# NETSCC, HTA

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**High Frequency OSCillation in ARDS**

# A Collaborative Randomised Controlled Trial

Comparing:

Conventional positive pressure ventilation with high frequency oscillatory ventilation (HFOV) for adults with acute respiratory distress syndrome

# FULL PROTOCOL

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SUMMARY

This protocol describes a multicentre, randomised controlled trial (RCT) comparing conventional positive pressure ventilation with high frequency oscillatory ventilation (HFOV) for adults with acute respiratory distress syndrome (ARDS). The trial is funded by the Health Technology Assessment programme and sponsored by the University of Oxford.

The trial will take place in 10 or more Adult Intensive Care Units (ICUs) in the NHS in the United Kingdom able to care for Level 3 patients as defined by "Comprehensive Critical Care" [1]. A total of 802 patients will be recruited.

For the purposes of the trial patients are deemed suitable if they have acute hypoxaemic respiratory failure as defined by (a) a $PaO_2/FiO_2$ ratio measured between onset of artificial ventilation and time of screening of ≤ 26.7 kPa with a positive end expiratory pressure (PEEP) ≥ 5 $cmH_20$, and (b) bilateral infiltrates on chest radiograph. In addition the patient must be ventilated for less than 7 consecutive days (≤ 168 hours) at the point of randomisation, and the attending clinician predicts the patient will not be extubated by the following evening.

Patients in the ICU will be identified and (if meet the inclusion criteria and consent obtained), will be randomised to receive *either;*

Treatment A: Conventional positive pressure ventilation, or
Treatment B: High frequency oscillatory ventilation.

The primary outcome is mortality at 30 days after randomisation. An economic analysis will be carried out.

The control group will be ventilated using conventional positive pressure ventilation using pressure-controlled artificial ventilation.

The intervention group will receive high frequency oscillatory ventilation. This will be delivered using the Vision Alpha ventilator. This machine has a long history of use in Japan but has only recently been CE marked for European use (May 07).

Whilst 18 randomised controlled trials of HFOV have been carried out in infants with respiratory distress syndrome [38-42], only two small RCTs in adult with ARDS were identified in a systematic review carried out in 2006 [9-10]. The inconclusive results of previous trials are largely the result of their small size. As recognised by the referees reviewing the protocol and existing evidence on behalf of the Health Technology Assessment programme (the funder), a much larger trial is required; the OSCAR Trial.

Full details follow in the main section of the Protocol.

MAIN SECTION

# 1 THE NEED FOR A TRIAL OF HIGH FREQUENCY OSCILLATORY VENTILATION IN ADULTS

The acute respiratory distress syndrome (ARDS) is a severe lung condition that accompanies many critical illnesses. Though ARDS is reasonably uncommon, with an incidence estimated at about 78-280 cases per million population per year, it is associated with a very high mortality (40% or greater). Many of the deaths occur in young or middle aged patients. In survivors, ARDS causes derangement of lung function for two years or more after hospital discharge [2,3], as well as marked reductions in quality of life. Although patients with ARDS only account for 8% of ICU admissions, because they have a long average stay in ICU they use about a quarter of ICU bed-days [4].

To date only one treatment has been shown to decrease mortality in patients with ARDS, pressure- and volume-limited artificial ventilation. This technique reduces pressure swings within the lung, and so reduces the secondary lung damage caused by artificial ventilation [5].

The benefits of volume-limited artificial ventilation may increase as the tidal volume (breath volume) 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 from secondary lung damage. Yet in spite of years of largely positive experimental studies, case series and small clinical trials, there are no adequate, large-scale randomised controlled trials to determine whether HFOV confers any advantage to patients requiring artificial ventilation for acute hypoxaemic respiratory failure, when compared with conventional artificial ventilation. A recent Cochrane systematic review, also published as a journal paper, [6, 7] located only two methodologically sound RCTs in this area, one in children [8] and one in adults [9]. One further trial [10] has been published since the review. Both studies involving adults were small (148 and 61 patients respectively) and therefore could not be expected to detect clinically meaningful differences in outcome.

There is increasing use of HFOV in UK adult ICUs. In the last five years 26 ventilators were sold in the UK, with 10 of these purchased in the last year. This increasing use is occurring without any clear evidence of efficacy, in a patient population and setting where a trial to obtain this information is perfectly feasible.

# 2 EXISTING STATE OF KNOWLEDGE

## 2.1 Overview of acute respiratory distress syndrome and acute lung injury

Acute hypoxaemic (“type 1”) respiratory failure 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 extra-pulmonary pathology. The term acute (or adult) respiratory distress syndrome (ARDS) was coined nearly forty years ago [11] to describe the acute respiratory failure that accompanies severe systemic disease, but over the years has expanded to cover virtually all non-cardiogenic causes of hypoxaemic respiratory 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 [12]. Two degrees of severity were recognised, Acute Lung Injury (ALI) and the more severe Acute Respiratory Distress Syndrome (ARDS). Features common to both were:

- Acute onset of impaired oxygenation
- Bilateral infiltrates on chest radiograph
- Pulmonary artery wedge pressure <18mmHg or exclusion of cardiogenic pulmonary oedema by other means
- A known precipitant of acute respiratory failure.

The degree of severity was determined from the ratio of arterial oxygen tension to the fractional concentration of inspired oxygen, the $PaO_2/FiO_2$ ratio or P/F ratio. If this was 26.7 – 40kPa (200-300mmHg) the patient had ALI, if it was less than 26.7kPa (200mmHg) 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 [13], and between large national and sub-national epidemiological studies [14-18]. There is now a large literature on the incidence and short-term outcome from ARDS.

As ARDS never occurs in isolation, but is always 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 gas exchange, such as extra-corporeal membrane oxygenation (ECMO), 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 [5] 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, whilst immediately life saving, could in the longer term cause lung damage in addition to that caused by the primary disease. For this reason attention has again focussed on artificial ventilation techniques like HFOV which, at least in experimental studies [19, 20], minimise secondary lung injury.

## 2.2 Background to high frequency ventilation

### *2.2.1 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 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 [21] 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 minor 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 [22]. Automatic

artificial ventilators which did not require a human as a power source were proposed by Fell 150 years later [23] and made commercially available by Draeger in 1907 [24]. These were still resuscitation devices, the Draeger 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 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 [25]. 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.

### *2.2.2 History of high frequency ventilation*

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 alveolar gas exchange takes place. Anatomical dead space is usually about 2ml $kg^{-1}$ in adults, and tidal volumes are usually set at about 10ml $kg^{-1}$ in anaesthetic practice, and 6-8ml $kg^{-1}$ 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 [26] noted that panting dogs were able to eliminate carbon dioxide, even though each breath was less than their anatomical dead space. In 1954 Briscoe [27] 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 variously attributed to either Lunkenheimer in 1972 [28] or Jonzon in 1971 [29], both of whom used the technique to minimise the cyclical effects of intermittent positive pressure on the cardiovascular system. Subsequent research into high frequency ventilation initially concentrated on three techniques to deliver the breaths, high frequency oscillatory ventilation (HFOV), high frequency positive pressure ventilation (HFPPV) and high frequency jet ventilation (HFJV). External high frequency oscillatory ventilation (EHFOV) using either a cuirass ventilator [30] or a pneumatic vest [31] 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 eventually became apparent that high frequency jet ventilation and high frequency positive pressure ventilation probably had no special properties and conformed to the conventional, convective, model of gas exchange [32]. However, it also became clear that carbon dioxide clearance could be achieved with HFOV in animals [33] and humans [34] 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 a net inward movement of gas in the core of the large airways and a net outward movement near the wall [35]. These theories have been extensively reviewed [36, 37].

As tidal volumes during HFOV are very small, the peak and mean pressures generated in the lungs 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. This was the rationale behind the early trials of HFOV in infants.

### *2.2.3 Trials of HFOV in infants*

In preterm infants with immature lungs, (infant) respiratory distress syndrome (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 NIH first convened a conference [38] and then commissioned a randomised controlled study. The HiFi Study, published in 1989 [39], recruited 673 preterm 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. Thirteen of these are described in three separate Cochrane reviews [40-42] last updated in 2003. There have been two trials published since 2003, and there are a further 3 independent systematic reviews identifying a further three studies of HFOV. All these studies and reviews are listed in Appendix 1.

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 [43] is that the negative results may be partially due to errors in trial design.

### *2.2.4 Trials of HFOV in adults*

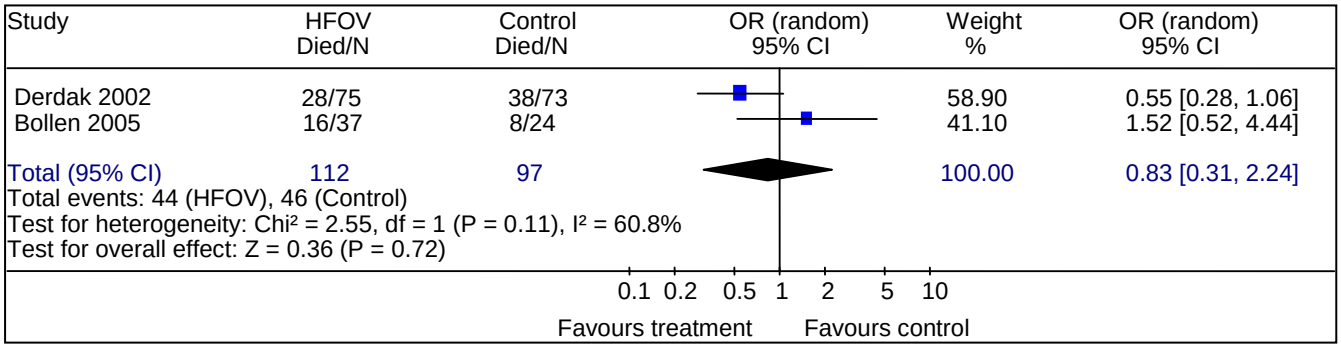
We undertook a systematic review of HFOV in patients with ARDS and ALI in July 2006 to update the 2004 Cochrane review [6]. Amongst the 319 papers identified, there were only two randomised controlled trials of HFOV in adults. Other uncontrolled and retrospective studies of HFOV in patients with ARDS and ALI identified in the systematic review are listed in Appendix 2.

The first and largest randomised controlled trial was published in 2002 [9]. 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, a PEEP of ≥ 10cm$H_2O$, and a predicted 6 month survival of 50% or greater. They initially set the HFOV ventilator to a frequency of 5Hz (breaths per second) and a mean pressure 5cm$H_2O$ 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 10ml $kg^{-1}$. The HFOV group had better oxygen exchange as measured by $PaO_2/FiO_2$ 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 [10]. Recruitment took place in 4 University-affiliated medical centres 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 arm which was not statistically significant.

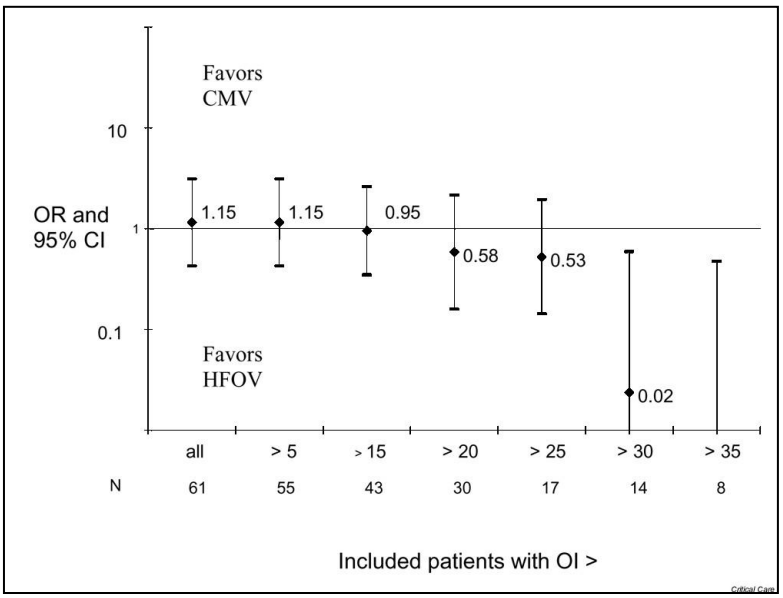
The results for 30 day mortality from both studies have been combined in the forest plot in figure 1. There is no statistically significant benefit for HFOV seen.

*Figure 1: Forest plot showing 30 day mortality in both methodologically sound trials of HFOV in adult patients with ARDS.*



The report from Bollen et al [10] 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. However, 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 lung injury. The figure is reproduced below.

*Figure 2: Post hoc analysis of the treatment effect on mortality relative to baseline oxygenation index (OI). N denotes the number of patients in each subgroup. Taken from Bollen et al [10].*



# 3 IDENTIFICATION OF OTHER DATA TO INFORM THE PROTOCOL DEVELOPMENT

## 3.1 Types of high-frequency oscillatory ventilators available

Although there is a range of high frequency oscillatory ventilators available for neonatal use (e.g. SensorMedics 3100A, Stefan SHF3000, Hummingbird V, Dufour OHF1), there are only two commercially available positive pressure high frequency oscillatory ventilators suitable for adults. The ventilator used in the studies described above is the "SensorMedics Model 3100B high-frequency oscillatory ventilator" manufactured by SensorMedics Corporation in California and distributed in the UK by Viasys Healthcare. This ventilator was approved by the FDA in 2001 for ventilation of "selected patients" over 35kg in weight with acute respiratory failure. The second is the Vision Alpha manufactured in Japan and distributed in the UK by Inspiration Healthcare, which has a long history of use in Japan but has only recently been CE marked for European use. A negative pressure external high frequency oscillatory ventilator for adults ("Hayek Oscillator") is also marketed in the UK.

## 3.2 Current users of HFOV in the UK

Viasys Healthcare has provided us with details of all 3100B ventilators ever sold in the UK. A total of 38 ventilators have been sold to 25 adult intensive care units in England, Wales and the Isle of Man in the last 8 years. Eighteen units have one ventilator; the remainder have two or three devices.

## 3.3 'Substantial uncertainty' within units already using HFOV

To run a randomised controlled trial of HFOV in intensive care units 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 will to be randomised in a 1:1 ratio to conventional positive pressure ventilation or HFOV, up to 50% of the patients that the clinicians would treat with HFOV under 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 ICU's, where each consultant works for a block of time before handing onto a colleague, means that 'substantial uncertainty' has to be present in the whole team to ensure the allotted trial treatment is 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 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. Cross-over 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 these problems had occurred in previous trials. In the clinical trial of HFOV reported by Bollen in 2005 [10] 61 patients were recruited from four major European ICUs in 41 months, or about 1 patient per centre per 3 months. This would be about 0.4% of total admissions. All these ICUs had

prior experience with HFOV. The inclusion criteria for the study were the standard Consensus criteria for ARDS [44] which include patients with a $PaO_2/FiO_2$ ratio of less than 26.7kPa (200mmHg). The mean $PaO_2/FiO_2$ ratio in the treatment arm was 12.6kPa and in the control arm 16.0kPa. No CONSORT diagram was published. From published data we know that about 8% of admissions 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 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. Cross-overs (18%) occurred by protocol in this study.

The other clinical trial reported by Derdak in 2002 [9] took place in 13 University-affiliated medical centres in the USA and Canada over 38 months, a recruitment rate of 1 patient per centre per 3.6 months. There are no data on whether these centres had prior experience with HFOV but at least 7 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 $PaO_2/FiO_2$ ratio in the treatment arm at enrolment was 15.0kPa and in the control arm 14.6kPa. Again no CONSORT diagram was published. Cross-overs 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 the trial.

We discussed the OSCAR trial with the clinical leads or senior clinicians in 5 ICUs where HFOV is currently used. Although all initially expressed interest in the study, when we explained that the study would require withholding HFOV in some patients, four clinicians suggested they could not take part in a trial under these circumstances.

Finally, we reviewed the experience gained by the chief investigator as a member of the management group for the Pac-Man study. This study faced a similar problem as it was examining the effectiveness of a monitoring device already in widespread use in nearly all UK ICUs. The clinicians in ICUs were asked to withhold a pulmonary artery catheter in half the patients they would normally have used one in. Although the study was successful [45], 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.

Based on the data and arguments above, we believe there are considerable risks to running the trial in centres which already have high frequency oscillatory ventilators. We believe the major risk is that HFOV will continue outside the trial as a rescue therapy and so the patients in the study would be an unrepresentative sample.

## 3.4 Identification of other trials of HFOV and trials competing for the same patient population

### *3.4.1 Identification of other ongoing or planned trials*

Drs Meade and Ferguson from the Canadian Critical Care Trials Group (CCCTG) have received funding for a national pilot study of HFOV. The OSCAR team are in contact with Dr Meade and will agree a common core dataset.

The NHLBI in the USA has funded a phase II study of HFOV using surrogate outcome measures (inflammatory cytokine concentrations in plasma) as a prelude to a full clinical trial. The OSCAR team are in contact with the investigators.

