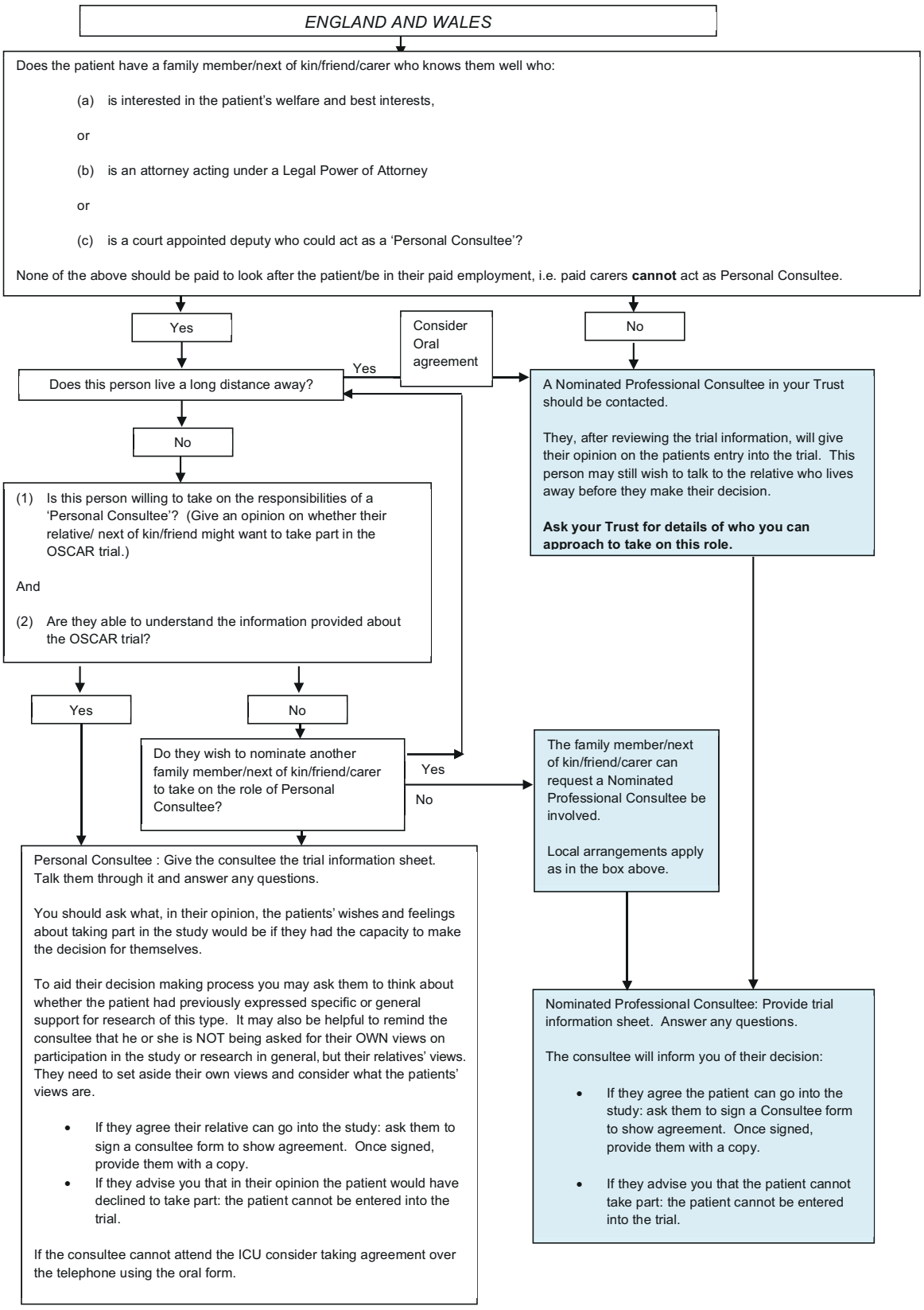
The Mental Capacity Act 2005[76] comes into force on 1 October 2007. This Act is relevant to research involving adults over the age of 16 years in England and Wales (except Clinical Trials of Investigational Medicinal Products).