We are not aware of any other studies planned or underway. The manufacturers and distributors (SensorMedics and Viasys) of the 3100B HFOV device and the distributor (Inspiration Healthcare) of the Vision Alpha are also not aware of any other studies. There are no ongoing adult studies registered on the International Standard Randomised Controlled Trial Number Register (ISRCTN).

### *3.4.2 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 be ongoing when this trial starts.

Three of the senior applicants are on the management group of BALTI-2 study, a trial of intravenous salbutamol in ARDS. This is in a pilot phase in the West Midlands, and if the pilot is successful will move to a full trial in the same region in May 2007. None of the study sites for BALTI-2 will be taking part in the OSCAR study.

There is a single centre RCT of the effects of simvastatin in patients with ARDS underway in the Royal Victoria Hospital, Belfast.

There are no other ongoing studies of adults with ARDS in the UK registered on the International Standard Randomised Controlled Trial Number Register (ISRCTN). We believe the risk to recruitment to the OSCAR trial because of competing studies is low.

## 3.5 Identification of data to inform estimates of the recruitment rate

A review of epidemiological studies of ALI and ARDS undertaken after the Consensus criteria were formulated in 1994 was recently published [17]. 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 below.

*Table 1. Epidemiological studies of the incidence of ARDS in Europe and Australasia since 1994.*

| Study | Population | Population incidence of ARDS | Percentage of ICU admissions with ARDS | Mortality for patients with ARDS |
|---|---|---|---|---|
| Brun-Buisson et al, 2004 [15] | 78 ICUs across Europe | Not calculated | 6.1% | 49.4% (hospital) |
| Bersten et al 2002 [46] | 21 ICUs in Australia | 28 per 100,000 population per year | Not calculated | 34% (time point not given) |
| Luhr et al 1999 [47] | 132 ICUs in Scandinavia | 13.5 per 100,000 population per year | | 41.2% (90 day) |
| Roupie et al [48] | 36 ICUs in France | Not calculated | 6.9% | 60% (28 day) |
| Monchi et al 1998 [49] | Single French ICU | Not calculated | 7.4% | 65% (28 day) |
| Sigvaldason et al 2006 [13] | All Icelandic ICUs | 7.8 per 100,000 population per year | Not calculated | 40% (hospital) |
| Hughes et al 2003 [4] | 23 Scottish ICUs | 16 per 100,000 population per year | 8.1% | 60.9% (hospital) |

From these studies it would appear the ICU incidence of ARDS in ICUs is about 6-8% of all admissions.

Three estimates of the incidence of ARDS in UK ICUs are 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 [4]. They recorded patients meeting the diagnostic criteria for ARDS (including chest radiographs) on a daily basis. The results are in the table above (Hughes et al).

Two other, unpublished, estimates of the number of cases of ARDS in UK ICUs are available. In both data sets the diagnosis of ARDS is based on the $PaO_2/FiO_2$ ratio only, and does 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 ten-year period to 2005 (more details in the sample size calculations in section 4.16) and found an incidence of ARDS, defined solely on the $PaO_2/FiO_2$ ratio in the first 24 hours of ICU admission, of 49.3%.

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 $PaO_2/FiO_2$ ratios to be calculated. The incidence of ARDS defined on $PaO_2/FiO_2$ ratio only, at any point in the patient's stay, of 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 $PaO_2/FiO_2$ ratio of less than 26.7kPa and any mention of ARDS in the discharge summary.

The true incidence of ARDS in ICU patients is 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 $PaO_2/FiO_2$ ratios of less than 26.7kPa 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 ($PaO_2/FiO_2$ ratio of less than 26.7kPa) only have a very transient reduction in the $PaO_2/FiO_2$ ratio which rapidly improves [50].

### 3.6 Selection of entry criteria, ALI and ARDS or just ARDS?

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 $PaO_2/FiO_2$ ratio of between 26.7 and 40kPa. The more severe band, where the $PaO_2/FiO_2$ ratio was less than 26.7kPa, was termed the 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 $PaO_2/FiO_2$ ratio less than 40kPa, and the term ARDS is used to describe a subset of these with a $PaO_2/FiO_2$ ratio of less than 26.7kPa. We have not used 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.

We have 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 and 30 and 45% inspired oxygen to maintain a normal $PaO_2$ of 12kPa. 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 5,183 mechanically ventilated patients in Europe and North America, patients with ALI had the same mortality as patients with no acute lung injury at all [51].

The two RCTs of HFOV to date have both only recruited patients with ARDS. In the Bollen study [10] 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 (see figure 2). 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 ventilation, most patients with this condition are managed on the general wards. In the Europe-wide epidemiological study of ALI and ARDS [15], only 62 out of 6,522 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 the reasons listed above we believe it would be inappropriate to undertake a study of HFOV that included patients with ALI.

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

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 [52, 53]. At that time the three measures of health-related quality of life that had been most commonly used in follow-up studies of critically ill patients were the SIP/FLP (Sickness Impact Profile/Functional Limitations Profile), the PQOL (Perceived Quality of Life) and the NHP (Nottingham Health Profile). In addition, the SF-36 (Short Form 36 Health Survey Questionnaire) was increasingly being used.

At the time the review was undertaken the EuroQoL (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 [54]. 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 quality of life in survivors of critical illness [55].

The SF-36 is a feasible and reliable instrument with sufficient discriminatory power to detect changes in the health-related quality of life of ICU patients with different levels of chronic health and varied severity of their acute illness [56]. SF-36 contains 36 items to measure 8 quality of life 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 [57].

EQ-5D is also a general health-related quality of life measure that has also proven to be a useful tool in a mixed critical care population [58]. The EQ-5D comprises 2 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 EQ-VAS, a self-rated health status using a visual analogue scale (VAS), 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) [54].

As part of the background work for the ICON study (a study of long-term ICU survival and quality of life being run by the principal investigator) a systematic review of all the ICU outcome studies that have used either EQ-5D, SF-36 or both was undertaken. The studies identified are listed in Appendix 3. Numerically there are more studies that use the SF-36, though there are 8 high-quality studies using the EQ-5D. A similar systematic review was published in 2005 but this only identified 5 of the 8 studies using EQ-5D [59].
A direct comparison of the EQ-5D and SF-36 as measures of health-related quality of life in ICU survivors was undertaken in Sheffield in 2004 [60]. 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. 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 has been made on a number of grounds. The EQ-5D serves both as a measure of health-related quality of life and as a utility measure for calculating quality-adjusted life years. There is a large (3,400) reference population database available, and the ICON study will generate data on a population of mixed ICU survivors at the same time as the OSCAR trial is running, so we will have two appropriate reference populations. There is a large 11 centre study of survivors of ARDS planned in Baltimore, USA [61] which will use EQ-5D as an outcome measure, allowing trans-Atlantic comparisons.

Practically the EQ-5D is the simpler of the two instruments for the patients to complete, and follow-up of non-responders is easier. Machine-readable questionnaires are already available (developed for ICON) and the required hardware is in the study office, along with software to log responses and store the data. For these reasons we will use EQ-5D in the study.

We had originally planned to use formal, laboratory pulmonary function tests to determine residual respiratory dysfunction in survivors. However, two recent, high quality studies suggest this may not be cost-effective. The studies followed survivors of ARDS for up to two years [2, 3]. At both one and two 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 [53]. The six-minute walk distance was also reduced compared with predicted values at both one and two 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 six-minute walk acts as a surrogate measure for muscle wasting. Thus the probability of distinguishing between treatment arms 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 is probably unwise.

Instead we will use a questionnaire to determine respiratory function. The general questionnaires most commonly used in respiratory medicine are the ATS Respiratory Function Questionnaire and the St. George's Respiratory Questionnaire (SGRQ). The latter has been extensively validated in non-ICU populations. It has good test-retest/reproducibility and internal consistency. It correlates well with other measures of disease activity ($FEV_1$, FVC, $SaO_2$ at rest, 6-minute walk distance, MRC dyspnoea grade, and symptom, activity, and impact domains in health-related quality of life instruments). As this instrument apparently has had only limited use in the critical care population [62] we will undertake a systematic review to determine if other validation studies are available.

# 4 DESIGN AND METHODOLOGY

## 4.1 Trial design

OSCAR is a UK multicentre, open, randomised controlled trial.

## 4.2 The hypothesis

The hypothesis is that patients with acute respiratory distress syndrome (ARDS) who are treated with high frequency oscillatory ventilation (HFOV) will have a decreased mortality at 30 days (post randomisation) compared with patients treated with conventional positive pressure ventilation.

## 4.3 Eligibility

### *4.3.1 Centres:*

Ten or more adult ICUs in the NHS in the United Kingdom able to care for Level 3 patients as defined by “Comprehensive Critical Care” [1] will be recruited.

An ICU will be considered for collaboration in the trial if it meets the following criteria:

- The number of annual admissions to the ICU suggests patients with ARDS will present frequently.
- The ICU has a history of collaborating in research and staff are keen to be involved.
- All consultants in the ICU have ‘substantial uncertainty’ about the use of HFOV generally and would be prepared to enter patients into a trial comparing HFOV with conventional treatment for patients with ARDS.
- Consultants will attend HFOV training.
- The Principal Investigator will negotiate the release of all other appropriate staff for HFOV training.

### *4.3.2 Patients:*

Patients are eligible for the trial if they meet the following inclusion criteria:

i. Age ≥16 years

ii. Weight ≥35 kg

iii. Receiving artificial ventilation via an endotracheal or tracheostomy tube

iv. Have acute hypoxaemic respiratory failure as defined by:

- √ 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 $cmH_20$
- √ Bilateral infiltrates on chest radiograph

v. Will not be extubated by tomorrow evening (predicted by attending clinician)

vi. Have been mechanically ventilated for LESS than 7 consecutive days (≤ 168 hours) at the point of randomisation.

Once a patient meets one of the exclusion criterion screening should be stopped.

See also Figure 3 (patient screening and recruitment flowchart).

## 4.4 Patient exclusion criteria prior to trial entry

Patients who could not benefit from HFOV:

i. Patients with left atrial hypertension from any cause, diagnosed clinically or with echocardiography or pulmonary artery catheterisation.

ii. Patients who have been mechanically ventilated for more than 7 consecutive days at the point of enrolment.

Patients in whom HFOV might be hazardous:

iii. Patients with moderate or severe airway disease expected to cause expiratory airflow limitation.

iv. Patients who have had a lung biopsy or resection during this hospital admission.

v. Patients with any other condition the clinician believes would make receiving HFOV hazardous.

Administrative, practical and ethical exclusions:

vi. Patients previously enrolled in the OSCAR trial.

vii. Patients (or their representative*) who refuse consent.

viii. Patients (or their representative*) who do not understand written or verbal information and for whom no interpreter is available.

ix. Patients enrolled in another therapeutic trial in the 30 days prior to randomisation.

x. Patients in whom active treatment has been withdrawn or withdrawal is planned.

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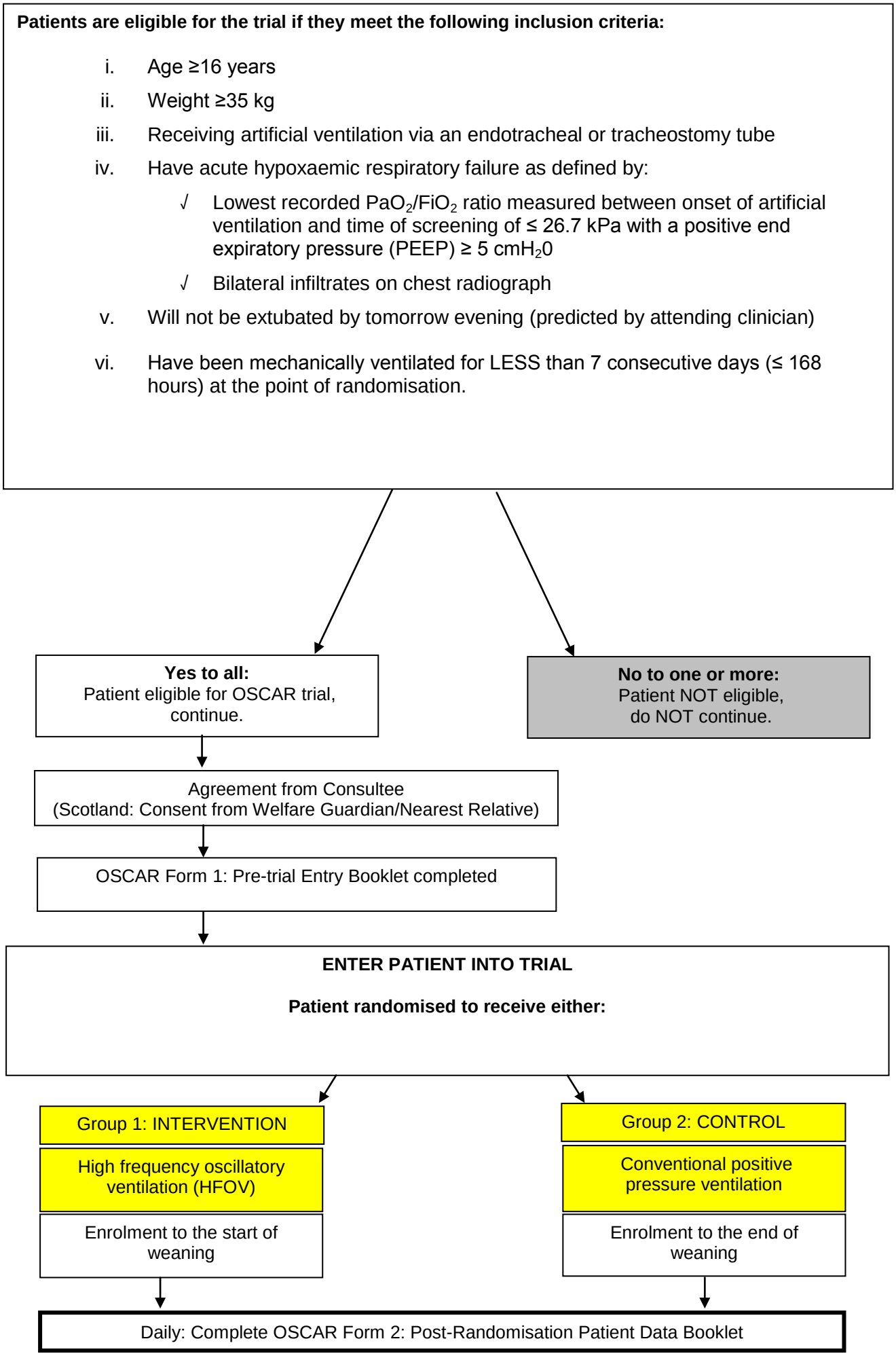
**'Consultee' (personal or nominated professional), in England and Wales; 'Welfare Guardian/Nearest Relative' in Scotland.*

**FIGURE 3: PATIENT SCREENING AND RECRUITMENT FLOWCHART**



## 4.5 The intervention and control groups

The study arms being compared in this trial are:

**Group 1: High frequency oscillatory ventilation (HFOV)**

*Versus*

**Group 2: Conventional positive pressure ventilation**

The control group will receive conventional positive pressure ventilation using conventional pressure-controlled, artificial ventilation.

The intervention is high frequency oscillatory (artificial) ventilation (HFOV) delivered using a Vision Alpha ventilator. The management of artificial ventilation with HFOV will be based on a simple algorithm as shown on page 25.

Both groups will begin the treatment following randomisation and the patient will remain on the ventilator until the start of weaning from artificial ventilation.

## 4.6 Patient consent

Patients will be unable to give informed consent due to alterations in conscious level caused by illness and therapeutic sedation. Consent will therefore be obtained in line with the legal requirements in England and Wales (Mental Capacity Act 2005), and in Scotland (Adults With Incapacity (Scotland) Act 2000). See appendix 4 for informed consent process, information and forms.

If a patient or their representative* refuses consent the patient will receive the usual treatment as defined by the clinician responsible for the patient's care.

## 4.7 Formal trial entry and random allocation of patients

Patients eligible for the trial should be randomised. Randomisation is carried out by telephoning a specialist randomisation service which is open 24-hours a day, 7 days a week. The call will take only a few minutes. Basic descriptive information will be requested and once these details have been supplied, the random allocation will be given in return. Stratification will be by recruiting ICU, age of patient and $PaO_2/FiO_2$ ratio.

## 4.8 Patients not in the trial

Brief details of patients initially eligible for the trial but not entered into the trial will be recorded on a 'Why not in trial' log at each collaborating unit. Recording this information is to establish an unbiased case selection and full reporting according to the CONSORT statement [64, 65]. See Appendix 12.

---

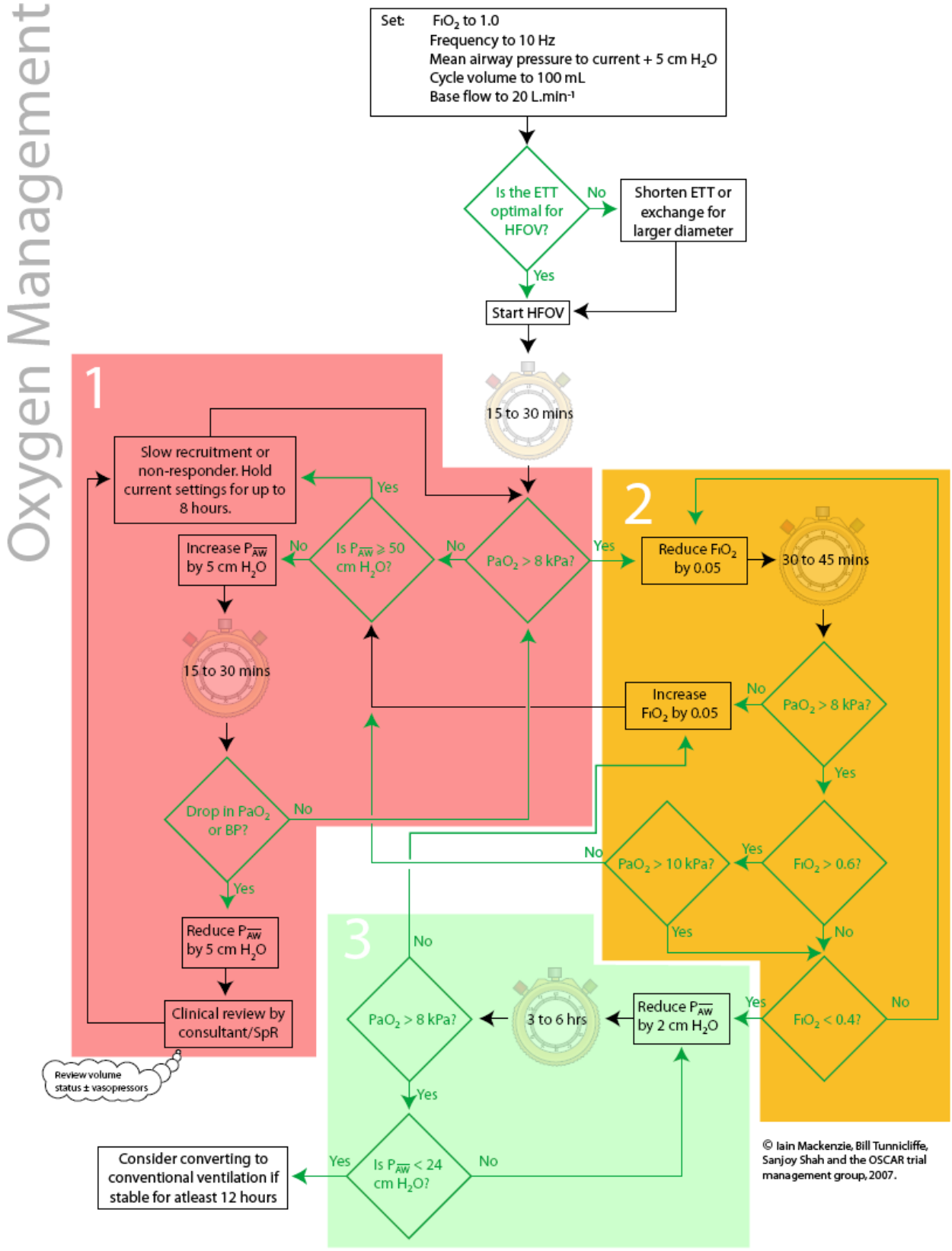
**'Consultee' (personal or nominated professional), in England and Wales; 'Welfare Guardian/Nearest Relative' in Scotland.*

## 4.9 Treatment

### *4.9.1 Clinical management of the patients in the high frequency oscillatory ventilation arm*

Clinicians will be trained to adjust the ventilator according to a protocol derived from guidelines which have been used successfully at Addenbrookes Hospital ICU (Cambridge) and the University Hospitals, Birmingham, for 5 years. It is virtually identical to the protocols used in the two published randomised controlled trials (MOAT and eMOAT). The flow diagram is shown on the next page.

*Figure 3: The algorithm for managing HFOV.*

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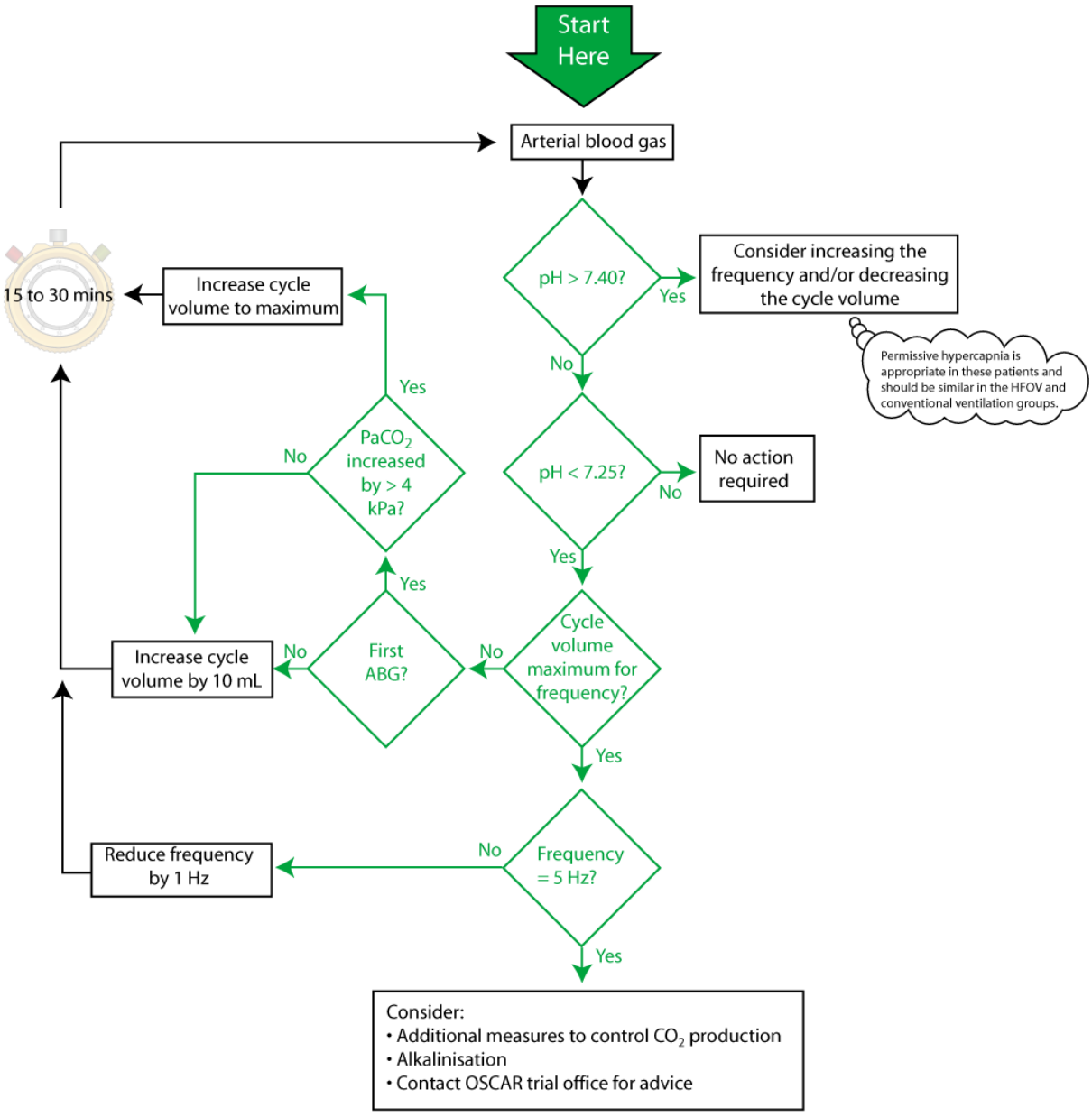
# Carbon Dioxide Management



*4.9.2 Clinical management of patients in the control arm (conventional ventilation)*

We will suggest but not mandate that control patients be managed using the current best conventional ventilation strategy. This is limited tidal volume, pressure controlled artificial ventilation using tidal volumes of 6-8ml $kg^{-1}$ body weight.

We recommended the following combinations of $FiO_2$ and PEEP:

| FiO2 | PEEP |
|---|---|
| 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 |

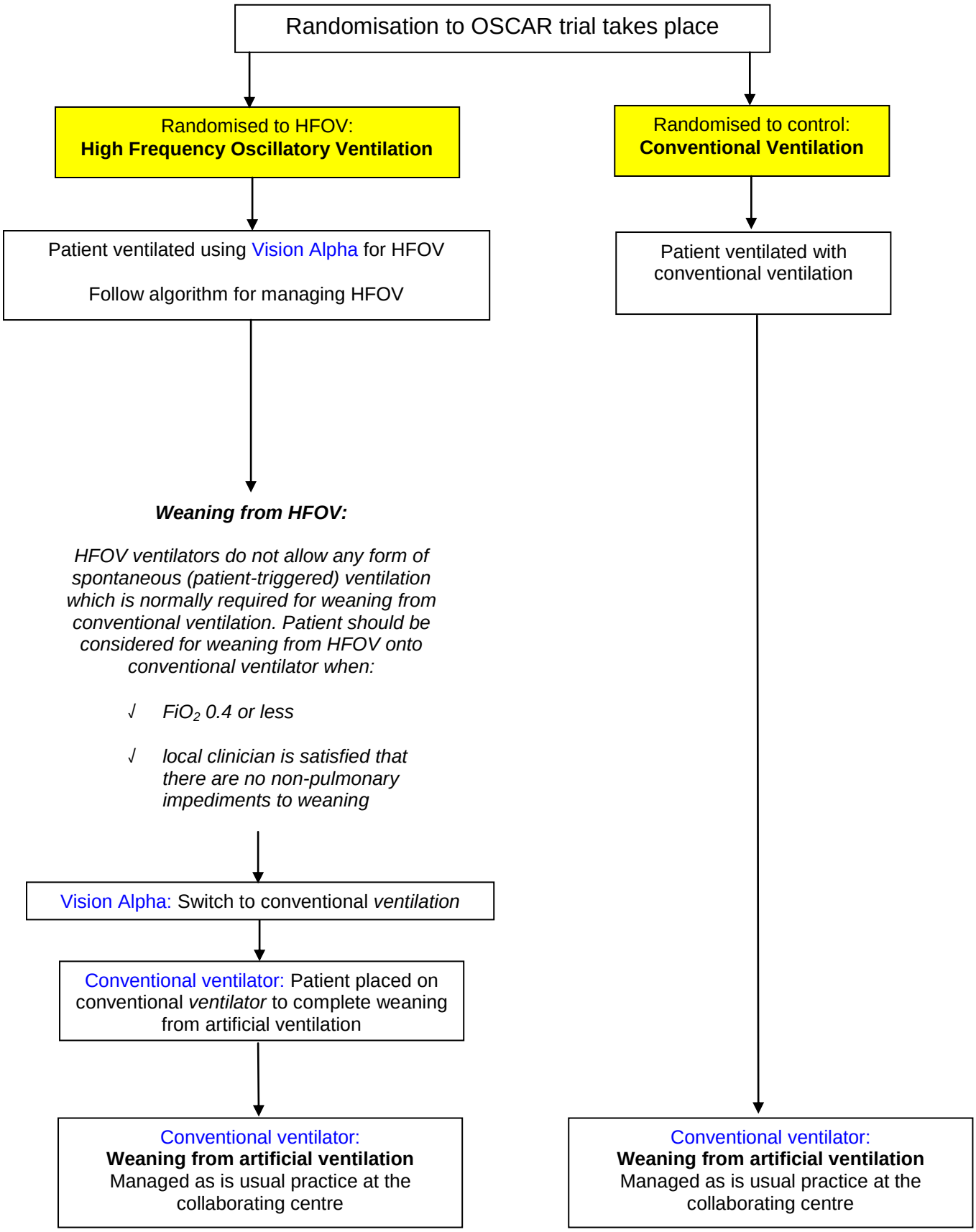
This ventilation strategy is normal practice in most UK ICUs.

*4.9.3. Proposed duration of treatment and weaning*

The patients will continue on HFOV until they have recovered sufficiently to be weaned from artificial ventilation when their $FiO_2$ is 0.4 or less, and the local clinician is satisfied that there are no non-pulmonary impediments to weaning. The HFOV ventilators do not allow any form of spontaneous (patient-triggered) ventilation which is normally required for weaning, so at this point the patients will be placed back on conventional ventilation and weaned according to local protocols using inspiratory pressure support.

The point at which patients can be weaned from conventional artificial ventilation depends on a large number of factors that cannot be protocolised.

**FIGURE 4:** PATIENT TREATMENT AND WEANING FLOWCHART



## 4.10 Serious adverse events (SAEs)

We are following the reporting guidelines from the National Research Ethics Service for safety reporting in research *other than* clinical trials of investigational medicinal products.

### *4.10.1 What is a SAE*

A SAE is an *untoward* and *unexpected* occurrence that a research participant experiences which:

i Results in death
ii Is life threatening
iii Requires hospitalisation or prolongation of existing hospitalisation
iv Results in persistent or significant disability or incapacity
v Consists of a congenital anomaly or birth defect.

### *4.10.2 Reporting a SAE:*

An SAE must be recorded on the appropriate trial form by the clinician caring for the patient and reported locally immediately to the Principal Investigator at that centre. The Principal Investigator will then report the SAE to the Chief Investigator of the OSCAR trial, Dr J D Young, within 3 working days of the event:

Dr Duncan Young, Chief Investigator, OSCAR Trial Office, Kadoorie Centre for Critical Care Research and Education, John Radcliffe Hospital, Oxford OX3 9DU. Tel: 01865 857613, Fax: 01865 857611, Email: OSCAR.trial@nda.ox.ac.uk.

Dr Young will give an opinion as to whether the event is:

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

A confirmed, related, SAE will be submitted to a Main Research Ethics Committee within 15 days of the Chief Investigator becoming aware of the event using the NRES report of serious adverse event form.

## 4.11 Expected events

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

1) Air trapping
2) Secondary effects of air trapping such as reduced carbon dioxide clearance.

## 4.12 Outcome measures

| | |
|---|---|
| Primary outcome measure: | Mortality (all causes) 30 days after randomisation. |
| Secondary outcome measures: | Mortality rate at first discharge from ICU<br>Mortality rate at first discharge from hospital<br>Mortality rate one year after randomisation<br>Non-pulmonary organ failures whilst treated on an intensive care unit<br>Health-related quality of life six months after randomisation<br>Health-related quality of life one year after randomisation<br>Pulmonary function one year after randomisation<br>Ventilator-free days<br>Antimicrobial-free days<br>Sedative-free days |
| Primary health care system benefit: | Cost per quality-adjusted life year gained one year after randomisation |
| Secondary health care system benefits: | Intensive care unit length of stay<br>Hospital length of stay<br>Utilisation of hospital resources after acute hospital discharge one year after randomisation<br>Utilisation of community care resources after acute hospital discharge one year after randomisation |

## 4.13 Data collection

Data related to the primary and secondary outcomes and for long term follow up of patients will be collected in a standardised way onto a trial specific case report form. Copies will be retained at the recruiting centre. Data will be transcribed onto the form from the patients' notes or the clinical information system (CIS) by the team responsible for the patients' care.

Before the study starts, data collection forms will be piloted to determine ease of use and other practical issues.

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

The trial office may 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 six months and one year after randomisation, 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.

### 4.14 Health Economics

Economic analysis will be undertaken to investigate the short and longer term cost-effectiveness of HFOV in ARDS patients. Analyses for this study will be undertaken from an NHS perspective. The main health economic outcome will be the health status of survivors of ARDS at 6 months (from EQ-5D data) which will be converted into Quality Adjusted Life years (QALYs) to allow cost-utility modelling. Additionally, a range of modelling techniques will be used to estimate longer-term cost-utility from one year follow-up data. Epidemiological and economic models will be used to estimate lifetime gains in QALYs from HFOV and savings in health care expenditures. A full literature review will be undertaken to explore the potential for providing monetary estimates of the long term impacts of HFOV. This work will be 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 will be prepared, and in at least one unit from each cell in the sampling frame we will undertake a micro costing study for patients with ARDS.

A research assistant will visit these units to observe the care patients with ARDS receive and then cost it, along with representative patients not suffering from ARDS. The units will 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, will be 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 quality of life beyond 12 months, patients recruited in the first year will receive 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 will received an additional EQ-5D questionnaire and questions concerning social and health service use at 18 months. This will allow us to model the time for health-related quality of life to return to population normal levels after ICU by group.

### 4.15 Sample size

The planned sample size is 802 patients (401 in each arm).