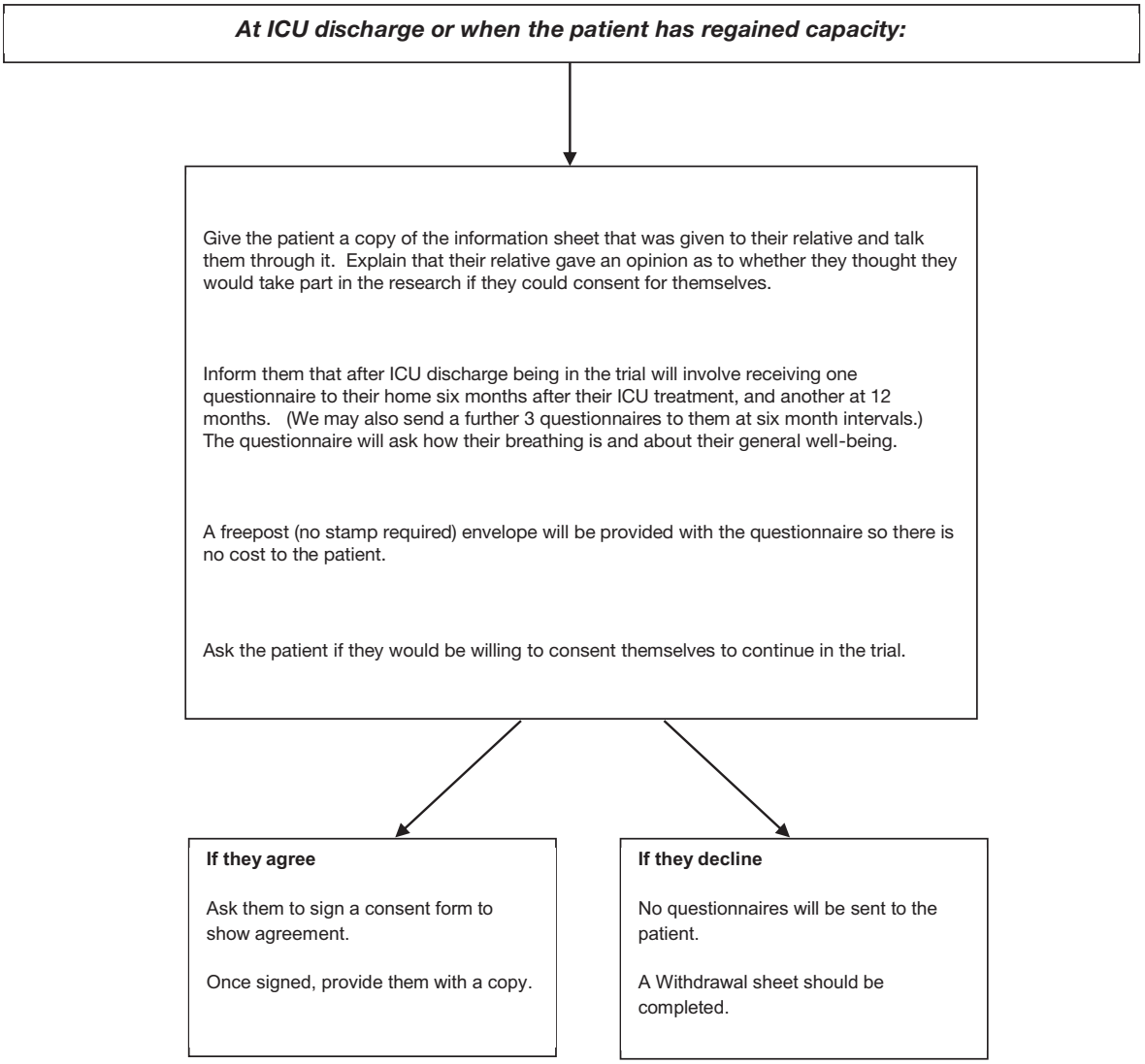
The Act provides the legal arrangements (1) to enable adults lacking capacity to consent to take part in research that would otherwise require the participant's consent, and (2) it enables adults with capacity to specify, in advance, their wishes should they lose capacity in the future with regard to taking part in research.