*Update October 2009: Section 4.15 to 4.17 details the required sample size (N=1006; with 503 per arm) and how it was planned to achieve this prior to this amendment.*

*The expected rate of recruitment, as detailed in section 4.17, was just over 2 patients per centre per month. Since 1st December 2007 (start of recruitment) to 1st 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 under recruiting.*

*After reviewing various strategies of increasing recruitment with experts in this research field, the Data Monitoring Committee (DMC) and the Trial Steering Committee (TSC), it was agreed that the effect size based on the clinical relevant difference should be re-visited and closely assessed. The original sample size was based on 9% absolute change in mortality and this was obtained from the only study of ventilation in ARDS (the 'ARDSnet' study), which showed a benefit.*

*The data was un-blinded (at the request of the HTA) and approval to un-blind the control rate mortality has been agreed jointly between the chairperson of the Trial Steering Committee (Professor Deborah Ashby) and the chair of the Data and Ethics Monitoring Committee (Professor David Torgerson). It was agreed that this information should be shared with the trial statistician and the HTA only. The sample size using a 10% absolute change in mortality was re-calculated, with 80% power and 5 % significance level, suggesting a total of 802 patients (with 401 per treatment arm). This re-calculated 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.*

## 4.16 Justification for sample size and details of the power calculation

[See October 2009 update in 4.15 above]
The sample size calculations are based on the primary outcome measure, 30 day all-cause mortality. Data are available for all-cause mortality in patients meeting the entry criteria for the proposed study from a number of sources.

Large epidemiological studies of ARDS in Europe have been undertaken at regular interval over the last decade. The most recent is the ALIVE study [15], which collected data from February to March 1999 from 78 ICUs across Europe. Cases of ARDS were identified at any point in their ICU stay using the American-European Consensus Conference criteria. A total of 401 cases of ARDS were identified amongst 6,522 admissions. Hospital mortality was 57.9%, 30 day mortality was not recorded.

These data are robust but are an average across multiple European ICUs, are 7 years old, and the 30 day mortality is not known.

Data collected and analysed by the Intensive Care National Audit & Research Centre (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 $PaO_2/FiO_2$ ratio recorded in the first 24 hours after ICU admission, and categorized into acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) using the American-European Consensus Conference on ARDS definitions [12] 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, median length of hospital stay was 16 days.

The main drawbacks with the ICNARC data are that they only identify patients who meet the study entry criteria in the first 24 hours following ICU admission, they are based on a single blood gas estimation, there is no chest radiograph data, and the quoted mortality is hospital, not 30 day mortality. More details on the limitations of the ICNARC data are given in section 3.5.

We 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 $PaO_2/FiO_2$ ratios to be calculated. The incidence of ARDS, defined using a $PaO_2/FiO_2$ ratio of less than 23.7kPa at any point during the patient's stay, was 78.9%. However only 2.5% of the patients had both a $PaO_2/FiO_2$ ratio of less than 26.7kPa and any mention of ARDS in the discharge summary. These patients had a 38% 30 day mortality.

The limitation of the Oxford data is that true incidence of ARDS in ICU patients is 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 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 [4]. They only recorded patients meeting the diagnostic criteria for ARDS, but unlike ICNARC determined whether patents had ARDS on a daily basis, rather than only on admission, and included chest radiographs in the inclusion criteria. They reported a 61% hospital mortality for patients meeting the ARDS criteria at any point in their ICU stay.

The main drawbacks of the SICSAG data are that they are now 7 years old, and the data are hospital not 30 day mortality.

To calculate the sample size we have assumed that hospital mortality is close to 30 day mortality, and have chosen a middle value from the available data, namely 45%. We have used the effect size from the only intervention known to alter mortality in ARDS [5] as our predicted effect size (9% absolute mortality reduction). This is close to the effect size in the unweighted pooled data from the two RCTs performed to date (8.1% absolute mortality reduction, see figure 1). We know that the loss of patients to the Pac-Man study [45] due to withdrawals was in the order of 3%. Cross-overs will be analysed on an intention to treat basis and so no correction is required. Using an 80% certainty of detecting this difference at $p \leq 0.05$ with a control group mortality of 45% requires 503 patients in each arm, a total study size of 1006.

Table 2 gives the reduction (or increase) in mortality detectable with 1006 patients using each of the estimates of hospital mortality. Note that the absolute mortality reduction detectable is insensitive to the mortality estimate used.

*Table 2: Hospital mortality estimates and detectable changes with 1006 patients.*

| Source of estimate | Hospital mortality (%) | Absolute mortality reduction detectable | Relative mortality reduction detectable |
|---|---|---|---|
| ALIVE study | 58% | 9% | 16% |
| ICNARC | 42% | 9% | 21% |
| SICSAG | 61% | 9% | 15% |
| Oxford data | 38% | 9% | 24% |

Table 3 gives the sample sizes required for increasing the power of the study.

*Table 3: Sample size calculations for varying power, p=0.05, control group mortality 45%.*

| Power | Total sample size | Sample size allowing for dropouts |
|---|---|---|
| 80% | 976 | 1006 |
| 90% | 1290 | 1330 |
| 95% | 1584 | 1632 |
| 99% | 2220 | 2288 |

## 4.17 Planned recruitment rate

[See October 2009 update in 4.15 above]

Recruiting patients from 12 large UK ICUs admitting at least 650 patients per year each gives a potential pool of patients of 7,800 admissions per annum or 23,400 in the 36 months OSCAR would recruit over. Based on the incidence of ARDS found in Scotland [4] of 8.1%, this would give a potential pool to recruit from of 1895 patients. From previous studies in ICU (the completed Pac-Man study and the ongoing TracMan, PERMIT and SimSepT studies) we know that the refusal rate for consent to research in ICU is approximately 30%. This would leave about 1320 potential patients for the OSCAR study, about 30% more than required. The required recruitment rate is just over 2 patients per month per site.

With a single HFOV ventilator at each site, it will only be possible to recruit when the ventilator is available. No data on the mean duration of ventilation with HFOV are contained in the reports of the RCTs, but in the SICSAG report patients with ARDS have a mean length of ICU stay of 13.6 days. As, even for patients randomised to receive HFOV, a significant proportion of this time will be a weaning phase on conventional ventilation, we predict unavailability of machines will not be a major bar to recruitment.

Adding additional centres to this study to give a greater safety margin for recruitment is very expensive in both equipment and personnel. We are reasonably confident that with local part time study staff, a manageable number of ICUs, and careful central trial management this recruitment is achievable.

## 4.18 Type of analysis

Dr Ranjit Lall, Senior Statistician at Warwick, will act as trial statistician and perform the analyses. A detailed clinical trial analysis plan will be submitted to the DMEC for approval. Standard approaches will be used to detect patterns in missing data. All analyses will be on an intention to treat basis. For the primary, and other, dichotomous outcomes risk ratios and 95% confidence intervals will be calculated. Time to event outcomes such as duration of ventilation or duration of hospital stay will be analysed using survival methods and reported as hazard ratios and 95% confidence intervals.

## 4.19 Subgroup and exploratory analyses

Additional analyses will explore:

- The effect of HFOV on length of 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 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 hospital stay, 30 day and hospital mortality in patients with differing severity of lung injury determined from their $PaO_2/FiO_2$ ratio.

## 4.20 Compliance and crossovers

The primary responsibility for the care of ventilated patients on ICUs passes from one consultant to the next on a daily or weekly basis depending on the type of duty roster. To ensure compliance with the trial protocol throughout a patient's stay, and to avoid cross-over after allocation, units will only be signed up to the trial and given access to an HFOV ventilator, if they agree to use it only for OSCAR patients. Only ICUs where *all* the consultants agree to abide by the protocol will be used as recruiting centres. Centres that use the HFOV ventilator outside of the trial will have the ventilator removed and a new site initiated.

All trial participants will be analysed according to the intention to treat principle. There is no provision in the protocol for cross-over from conventional ventilation to HFOV. Patients who suffer HFOV-specific complications will be placed on conventional ventilation.

## 4.21 Frequency and timing of interim analyses

The frequency and timing of analyses will be determined by the Data Monitoring and Ethics Committee (DMEC) in line with its Standard Operating Procedures.

# 5 ORGANISATION

## 5.1 The Data Monitoring and Ethics Committee (DMEC)

The DMEC will comprise of a senior statistician, a senior clinician, and a senior trialist (Chair), see Appendix 6 for membership details.

*Standard Operating Procedures for the DMEC:*

1) 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 will be supplied, in strict confidence, to the chairman of the DMEC, along with any other analyses that the committee may request.

2) In the light of these analyses, the DMEC will advise the Chairman of the Steering Committee if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management.

3) Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but the DMEC will work on the principle that a difference of at least 3 standard deviations in an interim analysis of a major outcome event may be needed to justify halting, or modifying, a study before the planned completed recruitment. These criteria have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed.

4) Following a report from the DMEC, the Steering Committee will decide whether to modify entry to the study (or seek extra data). Unless this happens the Steering Committee and the collaborators will remain ignorant of the interim results.

5) Data relating to the safety of patients will be reviewed by the Chair of the DMEC once 50 patients have been randomised to the trial. The data reviewed will specifically relate to:

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

6) The DMEC will meet to review at one year, or at 100 deaths, whichever occurs first. The DMEC will meet at intervals determined by the DMEC chair.

## 5.2 The Steering Committee

The trial will be guided by a group of respected and experienced critical care personnel and trialists as well as a 'lay' representative. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email and post (see Appendix 7 for membership details).

*Standard Operating Procedures for the Steering Committee:*

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility 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.

## 5.3 Project Management Groups Responsibilities

This group is made up of the investigators on the grant application to the Health Technology Assessment programme plus the OSCAR co-ordinating team (see Appendix 8 for membership details). They will be responsible for:

- Monitoring the progress of the trial and discussing project milestones
- Reviewing centre and patient recruitment to the trial
- Discuss day to day management issues that arise.

## 5.4 Collaborators Responsibilities

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

- Comply with the protocol at all times
- Discuss the trial with medical and nursing staff who treat ICU patients and ensure that they remain aware of the state of the current knowledge, the trial and its procedures (posters and other 'reminders' will be provided by the trial office).
- Ensure that patients in the ICU are considered promptly for the trial
- Ensure that the trial case report forms and consent forms are completed in full

- Ensure the trial is conducted in accordance with the Research Governance Framework and Good Clinical Practice and fulfils all national and local regulatory requirements
- Allow access to source data for audit and verification.

### 5.5 Co-ordinating Centre Responsibilities:

The trial will be co-ordinated by the ICS Trials Group based at the Kadoorie Centre for Critical Care Research and Education at the John Radcliffe Hospital in Oxford. Administrative support will be supplied by the Nuffield Department of Anaesthetics,

University of Oxford. Assistance with trial management and the statistical elements of the trial will be supplied by the Clinical Trials Unit at Warwick University. Health economic support and analysis will be provided by the Academic Unit of Health Economics at the University of Leeds.

- 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 Steering Committee, DMEC and Collaborators meetings
- Carry out the trial according to the Research Governance Framework and Good Clinical Practice.

### 5.6 Publication of Results

The success of the trial depends on the collaboration of nurses and doctors in the participating hospitals. Therefore chief credit for the study will be assigned to the collaborators from each participating centre and they will be named personally in the main publications. The results of the trial will be reported first to trial collaborators.

Dissemination of results to patients will take place via the media, the website for the Intensive Care Society (http://www.ics.ac.uk/) and the trial website, and through relevant patient organisations.

### 5.7 Trial Sponsor and Indemnity

Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment with Trust Indemnity available through the NHS Litigation Authority Scheme.

## 5.8 Financial Support

The Health Technology Assessment programme is providing the co-ordination costs for the OSCAR trial along with the costs for leasing the HFVO ventilators.

The NHS cost implications during and after the trial are:

5.8.1 Additional outgoings during the study:

- Drug expenditure

  It is anticipated the total dose of sedative drugs used in the treatment (HFOV) may exceed that used for the usual care arm. As the actual cost depends on the particular sedative used and this is not protocolised, we cannot accurately estimate this. A one-third increase in the average patient's drug costs in the Adult ICU in Oxford would be about £40.

- Laboratory and imaging costs

  No additional cost

- Opportunity costs during the study
  - Time for training clinical staff to perform HFOV
    - Senior clinician 15 hours
    - Senior nurses x 2 15 hours
  - Time for clinicians to recruit to the OSCAR trial
    - Senior clinician 2 hours/patient
  - Time for clinicians to collect data
    - Senior clinician 4 hours/patient

5.8.2 Costs continuing after the trial:

There are no ongoing additional treatment costs after the trial finishes, other than those which may result if survival is improved. Calculating the cost per survivor is one of the outcome measures for the trial.

## 5.9 Ethics Approval

Ethical approval will be sought from one of the NHS Research Ethics Committees set up by NRES with the relevant experience in reviewing research involving medical devices. The ethics application made by the Chief Investigator (Duncan Young), once approved, will cover all collaborating sites.

## 5.10 Local Approvals

A Site Specific Assessment (SSA) approval is required along with Research and Development approval for each Trust. A SSA is not an *ethical* review, but a process of confirming that there are no objections to the trial on site-specific grounds. The Principal Investigator at each ICU will be notified by the Trial Office when it is time to apply for the required approvals.

## 5.11 Patient Information Advisory Group Approval

This is not required as data will only be held on patients for whom we have consented to the study.

## 5.12 Medical Devices Regulations 2002

As the trial will be employing a medical device for a purpose for which it has approval, and the Vision Alpha ventilator has a CE mark, approval from the competent authority (the Medicines and Healthcare Regulatory Authority (MHRA) will not be required.

## 5.13 Supplying the Vision Alpha Ventilators to Collaborating Centres

Collaborating ICUs will have access to a Vision Alpha high frequency oscillatory ventilator, with associated high pressure air/oxygen blenders and humidifiers (leased from the UK distributors by the OSCAR Trial Office). Inspiration Healthcare will supply service replacements within 48 hours if a ventilator, blender or humidifier fails.

Centres will be asked to confirm:

That the machine

- will not be used until the trial office notifies them the appropriate national and local approvals are in place
- will not be used for patients outside of the OSCAR trial
- will be removed from their ICU if there is evidence of violation of its use.

### *5.13.1 Violation of the use of the Vision Alpha*

Should a machine violation take place (evidence that the Vision Alpha has/is being used outside of the trial) the machine will be removed and the lease to that ICU cancelled. A new centre will be invited to collaborate in their place.

### *5.13.2 Vision Alpha/HFOV training*

As HFOV will not have been used previously in most of the intensive care units in the study, before the study starts the clinicians in these units will be trained to operate the HFOV ventilator and follow the treatment algorithm. Experience in neonatal trials where HFOV was introduced into special care baby units that had not previously used the technique suggests a major investment in training is required [39, 43].

Training will be 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 will be organised locally. In addition follow up ‘drop-in’ sessions will be offered. These shorter sessions will suit busy units and allow staff to dip in when possible to top up their skills.

This training will 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 will use the teaching suites equipped with patient simulators ("SimMan") available at Birmingham and Oxford. The trial has a full time, clinically trained, research fellow in the team for the first year to lead and organise the training both centrally and locally.

Inspiration Healthcare will also offer local training based on the need at individual centres.

Teaching material will be prepared at the trial office and distributed to the ICUs taking part, both electronically and on paper.

Inevitably staff at ICUs will need support at the start of recruitment and a member of the OSCAR team will be available to provide advice. In addition a member of the team will regularly travel to collaborating centres to support the use of the HFOV. A website and newsletter will also be used to share any problems and solutions related to HFOV.

### 5.14 Good Clinical Practice and Research Governance

The OSCAR trial does not fall under the EU Clinical Trials Directive (Directive 2001/20/EC) as it is not a medicinal product trial. It is therefore not required by law to work to ICH GCP although works to the *principles* outlined in ICH GCP. All HTA funded projects are expected to conduct their research in accordance with the Medical Research Council's Good Clinical Practice guidelines and the Department of Health's Research Governance Framework.

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## Appendix 1: Randomised controlled trials and systematic reviews of HFOV in infants

Trials

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**Appendix 2: Randomised controlled trials and case series of HFOV in adults identified in a systematic literature search, August 2006.**

## a) Prospective trials (RCTs) of HFOV compared with conventional ventilation as a primary intervention

| First author | Bollen [10] | Derdak [9] |
|---|---|---|
| Publication year | 2005 | 2002 |
| Aim of HFOV | Primary treatment | Primary treatment |
| Patient population | Adults with ARDS | Adults with early-phase ARDS |
| Study type | Multi-centre RCT | Multi-centre RCT (MOAT trial) |
| Setting | 4 ICUs (2 UK, 1 French, 1 German) | 13 US Medical Centres |
| Age limits | | 16 or older |
| Inclusions | Adults with ARDS | Adults with ARDS, PaO2/FiO2 ratio ≤200mmHg while on PEEP ≥10cm H2O, bilateral radiographic pulmonary infiltrates, no clinical evidence of left atrial hypertension |
| Exclusions | Weight less than 35kg, non-pulmonary terminal disease, severe COPD or asthma, grade 3 or 4 airleak, patients with $FiO_2$>0.80 for 48 hour or more than 10 days of MV | Weight less than 35kg,<br>Severe COPD,<br>Asthma, Intractable shock,<br>Severe air leak,<br>Non-pulmonary terminal diagnosis with an est. 6 mo mortality of more than 50% and FiO2 of more than 0.80 for more than 48 hours, participated in other ARDS or Septic shock trials within 30 days. |
| Total sample size | 61* recruited halted early because of low inclusion rate and completion of Derdak trial. (Powered for 106 patients) | 148 |
| Randomised? | Yes | Yes |
| Method of randomisation | Sequentially numbered computerized randomisation algorithm | Computerised randomisation locally |
| First arm definition | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) |
| Second arm definition | Conventional ventilation (CV) | Conventional ventilation (CV) |
| Third arm definition | Not applicable | Not applicable |
| HFOV/CV n | 37:24 | 75:73 |
| Physiologic targets | The oxygenation goal was an $O_2$ saturation of 88% or more or | The oxygenation goal was an $O_2$ saturation of 88% or more on $FiO_2$ ≤0.60 with |

| | | |
|---|---|---|
| | **$PaO_2$>60mmHg with a $FiO_2$<0.60. The ventilatory goal was to establish an arterial pH>7.20 and a $HCO_3$>19mmol $l^{-1}$ while minimizing peak inspiratory pressures irrespectively of arterial carbon dioxide pressure ($PaCO_2$).** | **maintenance of mPaw in the HFOV or PEEP in the CV group under $FiO_2$, could be reduced to 0.60 or less.** |
| **HFOV employed** | **SensorMedics 3100B** | **SensorMedics 3100B** |
| **HFOV settings** | **Mean airway pressure 5cm$H_2O$ above mean airway pressure setting on conventional ventilation.** | **Initial ventilation settings: $FiO_2$ of 0.8-1.0, frequency of 5Hz, inspiratory time of 33%, bias flow of 40L $min^{-1}$, mean airway pressure 5cm$H_2O$ above mean airway pressure setting on conventional ventilation.** |
| **Primary outcome** | **Cumulative survival without mechanical ventilation or oxygen dependency at 30 days, mortality at 30 days, therapy failure, crossover rate, persisting pulmonary problems defined as oxygen dependency or still being on a ventilator at 30 days** | **Survival without the need for mechanical ventilation at 30 days after study entry.** |
| **Secondary outcomes** | | **New of worsening air leak, mucus plugging requiring endotracheal tube change, 6 month mortality.** |
| **Primary outcome results** | **Alive with no mechanical ventilation or oxygen**<br>**HFOV: 12/37**<br>**CV: 9/24**<br><br>**Mortality**<br>**HFOV: 16/37**<br>**CV: 8/24**<br><br>**Therapy failure**<br>**HFOV: 10/37**<br>**CV: 5/24**<br><br>**Cross over**<br>**HFOV: 7/37**<br>**CV: 4/24**<br><br>**Supplemental oxygen or on ventilator at 30 days**<br>**HFOV: 9/37**<br>**CV: 7/24** | **Alive with no mechanical ventilation**<br>**HFOV: 27/75 (36%)**<br>**CV: 23/73 (31%)**<br><br>**Mortality**<br>**HFOV: 28/75**<br>**CV: 38/73** |
| **Secondary outcome results** | | **$PaO_2/FiO_2$ ratio (p=0.008)**<br><br>**Six month mortality %**<br>**HFOV: 35**<br>**CV: 43**<br><br>**Mean duration of mechanical ventilation, days**<br>**HFOV: 22 ± 21**<br>**CV: 20 ± 31** |
| **Intention to treat analysis** | **Yes** | **Yes** |

## b) Prospective uncontrolled trials of HFOV after failure of conventional ventilation

| First author | David [66] | Mehta [67] | Claridge [68] | Fort [69] |
|---|---|---|---|---|
| Publication year | 2003 | 2001 | 1999 | 1997 |
| Aim of HFOV | Rescue treatment | Rescue treatment | Rescue treatment | Rescue treatment |
| Patient population | Adults with ARDS | Adults with ARDS and oxygenation failure | Adult trauma patients with refractory lung dysfunction | Adults with severe ARDS |
| Study type | Prospective single-centre observational study | Two-centre prospective uncontrolled trial | Prospective study | Prospective uncontrolled study |
| Setting | German ICU | 2 Canadian ICU and Burns units | US ICU | Medical and surgical ICUs of a US hospital |
| Age limits | | 16 or older | | 16 or older |
| Inclusions | Adults with ARDS who failed conventional ventilation – $PaO_2/FiO_2$ ratio less than 200mmHg and improvement in oxygenation following 2 hours of optimized pressure-controlled ventilation. | Adults with severe ARDS failing conventional ventilation - an $FiO_2$ of ≥0.6 with a $PaO_2$ of ≤65mmHg, or plateau pressure of ≥ 35cm $H_2O$. | Adult trauma patients with refractory lung dysfunction. | Adults with severe ARDS failing conventional ventilation - an $FiO_2$ of ≥0.7 with a $PaO_2$ of ≤ 8.7kPa, a peak inspiratory pressure of ≥ 65cm$H_2O$, or a PEEP of ≥15cm$H_2O$. |
| Exclusions | Lack of informed consent, weight less than 35kg, pregnancy, anticipated death, withdrawal of life support because of poor prognosis within 24hr, heart failure, severe obstructive lung disease. | Weight less than 35kg, historical and or clinical evidence of left ventricular failure or severe obstructive lung disease. | | Weight less than 35kg, cardiogenic pulmonary oedema, severe obstructable lung disease, intractable septic shock requiring 15ug $kg^{-1}$ $min^{-1}$ of dopamine or >4 ug $kg^{-1}$ $min^{-1}$ of norepinephrine, pregnancy. |
| Total sample size | 42 | 24 | 5 | 17 |
| Randomised? | No | No | No | No |
| First arm definition | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) |
| HFOV/CV n | 48:0 | 24:0 | 5:0 | 17:0 |
| Physiologic targets | | Target oxygenation parameters were pulse oximetry of 88% to 93%, and FiO2 ≤0.60. | | Target oxygenation was ~90% and a target FiO2 of ≤0.60. |
| HFOV employed | SensorMedics 3100B | SensorMedics 3100B | Sensormedics 3100B | SensorMedics 3100B |

| | | | | |
|---|---|---|---|---|
| **HFOV settings** | **Initial ventilation settings: $FiO_2$ of 1.0, frequency of 5Hz, inspiratory time of 33%, bias flow of 30L $min^{-1}$, mean airway pressure 5cm$H_2O$ above mean airway pressure setting on conventional ventilation.** | **Initial ventilation settings: $FiO_2$ of 0.8-1.0, frequency of 5Hz, inspiratory time of 33%, bias flow of 40 L $min^{-1}$, mean airway pressure 5cm$H_2O$ above mean airway pressure setting on conventional ventilation.** | | **Initial ventilation settings: $FiO_2$ of 1.0, frequency of 5Hz, inspiratory time of 50%, bias flow of 30 L $min^{-1}$, mean airway pressure 2 to 3cm$H_2O$ above mean airway pressure setting on conventional ventilation.** |
| **Primary outcome** | **a) $PaO_2/FiO_2$ ratio 24h after start of HFOV treatment or the last point of measurement if HFOV ended within the first 24h; or b) HFOV-related complications.** | **Physiologic improvement.** | | **Gas exchange improvement and oxygenation index.** |
| **Secondary outcomes** | **30 day mortality, relationship between endpoint outcomes and HFOV treatment response.** | **HFOV oxygenation and/or ventilatory failure, duration of HFOV, ICU mortality, complications.** | | **30 day mortality.** |
| **Primary outcome results** | **Median $PaO_2/FiO_2$ ratio from baseline to 24 hours 95(62-129) to 165 (88-225) mmHg. HFOC-related complications: 1/48.** | **Cardiac output decreased significantly immediately after starting HFOV, and remained lower than the baseline value throughout the study (ns).** | **All patients improved after initation of HFOV.** | **HFOV caused significant increases in $PaO_2/FiO_2$ ratio and significant reductions in the oxygenation index.** |
| **Secondary outcome results** | **30 day mortality<br>HFOV: 18/42** | **Complications<br>HFOV: 6<br><br>ICU mortality<br>HFOV: 16<br><br>Hospital mortality<br>HFOV: 16** | | **30 day mortality<br>HFOV: 9/17<br><br>Alive no mechanical ventilation<br>HFOV: 3/17** |
| **Intention to treat analysis** | **Not applicable** | | **Not applicable** | **Yes** |

## c) Prospective trials of HFOV without usual care control group

| First author | Ferguson [70] | Papazian [71] |
|---|---|---|
| Publication year | 2005 | 2005 |
| Aim of HFOV | Primary treatment | Primary treatment |
| Patient population | Adults with early ARDS | Adults with severe ARDS |
| Study type | Prospective multi-centre single intervention pilot study | Prospective comparative randomised study |
| Setting | Canadian ICU, UK ICU and French ICU | French Medical ICU |
| Age limits | 18 – 74 | 18 or older |
| Inclusions | Endotracheal intubation and mechanical ventilation. Presence of one or more risk factors for ARDS.<br>Bilateral infiltrates as seen on frontal chest radiograph.<br>$PaO_2/FiO_2$ ratio <200mmHg. | $PaO_2/FiO_2$ ratio ≤150mm Hg while on PEEP ≥5cm$H_2O$, bilateral radiographic pulmonary infiltrates, and pulmonary artery occlusion pressure of ≤18mmHg. |
| Exclusions | Anticipated duration of ventilation <48 hours.<br>>48hrs elapsed since all inclusion criteria were met.<br>Minimal chance of ICU survival as judged by attending physician.<br>Significant heart disease.<br>History of significant COPD or asthma.<br>Chronic insterstitial lung disease associated with bilateral pulmonary infiltrates.<br>Lung biopsy or resection on current admission.<br>Known intercranial abnormalities.<br>Pregnancy<br>Previous lung or bone marrow transplant.<br>Inability to wean from experimental ARDS therapies.<br>Enrollment in another interventional study. | Lack of informed consent, moribund status, severe chronic respiratory insufficiency requiring long-term oxygen therapy or long-term mechanical ventilation, head injury, unstable pelvic or vertebral fracture, extra-alveolar air in the chest radiograph, or a chest tube in place with persistent air leak, or patients who had participated in other investigational trials within 30 days. |
| Total sample size | 25 | 39 |
| Randomised? | No | Yes |
| Method of randomisation | Not applicable | Sealed opaque envelopes |
| First arm definition | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV-P) in prone position |
| Second arm definition | Not applicable | High Frequency Oscillatory Ventilation (HFOV-S) in supine position |
| Third arm definition | Not applicable | Conventional ventilation in prone position (CV-P) |
| HFOV/CV n | 25:0 | 13:13:13 |

| | | |
|---|---|---|
| **Physiologic targets** | | **Target $PaCO_2$ was 40-80mmHg with a pH >7.15** |
| **HFOV employed** | **Sensormedics 3100B** | **SensorMedics 3100B** |
| **HFOV settings** | **Initial ventilation settings: $FiO_2$ of 1.0, frequency of 5Hz** | |
| **Primary outcome** | **Safety, feasibility and lung-recruitment efficacy of an explicit ventilation protocol.** | **Compare the effects of prone position, HFOV, and their combination on gas exchange.** |
| **Secondary outcomes** | | **Evolution of inflammatory mediators, number of complications (mucus obstruction, pulmonary air leak, vasopressor requirements).** |
| **Primary outcome results** | **HFOV and the explicit recruitment maneuvers were well tolerated and resulted in rapid and sustained improvement in oxygenation** | **CV-P and HFOV-P produced significant improvements in $PaO_2/FiO_2$ 138±58mmHg to 217±110mmHg ($p<0.0001$) and from 126±40mmHg to 227±64mmHg ($p<0.0001$) HFOV-S did not improve $PaO_2/FiO_2$ 134±57mmHg to 138±48mmHg nor oxygenation index.** |
| **Intention to treat analysis** | **Not applicable** | **Yes** |

## d) Retrospective trials/multiple case studies of HFOV

| First author | Finkielman [72] | David [73] | Cartotto [74] | Mehta [75] | Andersen [76] | Cartotto [77] |
|---|---|---|---|---|---|---|
| Publication year | 2006 | 2005 | 2004 | 2004 | 2002 | 2001 |
| Aim of HFOV | | Rescue treatment | | Rescue treatment | Rescue treatment | |
| Patient population | Adults (11 ARDS, 2 unilateral pneumonia with septic shock, 1 pulmonary oedema) | Adulta with traumatic brain injury and ARDS | Adult burns patients with ARDS | Adults with severe ARDS | Adults with severe ARDS | Adults with burns and ARDS |
| Study type | Retrospective study | Retrospective study | Retrospective cohort review | Retrospective chart review | Retrospective study | Retrospective review |
| Setting | 2 US ICU | German ICU | Canadian Burn Unit | 3 Canadian ICUs | Norwegian general ICU and burn unit | Canadian Burn Unit |
| Age limits | | - | - | - | 18 or older | |
| Inclusions | All patients treated with HFOV. | Patients treated with HFOV with concomitant TBI and ICP monitoring during period reviewed. | Adults with burns. | All patients treated with HFOV (all had ARDS and severe hypoxaemia). | Adults with severe ARDS who failed conventional ventilation. | All patients treated with HFOV. |
| Exclusions | | - | Diagnosis other than a burn, if HFOV had been used for less than 2 hours, or if records were incomplete or missing. | | | |
| Total sample size | 14 | 5 | 25 | 156 | 16 | 6 |
| Randomised? | No | No | No | No | No | No |
| Method of randomisation | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable |
| First arm definition | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) | High Frequency Oscillatory Ventilation (HFOV) |
| HFOV/CV n | 14:0 | 5:0 | 25:0 | 156:0 | 16:0 | 6:0 |
| HFOV employed | SensorMedics 3100B | Sensormedics 3100B | SensorMedics 3100B | SensorMedics 3100B | SensorMedics 3100B | SensorMedics 3100B |
| HFOV settings | | Initial ventilation settings: $FiO_2$ of 1.0, frequency of 5Hz, | Initial ventilation settings: $FiO_2$ of 0.7-1.0, frequency of between 3- | | | Mean airway pressure 5cm$H_2O$ above mean airway pressure setting |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | **inspiratory time of 33%, bias flow 30L $min^{-1}$, mean airway pressure setting on conventional ventilation.** | **6Hz, mean airway pressure 5cm$H_2O$ above mean airway pressure setting on conventional ventilation.** | | | **on conventional ventilation, frequency of 5Hz, $FiO_2$ of 1.0.** |
| **Primary outcome** | **Response to HFOV** | **Response to HFOV and adverse events** | **Response to HFOV** | **Response to HFOV** | **Physiologic improvement** | **Response to HFOV** |
| **Secondary outcomes** | **Hospital Mortality** | | **Mechanical ventilation duration, mortality** | **Mortality rates** | **3 month mortality** | **Mortality** |
| **Primary outcome results** | **Mean $PaO_2/FiO_2$ ratio increased from 82 at baseline to 90, 107, 105mmhg at 6hr, 24hrs and last setting before change to CV ($p<0.05$).** | **No typical HFOV related adverse events, and no HFOV termination due to decreased CPP, increased ICP, or deteriorated $PaCO_2$ for more than 60 minutes and unresponsive to treatment.** | **$PaO_2/FiO_2$ ratio immediate and sustained increase.** | **$PaO_2/FiO_2$ ratios and OI improved significantly.** | **After 12h HFOV, $PaO_2/FiO_2$ ratio increased 47.6% compared to baseline.** | **$PaO_2/FiO_2$ ratio increases which became significant by 12 hours ($p=0.02$).** |
| **Secondary outcome results** | **Hospital Mortality 8/14** | | **Duration of mechanical ventilation 29 ± 18 days.**<br><br>**In-hospital mortality rate 8/25.** | **Mortality rate at 30 days 61.7%** | **3 month mortality: 5/16** | **Mortality 5/6** |

## Appendix 3: Studies of ICU survivors using EQ-5D or SF-36

| Study | SF-36 | EQ-5D | Time points |
|---|---|---|---|
| Azoulay [78] | x | | 1. 90 days after death or ICU discharge |
| Badia [58] | | x | 1. Admission (proxy rating for 3 months prior to admission)<br>2. 12 months post ICU discharge |
| Badia [79] | | x | 1. Pre ICU<br>2. ICU |
| Chaboyer [80] | x | | 1. 6 months post ICU discharge<br>2. 12 months post ICU discharge |
| Chrispin [81] | x | | 1. Pre-existing health |
| Cuthbertson [82] | x | x | 1. Time of stabilisation in ICU (with proxy)<br>2. 3 months post discharge<br>3. 6 months post discharge<br>4. 12 months post discharge (EQ-5D) only measured at this time point |
| Davidson [83] | x | | 1. After hospital discharge |
| Eddleston [84] | x | | 1. 3 months after ICU |
| Elliott [85] | x | | 1. Pre crisis health(by patient and proxy)<br>2. 6 months post discharge |
| Flaaten [86] | x | | 1. 12 years later |
| Garcia Lizana [87] | | x | 1. 18 months post discharge |
| Graf [88] | x | | 1. Within 24hours of ICU admission<br>2. 1 month post ICU discharge<br>3. 9 months post ICU |
| Granja [89] | | x | 1. 6 months |

| | | | |
|---|---|---|---|
| | | | after ICU discharge |
| Granja [90] | | x | 1. 6 months after ICU discharge |
| Granja [91] | | x | 1. 6 months post ICU discharge |
| Heyland [92] | x | | Mean 16.6 months post ICU |
| Kaarlola [93] | | x | 1. Between 1 and 6 years post ICU discharge |
| Kleinpell [94] | x | | 1. 3 months post ICU discharge<br>2. 6 months post ICU discharge<br>3. 9 months post ICU discharge |
| Kvale [95] | x | | 1. 6 months post ICU discharge |
| Ridley [96] | x | | 1. ICU discharge<br>2. 6 months post-discharge |
| Schelling [97] | x | | Variable median time 4 years post discharge |
| Sukantarat[98] | x | | 1. ~ 3 months post ICU discharge<br>2. ~ 9 months post ICU discharge |
| Sznajder [99] | | x | 1. 6 months post ICU discharge |
| Wehler [56] | x | | 1. 1 month before (proxy)<br>2. 6 months post |
| Welsh [100] | x | | 1. Within 72 hours of first ICU admission<br>2. 6 weeks post ICU admission<br>3. 6 months post ICU admission |

# Appendix 4:

# CONSENT PROCESS AND DOCUMENTATION

# FOR THE OSCAR TRIAL

# - BY COUNTRY

**(FOR COLLABORATING HOSPITALS)**

# 1 ENGLAND AND WALES

## OSCAR trial agreement processes

## England and Wales - Mental Capacity Act 2005 (relates to collaborating hospitals in England and Wales)

*MREC:* 07/H0502/98 / *Version 2 – 3 Sept 2007*

The Mental Capacity Act 2005 comes into force on 1st October 2007. This Act is relevant to research involving adults over the age of 16 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 participants 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 due to alternations in consciousness. The table overleaf 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* published 22nd June 2007. This draft guidance is for consultation on how to identify an appropriate a "consultee" for the purposes of section 32 of the Mental Capacity Act 2005. 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.