In the OSCAR trial, patients will usually be unable to give consent prior to trial entry owing to alternations in consciousness. The diagram below specifies the process, approved by the Research Ethics Committee, that must be followed with regard to obtaining consent to take part in the OSCAR trial.

The following has been guided by the Department of Health's document {issued by the Secretary of State and National Assembly for Wales in accordance with section [32(3)] of the Mental Capacity Act 2005[76]; URL: www.dh.gov.uk/en/Consultations/Liveconsultations/DH_076216} published 22 June 2007. This draft guidance is for consultation on how to identify an appropriate 'consultee' for the purposes of section 32 of the Mental Capacity Act 2005[76]. The guidance indicates how researchers should go about identifying an appropriate person to consult when they wish to carry out research which involves someone who lacks capacity to consent to take part.

THE OSCAR TRIAL CONSENT PROCESS - England and Wales





2. Scotland OSCAR trial consent processes

Scotland – Adults with Incapacity (Scotland) Act 2000[77] (relates to collaborating hospitals in England and Wales)

Multicentre Research Ethics Committee: 07/MRE00/73/version 2 – 3 September 2007

Scottish collaborators should follow the table:

THE OSCAR TRIAL CONSENT PROCESS - Scotland

REC: 07/MRE00/73 / Version 2 – 3 Sept 07

Patient fulfils eligibility criteria but does **not** have capacity to consent to trial
Has the patient a Welfare Guardian or Nearest Relative?

YES	NO
Is this person willing and able to take on the responsibilities of Welfare Guardian/Nearest Relative (WG/NR) in this situation? If **No** If **Yes** Explanation to be given in person and questions encouraged. Information sheet to be provided. Written consent to be signed by WG/NR If WG/NR not present in person, verbal consent to be obtained by telephone using 'Welfare Guardian/Nearest Relative *Verbal Consent*' form. Written consent to be obtained as soon as possible if practical Local investigators will ensure that the WG/NR receives a copy of the consent form.	The patient cannot be entered into the trial

The quality of consent should be ascertained from the responses given. Questions should be encouraged, and an opportunity to clarify information provided.

At ICU discharge or before when the patient has regained capacity:

Give the patient a copy of the *Patient* information sheet (retrospective information), and talk them through it.

Inform the patient that after ICU discharge being in the trial will involve receiving one questionnaire to their home six months after their ICU treatment, and another at 12 months. (We may also send a further 3 questionnaires to them at six month intervals.) The questionnaire will ask how their breathing is and about their general well-being.

A freepost (no stamp required) envelope will be provided with the questionnaire so there is no cost to the patient.

Ask the patient if they would be willing to consent themselves to continue in the trial.

If they agree

Ask them to sign a consent to continue form to show agreement.

Once signed, provide them with a copy.

If they decline

No questionnaires will be sent to the patient.

A Withdrawal From Trial sheet should be completed.

Appendix 3 OSCAR Trial Steering Committee

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Appendix 6 Details of randomisation by centre

TABLE 95 Randomised patients by the randomisation strata (centre, age, P : F ratio and intervention)