**Issued by the Secretary of State and National Assembly for Wales in accordance with section (32(3)) of the Mental Capacity Act 2005.* http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_076216.

# THE OSCAR TRIAL CONSENT PROCESS - England and Wales

*REC:* 07/H0502/98 / *Version 2 – 3 Sept 07*

*ENGLAND AND WALES*

**Patient fulfils eligibility criteria but does not have capacity to consent**

Does the patient have a family member/next of kin/friend/carer who knows them well who:

(a) is interested in the patient's welfare and best interests,
or
(b) is an attorney acting under a Legal Power of Attorney
or
(c) is a court appointed deputy

who could act as a 'Personal Consultee'?

None of the above should be paid to look after the patient/be in their paid employment, i.e. paid carers **cannot** act as Personal Consultee.

Yes

Does this person live a long distance away?

Yes → Consider Oral agreement

No

(1) Is this person willing to take on the responsibilities of a 'Personal Consultee'? (Give an opinion on whether their relative/ next of kin/friend might want to take part in the OSCAR trial.)
And
(2) Are they able to understand the information provided about the OSCAR trial?

Yes

No

Do they wish to nominate another family member/next of kin/friend/carer to take on the role of Personal Consultee?

Yes → (back to Does this person live a long distance away?)

No → The family member/next of kin/friend/carer can request a Nominated Professional Consultee be involved.

Local arrangements apply as in the box above.

Personal Consultee : Give the consultee the trial information sheet. Talk them through it and answer any questions.

You should ask what, in their opinion, the patients wishes and feelings about taking part in the study would be if they had the capacity to make the decision for themselves.

To aid their decision making process you may ask them to think about whether the patient had previously expressed specific or general support for research of this type. It may also be helpful to remind the consultee that he or she is NOT being asked for their OWN views on participation in the study or research in general, but their relatives. They need to set aside their own views and consider what the patients views are.

- If they agree their relative can go into the study: ask them to sign a consultee form to show agreement. Once signed, provide them with a copy.
- If they advise you that in their opinion the patient would have declined to take part: the patient cannot be entered into the trial.

If the consultee cannot attend the ICU consider taking agreement over the telephone using the oral form.

No

A Nominated Professional Consultee in your Trust should be contacted.

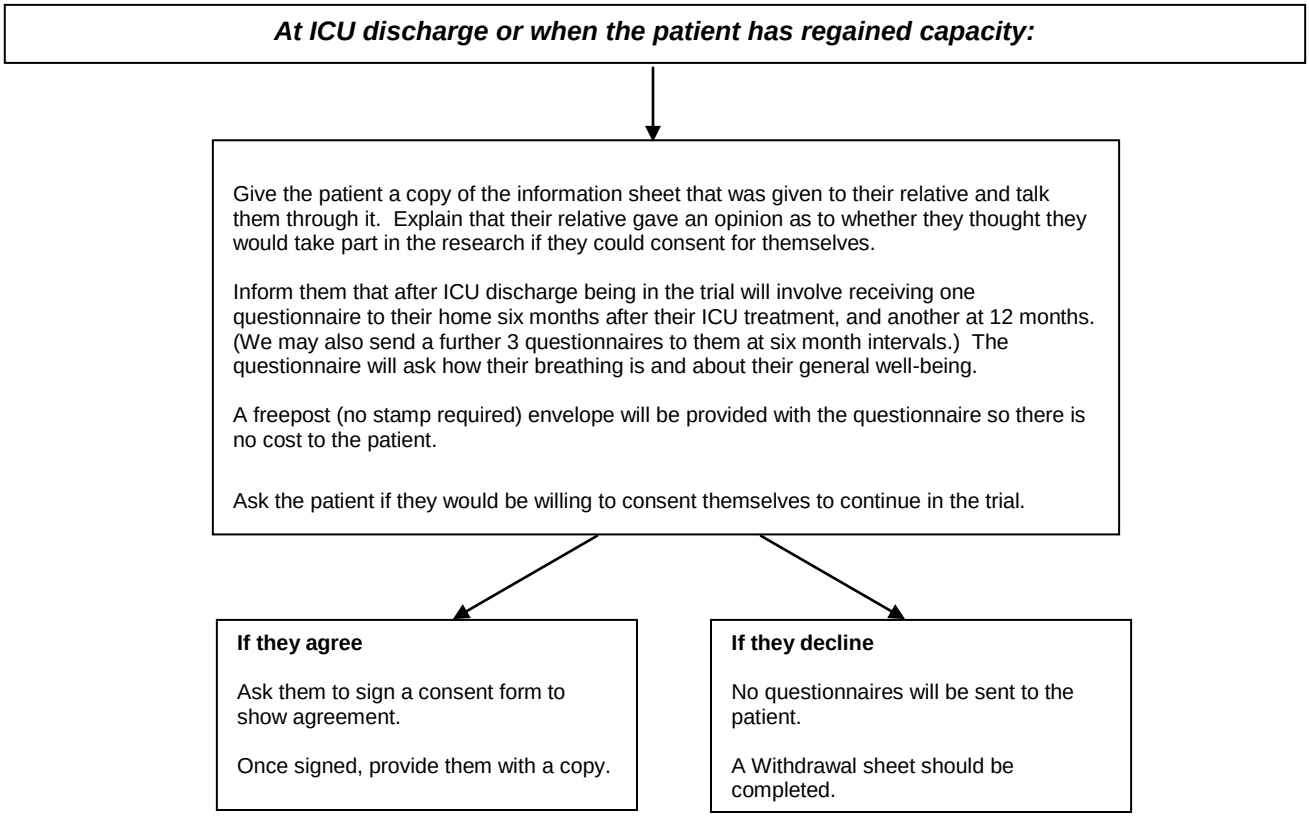
They, after reviewing the trial information, will give their opinion on the patients entry into the trial. This person may still wish to talk to the relative who lives away before they make their decision.

**Ask your Trust for details of who you can approach to take on this role.**

Nominated Professional Consultee: Provide trial information sheet. Answer any questions.

The consultee will inform you of their decision:

- If they agree thr patient can go into the study: ask them to sign a Consultee form to show agreement. Once signed, provide them with a copy.
- If they advise you that the patient cannot take part: the patient cannot be entered into the trial.




If a patient in the trial dies before regaining consciousness the patient's data will be included in the study.

Documentation related to this process follows over the page.

**[To be printed on OSCAR headed paper]**

**OSCAR STUDY**
**INFORMATION ABOUT THE RESEARCH**
*(for Consultees)*

REC reference: 07/H0502/98 / Version 3 – 27 June 2011
ISRCTN10416500

Centre No. [xxxx]

*Title of project: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

**Principal Local Investigator** [PI Name & Telephone No. here]

PART ONE - INVITATION TO JOIN THE OSCAR STUDY

You will know from talking with the doctor that your relative, friend, or person you are representing has a serious breathing problem. This must be an extremely anxious time for you. We would however be grateful if you would take a little time to read this information. It asks you to think about whether the person you are representing would have any objection to taking part in a study which is taking place in many hospitals in the UK.

**What is the purpose of the study?**

This study is comparing two ways of providing help with breathing for patients with serious breathing problems:

1. conventional ventilation (often called artificial ventilation or "breathing machine")
2. high frequency oscillatory ventilation.

Conventional ventilation

This sort of ventilation helps breathing by pushing a mixture of air and oxygen into the lungs every 2-4 seconds. We call this conventional ventilation because it is the most common method used.

Your relative, friend or person you are representing is already receiving conventional ventilation. This form of care is standard treatment, and has been used for many years. However, using a conventional ventilator to deliver air and oxygen may itself sometimes cause some further damage to the air sacs (alveoli) in the lungs and delay recovery. This happens in about 1 in 12 patients who are ventilated.

High frequency oscillatory ventilation

Another way of ventilating patients is called 'high frequency oscillatory ventilation', sometimes abbreviated to HFOV. This involves giving very small breaths of air and oxygen very rapidly (up to 5 times per second). As the breaths are very small they do not stretch the lungs very much and so might reduce the chances of causing further lung damage. However, the disadvantage with this type of ventilation is that the patient usually requires more sedatives.

This way of ventilating patients with severe breathing problems might be as effective, better, or worse than conventional ventilation but currently there is not enough information to know which. This is why we are undertaking the study.

**What would being in the study involve?**

Whilst in the Intensive Care Unit:

If you know of no reason why your relative, friend or person you are representing would not want to take part in the study, they will be assigned to receive one of the two forms of ventilation offered:

- Half the patients in the study will continue to be treated on conventional ventilation.
- The other half will be treated with high frequency oscillatory ventilation.

Neither you nor the doctor (nor anyone else) will know beforehand which of these two treatments they will receive. This will be determined by the play of chance, rather like the toss of a coin. This element of chance is important so that the two methods can be tested fairly. When one of the two ways of ventilating has been allocated, they will either remain on a conventional ventilator or be placed onto a high frequency oscillatory ventilator.

Information from the patient's medical record will be collected during their stay in the Intensive Care Unit. This information will be kept strictly confidential.

The study is only looking at the different forms of ventilation; other elements of care are not affected and will be decided in the usual way.

After the Intensive Care Unit:

As we are interested in the long term wellbeing of patients, we may send out questionnaires at six months after treatment in the Intensive Care Unit. The questionnaire will ask how breathing is affecting day-to-day activities, and about general health. We may also send a questionnaire after 12 months. We may send up to three more questionnaires, again spaced six month apart.

There are *no* further tests or hospital visits involved in taking part in the study.

Over 1,000 patients in Intensive Care Unit's from hospitals across the UK will take part in this study. They are all helping to help find out which procedure is the safer, and more effective, at aiding breathing both in the short and long term.

**Why am I being asked to consider the study?**

Normally we ask patients themselves if they would consider taking part in research studies, but as your relative, friend or person you are representing is on a breathing machine we can't discuss it with him or her. We are, therefore, approaching you (someone who has their welfare and best interests in mind), to confirm that you know of no reason why they would not want to take part in the study.

- If you believe they would have wanted to take part then we would like to include them in the study.

- If you believe they would *not* have wanted to take part, then we will not include them in the study.

Declining to join the study will not affect the standard of care they receive.

If you (or the patient when he/she regains capacity), change your mind, they can be withdrawn from the study at any time. If you do withdraw, this will not adversely affect their care. The patients (and their doctors) who take part in this study are not paid to do so and participate freely.

**Do I have to agree?**

It is up to you to think about the wishes of your relative, friend or person you are representing and decide.

We will describe the study and go through this information sheet with you, which we will then give to you. If you agree that your relative, friend or person you are representing would have wanted to take part, we will ask you to sign a form to confirm this and provide you with a copy.

When your relative, friend or person you are representing is well enough to make a judgment about being in the study we will ask them. If they decide not to continue in the study they can withdraw.

**I'm not sure I'm the right person to make the decision, what should I do?**

If you feel that you are not the right person to give an opinion on behalf of the patient you can either:

(a) nominate another family member/friend to take on this role as they may know the patients wishes/opinions better, or

(b) ask for a professional individual to consider the information about the study and make what they believe is the best decision for the patient. This individual may wish to talk to you further but they would take on decision-making formally. However whether you want a professional individual to be involved in entirely up to you.

**If, after reading Part One, the study sounds like something your** relative, friend or person you are representing **might have agreed to, you may find it helpful to read the further information in Part Two before you make your decision.**

PART TWO - ADDITIONAL INFORMATION ABOUT THE OSCAR STUDY

**Who is organising and funding the research?**

The Intensive Care Society's Trials Group at the University of Oxford are organising this research and work with the consultants and nurses in hospitals around the UK.

The National Coordinating Centre for Health Technology Assessment (part of the Department of Health/UK Government) is funding the research.

**Who has approved the study?**

Any research involving a person who lacks capacity may only be lawfully carried out if an NHS Research Ethics Committee (REC), has given the research their favourable opinion. They look after the rights, well being and dignity of patients.

This study has been reviewed and given a favourable option by a REC. The REC reference number is given on the front page of this document.

This study was also reviewed by the National Coordinating Centre for Health Technology Assessment before it was awarded funding to ensure it met the necessary scientific standards.

**Is there a contact point where I can seek independent advice about participating in the study?**

Yes, the Trust's Research and Development (R&D) Office can be contacted. They will give you advice about how to contact an Independent Mental Capacity Advocate, or some other individual you can talk to for independent advice. Ask one of the doctors or nurses for the R&D telephone details.

If you would like more information about the study itself you can ask to speak to the research lead for the OSCAR study at this hospital. His/her contact details are on the front of this information.

**More about conventional and high frequency oscillatory ventilation:**

Conventional ventilation is usually undertaken with an artificial ventilator which fills the lungs with an air/oxygen mixture at regular intervals. Even though the breaths are small (about half a litre), patients who have lung conditions that cause stiff lungs may have their recovery delayed because the lungs expand unevenly and some areas get overstretched and damaged. We believe this happens in at least one in twelve patients.

If the breaths are made really small (a twentieth of a litre or less) it may be possible to reduce the damage caused by stretching. However, to move enough oxygen in and out of the lungs, the breaths have to be delivered very rapidly, at about 5 breaths per second. An analogy is often made with panting dogs, who breathe rapidly with small breaths. However, as very rapid breathing is not "natural" for humans, patients receiving high frequency oscillatory ventilation often require more sedation to allow them to tolerate the breathing machine.

We would like to determine which technique for artificial ventilation is best, and so we are conducting a study where half of the patients receive conventional ventilation and half receive high frequency ventilation. As well as looking at how long patients require treatment in the ICU, we will follow patients with questionnaires for up to two and a half years to see if the type of ventilation they received has any effect on their longer-term health.

**Are there any risks?**

All forms of artificial ventilation are used to treat very severe lung problems and all carry risks. One possible risk with high frequency oscillation is that air will not have time to leave the lungs and will be trapped. This risk is minimised by not including patients likely to suffer this problem in the study, and by carefully monitoring the pressures and gas volumes delivered by the ventilator.

**What if something goes wrong?**

Compensation for harm arising from an accidental injury and occurring as a consequence of your participation in the study will be covered by the University of Oxford. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Oxford (in respect of any harm arising out of the participation in the study) or the NHS (in respect of any harm which has resulted from the clinical procedure being undertaken).

**You mention sending a questionnaire later. What will the questionnaire contain?**

The questionnaire is in two parts. One section will ask about their breathing, and asks how it affects day-to-day living. The second section is a more general assessment of well-being.