Age (years)	≤ 55				> 55			
P : F ratio (kPa)	***≤ 15***		***> 15***		***≤ 15***		***> 15***	
Intervention/centre	*Conv.*	*HFOV*	*Conv.*	*HFOV*	*Conv.*	*HFOV*	*Conv.*	*HFOV*
John Radcliffe, Oxford	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	3 (60.0)	2 (40.0)	3 (50.0)	3 (50.0)
Derriford Hospital, Plymouth	4 (44.4)	5 (55.6)	5 (41.7)	7 (58.3)	10 (47.6)	11 (52.4)	3 (75.0)	1 (25.0)
Aberdeen Royal Infirmary	1 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)
Medway Maritime Hospital	4 (66.7)	2 (33.3)	1 (33.3)	2 (66.7)	5 (45.5)	6 (54.5)	4 (57.1)	3 (42.9)
Selly Oak/Queen Elizabeth, Birmingham	7 (50.0)	7 (50.0)	18 (48.6)	19 (51.4)	11 (47.8)	12 (52.2)	14 (50.0)	14 (50.0)
Royal Sussex County Hospital, Brighton	4 (40.0)	6 (60.0)	3 (42.9)	4 (57.1)	4 (66.7)	2 (33.3)	11 (47.8)	12 (52.2)
University College Hospital, London	15 (51.7)	14 (48.3)	5 (50.0)	5 (50.0)	10 (52.6)	9 (47.4)	3 (60.0)	2 (40.0)
University Hospital of Wales, Cardiff	1 (100.0)	0 (0.0)	3 (50.0)	3 (50.0)	2 (66.7)	1 (33.3)	3 (50.0)	3 (50.0)
Royal United Hospital, Bath	0 (0.0)	1 (100.0)	3 (75.0)	1 (25.0)	3 (60.0)	2 (40.0)	5 (50.0)	5 (50.0)
Manchester Royal Infirmary	4 (57.1)	3 (42.9)	2 (50.0)	2 (50.0)	1 (50.0)	1 (50.0)	5 (45.5)	6 (54.5)
Ysbyty Maelor, Wrexham	3 (60.0)	2 (40.0)	4 (50.0)	4 (50.0)	7 (58.3)	5 (41.7)	3 (42.9)	4 (57.1)
Queen Elizabeth Hospital, Gateshead	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)	2 (50.0)	2 (50.0)
Royal Cornwall Hospital, Treliske	7 (53.8)	6 (46.2)	4 (50.0)	4 (50.0)	12 (50.0)	12 (50.0)	5 (45.5)	6 (54.5)
Stirling Royal Infirmary	3 (42.9)	4 (57.1)	1 (33.3)	2 (66.7)	2 (40.0)	3 (60.0)	2 (50.0)	2 (50.0)
Manchester Royal Infirmary, Cardiac ICU	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Leeds General Infirmary	4 (44.4)	5 (55.6)	2 (40.0)	3 (60.0)	6 (50.0)	6 (50.0)	2 (50.0)	2 (50.0)
James Paget Hospital, Great Yarmouth	3 (75.0)	1 (25.0)	2 (40.0)	3 (60.0)	3 (37.5)	5 (62.5)	4 (66.7)	2 (33.3)
Queen Alexandra Hospital, Portsmouth	4 (40.0)	6 (60.0)	3 (60.0)	2 (40.0)	9 (52.9)	8 (47.1)	2 (40.0)	3 (60.0)
Royal Blackburn Hospital	3 (50.0)	3 (50.0)	2 (66.7)	1 (33.3)	5 (41.7)	7 (58.3)	3 (60.0)	2 (40.0)
Wythenshawe Hospital, Manchester	2 (50.0)	2 (50.0)	1 (33.3)	2 (66.7)	3 (50.0)	3 (50.0)	1 (50.0)	1 (50.0)
University Hospital of North Staffordshire, Stoke-on-Trent	3 (60.0)	2 (40.0)	1 (50.0)	1 (50.0)	0 (0.0)	1 (100.0)	3 (42.9)	4 (57.1)

continued

TABLE 95 Randomised patients by the randomisation strata (centre, age, P : F ratio and intervention) (*continued*)