The questionnaire will be posted to the patient from the co-ordinating office at Oxford University. Once completed, it can be returned in a freepost envelope (no stamp required), which is supplied.

The first questionnaire may be sent six months after treatment in the Intensive Care Unit. The second six months later (12 months after intensive care). We may send a further three questionnaires. Each of these will be sent six months apart.

As people may move house, we also collect the names of two friends/relatives who can help us locate a patient who has moved.

**What if my relative, friend or person I am representing wishes to withdraw from the study once they get home?**

Once they get home the only involvement in the study is completing the follow up questionnaires asking how their breathing is. If they do **not** wish to receive a questionnaire they can tell us by telephoning the study co-ordinating office (tel: 01865 857613). No further questionnaires will be sent to them.

**Are patient details kept confidential?**

The information collected on study patients are kept in a secure area of the hospital behind double locked doors. All computer systems are on secure networks and all information is treated as strictly confidential. Any published reports will not identify patients. Parts of the medical records and the data collected for the study about your relative, friend or person you are representing will be looked at by authorised persons from the sponsor of the research and/or the funding body carrying out monitoring or auditing. This is to ensure the study is being carried out correctly. Identifying details will be sent to the Office of National Statistics and the National Health Service Central Register to aid follow up. All those involved in the research and the organisations supporting research have a duty of confidentiality .

**Communication with GP**

We will send a letter to the family doctor of your relative, friend or person you are representing to inform them that they were entered into the OSCAR study whilst in the Intensive Care Unit.

**What if we wish to complain?**

If you have a concern about any aspect of this study, you should ask to speak to the Principal Local Investigator in the first instance. Their contact details are on the front page of this information sheet. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

**Where can I find the results of the study?**

A detailed study report will appear on the National Coordinating Centre for Health Technology Assessment (NCCHTA, part of the Department of Health) website in 2013, and will be free to download. Printed copies will also be available. The study reports will also appear in the medical journals.

Thank you for taking the time to read this information.

If you know of no reason why the patient would not want to take part in the study please let one of the Intensive Care Unit staff know.

Please remember we will ask you for the contact details of two friends/relatives to help us keep in contact with the patient should they move house.

**Used when patient does not have capacity to consent**

**Centre No.**
**xxx**

**To go on Trust headed paper**

## CONSULTEE FORM

*Version 2 – 3 Sept 2007*
*MainREC number: 07/H0502/98*

Regarding patient: _____
(please write patients name here)

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

1 I confirm that I have read and understand the information leaflet dated [date and version here] for the above study and have had the opportunity to ask questions.

2 I confirm that I am voluntarily stating that I know of no reason why the above patient would not wish to take part in the study and that once they regain capacity they will be free to withdraw at any time, without giving any reason, and without their medical care or legal rights being affected.

3 I confirm that I am acting as consultee for the above named patient who is currently incapacitated, and know of no reason why the patient would not want to take part in the OSCAR study. In addition, I am not aware of any advanced statements that would prevent them from taking part in the study. I understand and agree to the following:

- That sections of their medical record can be looked at by responsible individuals involved with the study and transcribed onto the study form.
- That appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.
- That the Office of National Statistics can be used to aid follow up of their health (and that for this purpose their details may be sent, in confidence, to the study office).
- That their family doctor records may be looked at by their general practitioner to identify their location or health status in the future. These details may be shared with, and held at, the study office.
- That this form will be stored at the study office for monitoring purposes.
- That Members of the University of Oxford or Health Technology Assessment monitoring/auditing team may require access to the above named patients details. Confidentiality of personal details will be maintained throughout this process.
- I agree to discuss the study with the patient when they regain capacity.

**If you would like further information before signing this form please contact:**
[Name, title and telephone contact details of local OSCAR Principal Investigator here]

4 My relationship to the patient is: _____
(please write your relationship to the patient here, for example wife/partner/ brother etc. ) Or 'Nominated Professional Consultee'

| Name (PRINT) | Date | Signature |
|---|---|---|
| Name of person taking agreement | Date | Signature |

*Consultee form continued:*

**Friend/relative 1**

Name: _____

Address: _____

_____

_____ Post code: _____

Telephone (if known): _____ _____
(code)

**Friend/relative 2**

Name: _____

Address: _____

_____

_____ Post code: _____

Telephone (if known): _____ _____
(code)

*Top copy: Study file at site* *1 copy: Consultee* *1 copy: Patients hospital notes* *1 copy: Post to study office*

**Please provide contact details of 2 friends/relatives who can be written to for contact details if we lose contact with the patient named above (please PRINT)**

**Centre No.**
**xxx**

**Used when patient does not have capacity to consent**

**To go on Trust headed paper**

# ORAL AGREEMENT FROM CONSULTEE

(PRIOR TO PATIENTS TRIAL ENTRY)

*Version 1 – 3 Sept 2007*
*MainREC number: 07/H0502/98*

Regarding patient: _____
(please write patients name here)

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

Principal Local Investigator: [name and telephone number here]

Please initial boxes

1 I confirm that the patient's inclusion in the above study has been discussed with the appropriate person acting as their consultee and that they were offered the opportunity to ask questions/ask for clarification …….. ☐

2 The consultee confirmed that they knew of no reason why the patient would not want to take part in the trial and were not aware of any advanced statement that would prevent them from taking part in the OSCAR study. ……. ☐

3 I confirm the following was discussed and he/she agreed to the following:

- That sections of the patients medical record can be looked at by responsible individuals involved with the study and transcribed onto the study form.
- That appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.
- That the Office of National Statistics can be used to aid follow up of the patients health (and that for this purpose their details may be sent, in confidence, to the study office).
- That the patients family doctor records may be looked at by their general practitioner to identify their location or health status in the future. These details may be shared with, and held at, the study office.
- That this form will be stored at the study office for monitoring purposes.
- That Members of the University of Oxford or Health Technology Assessment monitoring/ auditing team may require access to the above named patients details. Confidentiality of personal details will be maintained throughout this process.
- They agree to discuss the study with the patient when they regain capacity.
- That personal identifying details will be collected for this patient and that the consultee does not object to this information being collected, stored and used for follow up purposes. ☐

Name of Consultee: _____

Relationship to patient: _____

Date and time consultee informed: Date: _____/_____/_____ Time: (24 hr clock) _____:_____

Comments, including any objections:

Please initial box

4 A copy of the information sheet (date and version) has been given or sent to the consultee *(please tick as appropriate)*: Yes ☐ No ☐ ☐

| Name of person informing consultee | Date | Signature |
|---|---|---|
| Name of Principal Local Investigator | Date | Signature |

*Top copy: Study file at site* *1 copy: Patients hospital notes* *1 copy: Post to study office*

**Centre No.**
**xxx**

**Used when patient regains capacity in the ICU (after consultee has given agreement for patient to go into trial)**

# PATIENT CONSENT FORM

(for patients regaining capacity in ICU after consultee agreement)
*Version 2 – 3 September 2007*
*REC reference: 07/H0502/98*

**To go on Trust headed paper**

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

1 I confirm that I have read and understand the information leaflet dated [date and version here] for the above study and have had the opportunity to ask questions.

2 I understand that I am voluntarily agreeing to participate in the study and that I am free to withdraw at any time, without giving any reason.

3 I confirm:

- That the study office can contact me by post to find out how I am in six months time, or, if necessary they can contact my family doctor, or my friends/relatives named on the Consultee Form.
- That sections of my medical record can be looked at by responsible individuals involved with the study and transcribed onto an anonymised study form
- That appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of my health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.
- That the Office of National Statistics will be used to help keep in touch with me or to help follow up my health (and that for this purpose my details may be sent, in confidence, to the study office).
- That my family doctor records may be looked at by my general practitioner to identify my location or health status in the future. These details may be shared with, and held at, the study office.
- That I understand I will be sent a questionnaire from the study office at six and 12 months after my treatment in the Intensive Care Unit to see how my health is. I also understand that I may be sent a further three questionnaires six months apart.
- That this consent form will be stored at the study office for monitoring purposes.
- That Members of the University of Oxford or Health Technology Assessment monitoring/auditing team may require access to my details. Confidentiality of personal details will be maintained throughout this process.

**If you would like further information before signing this form please contact:**
[Name, title and telephone contact details of local OSCAR Principal Investigator here]

| Name (PRINT) | Date | Signature |
|---|---|---|
| Name of person taking consent | Date | Signature |

*Top copy: Study file at site* *1 copy: Patient* *1 copy: Patients hospital record* *1 copy: Post to study office*

# 2 SCOTLAND

## OSCAR trial consent processes

### Scotland - Adults with Incapacity (Scotland) Act 2000 (relates to collaborating hospitals in England and Wales)

*MREC 07/MRE00/73 / Version 2 – 3 Sept 07*

Scottish collaborators should follow the table overleaf.

## THE OSCAR TRIAL CONSENT PROCESS - Scotland

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

## Process for obtaining consent in Scotland: Hospitals falling under the Adults with Incapacity (Scotland) Act 2000

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?<br>If **No** → <br>If **Yes**<br>• Explanation to be given in person and questions encouraged. Information sheet to be provided.<br>• Written consent to be signed by WG/NR<br>• If WG/NR not present in person, verbal consent to be obtained by telephone using 'Welfare Guardian/Nearest Relative *Verbal Consent*' form.<br>• Written consent to be obtained as soon as possible if practical<br>• 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.

If a patient in the trial dies before regaining consciousness the patient's data will be included in the study.

Documentation related to this process follows over the page.

[To be printed on OSCAR headed paper]

**OSCAR STUDY**

**INFORMATION ABOUT THE RESEARCH**

*(Welfare Guardian/Nearest Relative)*

REC reference: 07/MRE00/73 / Version 2 –3 Sept 2007
ISRCTN10416500

SCOTLAND ONLY

Centre No. [xxxx]

*Title of project: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

**Principal Local Investigator** [PI Name & Telephone No. here]

PART ONE - INVITATION TO JOIN THE OSCAR STUDY

You will know from talking with the doctor that your relative has a serious breathing problem. This must be an extremely anxious time for you. We would however be grateful if you would take a little time to read this information. It asks you to think about allowing your relative to join a study which is taking place in many hospitals in the UK. Normally we ask patients themselves to consider taking part in research studies, but as your relative is on a breathing machine we can't discuss it with him or her.

**What is the purpose of the study?**

This study is comparing two ways of providing help with breathing for patients with serious breathing problems:

1. conventional ventilation (often called artificial ventilation or "breathing machine")
2. high frequency oscillatory ventilation.

Conventional ventilation

This sort of ventilation helps breathing by pushing a mixture of air and oxygen into the lungs every 2-4 seconds. We call this conventional ventilation because it is the most common method used.

Your relative is already receiving conventional ventilation. This form of care is standard treatment, and has been used for many years. However, using a conventional ventilator to deliver air and oxygen may itself sometimes cause some further damage to the air sacs (alveoli) in the lungs and delay recovery. This happens in about 1 in 12 patients who are ventilated.

High frequency oscillatory ventilation

Another way of ventilating patients is called 'high frequency oscillatory ventilation', sometimes abbreviated to HFOV. This involves giving very small breaths of air and oxygen very rapidly (up to 5 times per second far faster than conventional ventilators can provide breaths). As the breaths are very small they do not stretch the lungs very much and so might reduce the chances of causing further lung damage. However, the disadvantage with this type of ventilation is that the patient usually requires more sedatives.

This way of ventilating patients with severe breathing problems might be as effective, or better than conventional ventilation but currently there is not enough information to know which. Studies to date have not shown a clear answer. This is why we are undertaking the study.

**What would being in the study involve?**

Whilst in the Intensive Care Unit:

If you agree to your relative taking part, he or she will be assigned to receive one of the two forms of ventilation offered:

- Half the patients in the study will continue to be treated on conventional ventilation.
- The other half will be treated with high frequency oscillatory ventilation.

Neither you nor the doctor (nor anyone else) will know beforehand which of these two treatments your relative will get if you agree. This will be determined by the play of chance, rather like the toss of a coin. This element of chance is important so that the two methods can be tested fairly. When one of the two ways of ventilating your relative has been allocated, they will either remain on a conventional ventilator or be placed onto a high frequency oscillatory ventilator.

Information from your relative's medical record will be collected during their stay in the Intensive Care Unit. This information will be kept strictly confidential.

The study is only looking at the different forms of ventilation; other elements of your relatives care are not affected and will be decided in the usual way by the doctor caring for them.

After your relative has left the Intensive Care Unit:

As we are interested in the long term wellbeing of your relative, we will send him/her a questionnaire at six months after treatment in the Intensive Care Unit. The questionnaire will ask how your relative's breathing is affecting day-to-day activities, and about their general health. We will also send the same questionnaire to him/her after 12 months. We may send up to three more questionnaires, again spaced six month apart.

There are *no* further tests or hospital visits involved in taking part in the study.

Over 1,000 patients like your relative from hospitals across the UK will take part in this study. They are all helping to help find out which procedure is the safer, and more effective, at aiding breathing both in the short and long term.

**Why am I being asked to consider the study?**

Normally we ask patients themselves if they would consider taking part in research studies, but as your relative is on a breathing machine we can't discuss it with him or her. We are, therefore, approaching you (someone who has patient's welfare and best interests in mind), whether, in your opinion, your relative would have wished to take part in this study if they were able to make the decision themselves.

- If you believe your relative *would* have wanted to take part in this study, we would like you to give your consent for him/her to take part.

- If you believe your relative would *not* have wanted to take part, we will not include him/her in the study.

Declining to join the study will not affect the standard of care your relative receives.

If you (or your relative when he/she regains capacity), change your mind, they can be withdrawn from the study at any time. This will not adversely affect he or she's care. The patients (and their doctors) who take part in this study are not paid to do so and participate freely.

**Do I have to agree to my relative being involved?**

It is up to you to think about your relative's wishes and decide.

We will describe the study and go through this information sheet with you and you will be given a copy read. If you agree, we will ask you to sign a consent form to show you have agreed, and provide you with a copy.

When your relative is well enough to make a judgment about being in the study we will ask them. If they decide not to continue in the study they can withdraw.

**If, after reading Part One, the study sounds like something your relative might have agreed to, you may find it helpful to read the further information in Part Two before you make your decision.**

PART TWO - ADDITIONAL INFORMATION FOR RELATIVES WHO WOULD LIKE TO KNOW MORE ABOUT THE OSCAR STUDY

**Who is organising and funding the research?**

The Intensive Care Society's Trials Group at the University of Oxford is organising this research and work with the consultants and nurses in hospitals around the UK.

The National Coordinating Centre for Health Technology Assessment (part of the Department of Health/UK Government) is funding the research.

**Who has approved the study?**

Any research involving a person who lacks capacity may only be lawfully carried out if an NHS Research Ethics Committee (REC), has given the research their favourable opinion. They look after your relative's rights, well being and dignity.

This study has been reviewed and given a favourable option by a REC. The REC reference number is given on the front page of this document.

This study was also reviewed by the National Coordinating Centre for Health Technology Assessment before it was awarded funding to ensure it met the necessary scientific standards.

**Is there a contact point where I can seek independent advice about participating in the study?**

Yes, the Trust's Research and Development (R&D) Office can be contacted. They will give you advice about who you can talk to for independent advice. Ask one of the doctors or nurses for the R&D telephone details.

If you would like more information about the study itself you can ask to speak to the research lead for the OSCAR study at this hospital. His/her contact details are on the front of this information.

**More about conventional and high frequency oscillatory ventilation:**

Conventional ventilation is usually undertaken with an artificial ventilator which fills the lungs with an air/oxygen mixture at regular intervals. Even though the breaths are small (about half a litre), patients who have lung conditions that cause stiff lungs may have a delayed recovery because the lungs expand unevenly and some areas get overstretched and damaged. We believe this happens in at least one in twelve patients.

If the breaths are made really small (a twentieth of a litre or less) it may be possible to reduce the damage caused by stretching. However, to move enough oxygen in and out of the lungs, the breaths have to be delivered very rapidly, at about 5 breaths per second. An analogy is often made with panting dogs, who breathe rapidly with small breaths. However, as very rapid breathing is not "natural" for humans, patients receiving high frequency oscillatory ventilation often require more sedation to allow them to tolerate the breathing machine, and so may be sleepier when you visit.

We would like to determine which technique for artificial ventilation is best, and so we are conducting a study where half of the patients receive conventional ventilation and half receive high frequency oscillatory ventilation. As well as looking at how long patients require treatment in the ICU, we will follow patients with questionnaires for up to two and a half years to see if the type of ventilation used has any effect on longer-term health.

**Are there any risks?**

All forms of artificial ventilation are used to treat very severe lung problems and all carry risks. One possible risk with high frequency oscillatory ventilation is that air will not have time to leave the lungs and will be trapped. This risk is minimised by not including patients likely to suffer this problem in the study, and by carefully monitoring the pressures and gas volumes delivered by the ventilator.