Age (years)	≤ 55				> 55			
Ipswich Hospital	1 (33.3)	2 (66.7)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Queen Margaret Hospital, Dunfermline	1 (50.0)	1 (50.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	2 (50.0)	2 (50.0)
Southampton General Hospital	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	5 (71.4)	2 (28.6)	0 (0.0)	2 (100.0)
St James's University Hospital, Leeds	14 (51.9)	13 (48.1)	4 (44.4)	5 (55.6)	13 (50.0)	13 (50.0)	3 (50.0)	3 (50.0)
York Hospital	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)	2 (66.7)	1 (33.3)	1 (50.0)	1 (50.0)
Victoria Hospital, Blackpool	5 (50.0)	5 (50.0)	1 (25.0)	3 (75.0)	4 (44.4)	5 (55.6)	3 (60.0)	2 (40.0)
Southend Hospital	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
Royal Victoria Infirmary, Newcastle	1 (100.0)	0	1 (50.0)	1 (50.0)	2 (50.0)	2 (50.0)	0 (0.0)	1 (100.0)
James Cook University Hospital, Middlesbrough	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)
Total	103 (51.0)	99 (49.0)	71 (47.3)	79 (52.7)	131 (50.6)	128 (49.4)	92 (50.0)	92 (50.0)

Conv., conventional.

TABLE 96 Randomised patients by centre and ventilation treatment

Intervention/centre	Conventional ventilation	HFOV	Total
John Radcliffe, Oxford	8 (66.7%)	4 (33.3%)	12
Derriford Hospital, Plymouth	22 (47.8%)	24 (52.2%)	46
Aberdeen Royal Infirmary	8 (61.5%)	5 (38.5%)	13
Medway Maritime Hospital	13 (72.2%)	5 (27.8%)	18
Selly Oak/Queen Elizabeth, Birmingham	47 (51.6%)	44 (48.4%)	91
Royal Sussex County Hospital	22 (55.0%)	18 (45.0%)	40
University College Hospital	33 (62.3%)	20 (37.7%)	53
University Hospital of Wales	9 (64.3%)	5 (35.7%)	14
Royal United Hospital	11 (64.7%)	6 (35.3%)	17
Manchester Royal Infirmary	12 (52.2%)	11 (47.8%)	23
Ysbyty Maelor	15 (53.6%)	13 (46.4%)	28
Queen Elizabeth Hospital, Gateshead	5 (45.5%)	6 (54.5%)	11
Royal Cornwall Hospital (Treliske)	28 (53.8%)	24 (46.2%)	52
Stirling Royal Infirmary	8 (50.0%)	8 (50.0%)	18
Manchester Royal Infirmary, Cardiac ICU	1 (100.0%)	0 (0.0%)	1
Leeds General Infirmary	14 (56.0%)	11 (44.0%)	25
James Paget Hospital	11 (50.0%)	11 (50.0%)	22
Queen Alexandra Hospital	18 (48.6%)	19 (51.4%)	37
Royal Blackburn Hospital	13 (54.2%)	11 (45.8%)	24
Wythenshawe Hospital	7 (46.7%)	8 (53.3%)	15

TABLE 96 Randomised patients by centre and ventilation treatment (*continued*)

Intervention/centre	Conventional ventilation	HFOV	Total
University Hospital of North Staffordshire	7 (46.7%)	8 (53.3%)	15
Ipswich Hospital	1 (25.0%)	3 (75.0%)	4
Queen Margaret Hospital	5 (62.5%)	3 (37.5%)	8
Southampton General Hospital	8 (57.1%)	6 (42.9%)	14
St James's University Hospital	33 (54.1%)	28 (45.9%)	61
York Hospital	7 (63.6%)	4 (36.4%)	11
Victoria Hospital Blackpool	13 (50.0%)	13 (50.0%)	26
Southend Hospital	1 (33.3%)	2 (66.7%)	3
Royal Victoria Infirmary	4 (50.0%)	4 (50.0%)	8
James Cook University Hospital	2 (66.7%)	1 (33.3%)	3
Total	386 (54.3%)	325 (45.7%)	711

% are based within each centre (row).

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HS&DR
HTA
PGfAR
PHR

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