**What if something goes wrong?**

Compensation for harm arising from an accidental injury and occurring as a consequence of your relative's participation in the study will be covered by the University of Oxford. If your relative is harmed and this is due to someone's negligence they may have grounds for legal action for compensation against the University of Oxford (in respect of any harm arising out of the participation in the study) or the NHS (in respect of any harm which has resulted from the clinical procedure being undertaken).

**You mention sending a questionnaire to my relative later. What will the questionnaire contain?**

The questionnaire is in two parts. One section is about your relative's breathing and asks how it affects day-to-day living. The second section is a more general assessment of your relative's well-being.

The questionnaire will be posted from the co-ordinating office at Oxford University to your relative's home address. Once completed, it can be returned in a freepost envelope (no stamp required), which is supplied.

The first questionnaire will be sent to your relative six months after treatment in the Intensive Care Unit. The second six months later (12 months after intensive care). We may send them a further three questionnaires. Each of these will be sent six months apart.

As people may move house, we also collect the names of two friends/relatives who can help us locate a patient who has moved.

**What if my relative wishes to withdraw from the study once he/she returns home?**

Once your relative goes home the only involvement in the study is completing the follow up questionnaires asking how his/her breathing is. If your relative does **not** wish to receive a questionnaire they can tell us by telephoning the study co-ordinating office (tel: 01865 857613). No further questionnaires will be sent to them.

**Are my relatives details kept confidential?**

The information collected about your relative during the study will be kept in a secure area of the hospital behind double locked doors. All computer systems are on secure networks and all information is treated as strictly confidential. Any published reports will not identify your relative or any other patients.

Parts of your relatives' medical records and the data collected for the study will be looked at by authorised persons from the sponsor of the research and/or the funding body carrying out monitoring or auditing. This is to ensure the study is being carried out correctly. Identifying details will be sent to the Office of National Statistics and the National Health Service Central Register to aid follow up. All those involved in the research and the organisations supporting research have a duty of confidentiality .

**Communication with GP**

We will send a letter to your relative's family doctor informing them that your relative was entered into the OSCAR study whilst in the Intensive Care Unit.

**What if I (my relative) wish to complain?**

If you have a concern about any aspect of this study, you should ask to speak to the Principal Local Investigator in the first instance. Their contact details are on the front page of this information sheet. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

**Where can I find the results of the study?**

A detailed study report will appear on the National Coordinating Centre for Health Technology Assessment website (NCCHTA, part of the Department of Health) in 2013, and will be free to download. Printed copies will also be available. The study reports will also appear in the medical journals.

Thank you for taking the time to read this information.

If you believe your relative would have wanted to take part in this study, and you would like to give your consent, please let one of the Intensive Care Unit staff know.

Please remember we will ask you for the contact details of two friends of your relative to help us keep in contact should your relative move house.

SCOTLAND ONLY

**Centre No.**
**xxx**

# WELFARE GUARDIAN/NEAREST RELATIVE CONSENT FORM

*Version 1 – 12 June 2007*
*MainREC number: 07/MRE00/73*

**Used when patient does not have capacity to consent**

**To go on Trust headed paper**

Regarding patient: _____
(please write patients name here)

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

1 I confirm that I have read and understand the information leaflet dated [date and version here] for the above study and have had the opportunity to ask questions.

2 I understand that I am voluntarily agreeing to the above named patient's participation in the study and that I (or at a later date they), will be free to withdraw at any time, without giving any reason and without their medical care or legal rights being affected.

3 I confirm that I am acting as Welfare Guardian/Nearest relative for the above named patient who is currently incapacitated, and give my consent for them to join the OSCAR study and agree to the following:

- That the study office can contact the above named patient by post to find out how they are in six months time, or, if necessary they can contact the family doctor, or the friends/relatives named below for this.
- That sections of their medical record can be looked at by responsible individuals involved with the study and transcribed onto the study form.
- That appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.
- That the Office of National Statistics can be used to aid follow up of their health (and that for this purpose their details may be sent, in confidence, to the study office).
- That their family doctor records may be looked at by their general practitioner to identify their location or health status in the future. These details may be shared with, and held at, the study office.
- That this consent form will be stored at the study office for monitoring purposes.
- That Members of the University of Oxford or Health Technology Assessment monitoring/auditing team may require access to my relatives details. Confidentiality of personal details will be maintained throughout this process.

**If you would like further information before signing this form please contact:**
[Name, title and telephone contact details of local OSCAR Principal Investigator here]

4 I confirm I am the patients (tick one box): Welfare guardian ☐ Nearest relative ☐

*If you answered 'nearest relative' above, please indicate:*
(a) Your degree of kinship to the participant: _____
(b) I confirm there is no nearer relative (tick box): ☐
(c) I confirm there is no welfare guardian (tick box): ☐

| Name (PRINT) | Date | Signature |
|---|---|---|
| Name of person taking consent | Date | Signature |

*Consent form continued:*

**Please provide contact details of 2 friends/relatives who can be written to for contact details if we lose contact with the patient named above (please PRINT)**

## Friend/relative 1

Name: _____

Address: _____

_____

_____ Post code: _____

Telephone (if known): _____ _____
(code)

## Friend/relative 2

Name: _____

Address: _____

_____

_____ Post code: _____

Telephone (if known): _____ _____
(code)

*Top copy: Study file at site 1 copy: Welfare guardian/nearest relative 1 copy: Patients hospital notes 1 copy: Post to study office*

**Centre No.**
**xxx**

SCOTLAND ONLY

**Used when patient does not have capacity to consent**

# VERBAL CONSENT FROM WELFARE GUARDIAN/NEAREST RELATIVE

(PRIOR TO PATIENTS TRIAL ENTRY)

*Version 1 – 12 June 2007*
*MainREC number: 07/MRE00/73*

**To go on Trust headed paper**

Regarding patient: _____
(please write patients name here)

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

Principal Local Investigator: [name and telephone number here]

Please initial boxes

1 I confirm that the patient's inclusion in the above study has been discussed with the appropriate relative and that they were offered the opportunity to ask questions/ask for clarification …….. ☐

2 I confirm he/she has given verbal assent for the patient to be in the study. He/she understands that relevant sections of the patient's notes may be looked at by responsible individuals involved with the study and does not object to these individuals having access to the patient's records …… ☐

3 I confirm he/she understands that personal identifying details will be collected for this patient and that he/she does not object to this information being collected, stored and used for follow up purposes ……. ☐

Name of relative: _____

Relationship to patient: _____

Date and time relative was informed: Date: _____/_____/_____ Time: (24 hr clock) _____:_____

Comments, including any objections: _____

Please initial box

4 A copy of the information sheet has been given or sent to the patient's relative *(please tick as appropriate)*: Yes ☐ No ☐ ☐

| | | |
|---|---|---|
| _____ | _____ | _____ |
| Name of person informing relative | Date | Signature |
| _____ | _____ | _____ |
| Name of Principal Local Investigator | Date | Signature |

*Top copy: Study file at site* *1 copy: Patients hospital notes* *1 copy: Post to study office*

**Centre No.**
**xxx**

SCOTLAND ONLY

**To go on Trust headed paper**

**Used when patient regains capacity in the ICU**

# PATIENT CONSENT TO CONTINUE

*Version 2 – 3 Sept 2007*
*REC reference: 07/MRE00/73*

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

1 I confirm that I have read and understand the information leaflet dated [date and version here] for the above study and have had the opportunity to ask questions.

2 I understand that I am voluntarily agreeing to participate in the study and that I am free to withdraw at any time, without giving any reason.

3 I confirm that:

4 That the study office can contact me by post to find out how I am in six months time, or, if necessary they can contact my family doctor, or my friends/relatives named on the original consent form signed by my legal representative.

5 That sections of my medical record can be looked at by responsible individuals involved with the study and transcribed onto an anonymised study form

6 That appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of my health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.

- That the Office of National Statistics will be used to help keep in touch with me or to help follow up my health (and that for this purpose my details may be sent, in confidence, to the study office).
- That my family doctor records may be looked at by my general practitioner to identify my location or health status in the future. These details may be shared with, and held at, the study office.
- That this consent form will be stored at the study office for monitoring purposes.
- That Members of the University of Oxford or Health Technology Assessment monitoring/auditing team may require access to my relatives details. Confidentiality of personal details will be maintained throughout this process.

**If you would like further information before signing this form please contact:**
[Name, title and telephone contact details of local OSCAR Principal Investigator here]

| Name (PRINT) | Date | Signature |
|---|---|---|
| Name of person taking consent | Date | Signature |

*Top copy: Study file at site* *1 copy: Patient* *1 copy: Patients hospital record* *1 copy: Post to study office*

**Appendix 5:**

# PATIENT FOLLOW UP DOCUMENTATION

All surviving patients are followed up at 6 months and 12 months post randomisation by postal questionnaire to their home.

Attached is:

1. Covering letter – 6 months
2. Covering letter – 12 months
3. Follow-up Summary/consent slip
4. Questionnaire

In addition, all surviving patients recruited to the trial in the:

- **first year:** will receive an additional questionnaire containing only the EQ-5 and social and health service use questions at 24 and 30 months

- **second year:** will receive an additional questionnaire containing only the EQ-5 and social and health service use questions at 18 months

# UNIVERSITY OF OXFORD

Telephone 01865 857613
Facsimile 01865 857611
Email: OSCAR.trial@nda.ox.ac.uk

ICS Trials Group
Kadoorie Centre for Critical Care
Level 3, John Radcliffe Hospital
Headley Way
Oxford OX3 9DU

*[date]*
*[Patients full name and postal address]*
[Trial number]

Ref: MREC: 07/H0502/98 ENGLAND VERSION
V2 / 3 Sept 07

6 m Letter to surviving patients who consented in ICU.
to accompany questionnaire.

Dear [name]

OSCAR STUDY

When you were treated in the Intensive Care Unit (ICU) in [xxxxxxx] hospital in [month/year], you needed some help with your breathing. You may remember that whilst in the ICU you were approached and agreed to take part in the OSCAR study.

We are writing to you now as we would like to know how your health is six months on.

Enclosed is a questionnaire which we invite you to complete. This should only take a few minutes of your time and a freepost envelope is provided for ease of return (no stamp required). The questionnaire asks about your current health and how your breathing is now.

Many hospitals around the UK are collaborating in this research which is co-ordinated by researchers from the University of Oxford. If you have any questions, or would like some help completing the questionnaire, please contact us on the telephone number above.

A summary sheet is enclosed containing further information about the study. A pen is also enclosed to help you complete the questionnaire.

Thank you very much for your time.

Dr Duncan Young
Chief Investigator OSCAR Study
Consultant in Adult Critical Care

Enc: 6m Questionnaire / Pen / Summary sheet / freepost envelope

# UNIVERSITY OF OXFORD

Telephone 01865 857613
Facsimile 01865 857611
Email: OSCAR.trial@nda.ox.ac.uk

ICS Trials Group
Kadoorie Centre for Critical Care
Level 3, John Radcliffe Hospital
Headley Way
Oxford OX3 9DU

*[date]*
*[Patients full name and postal address]*
[Trial number]

Ref: MREC: 07/H0502/98 & 07/MRE00/73
V2 / 3 Sept 07

6 m Letter to surviving patients who did not regain capacity in the intensive care unit to accompany questionnaire.

Dear [name]

OSCAR STUDY

When you were treated in the Intensive Care Unit (ICU) in [xxxxxxx] hospital in [month/year], you needed some help with your breathing. The machines used to help your breathing ("ventilators"), are being studied to see if one of two types leads to a faster recovery in patients. The study is called the "OSCAR study". At the time we discussed the study with a person who was best able to inform us of your wishes as you were ill in the ICU.

We are writing to you now as we would like to know how your health is six months on.

Enclosed is a questionnaire which we invite you to complete. This should only take a few minutes of your time and a freepost envelope is provided for ease of return (no stamp required). The questionnaire asks about your current health and how your breathing is now.

Many hospitals around the UK are collaborating in this research which is co-ordinated by researchers from the University of Oxford. If you have any questions, or would like some help completing the questionnaire, please contact us on the telephone number above.

A summary sheet is enclosed containing further information about the study. A pen is also enclosed to help you complete the questionnaire.

Thank you very much for your time.

Dr Duncan Young
Chief Investigator OSCAR Study
Consultant in Adult Critical Care

Enc: 6m Questionnaire / Pen / Summary sheet / Consent Slip / Information about the Research/ freepost envelope

# UNIVERSITY OF OXFORD

Telephone 01865 857613
Facsimile 01865 857611
Email: OSCAR.trial@nda.ox.ac.uk

ICS Trials Group
Kadoorie Centre for Critical Care
Level 3, John Radcliffe Hospital
Headley Way
Oxford OX3 9DU

Ref: MREC: 07/H0502/98 ENGLAND VERSION
V1/12 June 07

[date]
*Patients full name and postal address*
[Trial number]

Letter to all surviving patients at 12 months post randomisation – to accompany questionnaire.

Dear [name]

OSCAR STUDY

You may remember that six months ago we sent you a questionnaire to complete about how your health was following your stay in the intensive care unit in [xxxxxxx] hospital in [month/year]. This was in relation to the OSCAR study.

A further six months has passed and we would like to know how your health is now.

Enclosed is a questionnaire which we invite you to complete. This should only take a few minutes of your time and a freepost envelope is provided for ease of return (no stamp required). The questionnaire asks about your current health and your breathing.

Researchers at the University of Oxford are co-ordinating this project. If you have any questions, or would like some help completing the questionnaire, please contact us on the telephone number above.

A summary sheet is enclosed containing further information about the study. A pen is also enclosed to help you complete the questionnaire.

Thank you very much for your time.

Dr Duncan Young
Chief Investigator OSCAR Study
Consultant in Adult Critical Care

Enc: 12m Questionnaire / Pen / Summary sheet / freepost envelope

REC Ref: 07/H0502/98
& 07/MRE00/73
Version 2 – 3 Sept 07
ISRCTN10416500


To be sent with 6m follow up questionnaire and covering letter to survivors

# Summary

**Information about the OSCAR study**

TO THOSE WHO REGAINED CAPACITY/ALREADY CONSENTED IN INTENSIVE CARE UNIT

**What is the study about?**

The OSCAR study is looking at whether patients with acute respiratory distress syndrome (a breathing condition you had whilst in the Intensive Care Unit), benefit more from one of two types of machines to help their breathing. One type of breathing machine (ventilator), gives regular breaths every 2-4 seconds, the other uses several very small breaths per second. We do not know which is best, so we are treating half the patients in intensive care with conventional (slow) breaths, and half with the very rapid breaths (high frequency oscillatory ventilation). When the study finishes we will compare many aspects of the patients' recovery to find out which ventilator leads to the fastest recovery.

**Why have you sent me a questionnaire?**

When you were in the Intensive Care Unit agreement to participate in the study was obtained, and you were treated with one of the two types of ventilators above. As we are interested in your long term wellbeing, we have sent you the enclosed questionnaire so that you can tell us how your breathing is now, and how it affects your day-to-day living. Asking you to complete a questionnaire is the best way to do this without inconveniencing you with further hospital visits.

Over 1,000 other patients like yourself from hospitals across the UK will also be followed up by questionnaire. You, and they, are helping to find out which of the two types of ventilators are more effective at aiding breathing both in the short and longer term.

We would also like to send you another questionnaire in six months time, to see if there is any change in your breathing. We may also send up to three more questionnaires, again spaced six month apart, if this is agreeable to you.

**How do I fill in the questionnaire?**

Guidance is provided on the questionnaire itself. A pen is provided for ease of completion and most questions require a 'tick' response. It should take you about 10 minutes to complete. If you require any help completing the questionnaire please telephone the study office.

**What do I do when I've completed the questionnaire?**

Please check that you have answered ALL the questions and the front sheet of the questionnaire. Then place the questionnaire in the freepost envelope provided (no stamp required). You can then place it in the post in the usual way.

**Who regulates the study?**

The OSCAR study started in many hospitals around the United Kingdom (UK) in 2007. Before any patients could be recruited we were required to go through a variety of reviews to ensure that the study was ethically and scientifically worthwhile. Researchers at the University of Oxford co-ordinate the study and it is funded by the Health Technology Assessment Programme.

Thank you very much for your time.

Dr Duncan Young, Chief Investigator OSCAR Study, Consultant in Adult Critical Care, Tel: 01865 857613

REC Ref: 07/H0502/98
Version 2 – 3 Sept 07
ISRCTN10416500

TO THOSE WHO HAD **NOT** REGAINED CAPACITY BY INTENSIVE CARE UNIT DISCHARGE

To be sent with:
6m follow up questionnaire (plus covering letter & original 'Information about the research' & consent slip) to survivors

# Summary

**Information about the OSCAR study**

During your stay in the intensive care unit you took part in a research study called the OSCAR Study. Agreement was obtained at the time from a relative, friend or person representing you.

**What is the study about?**

The OSCAR study is looking at whether patients with acute respiratory distress syndrome (a breathing condition you had whilst in the Intensive Care Unit), benefit more from one of two types of machines to help their breathing. One type of breathing machine (ventilator), gives regular breaths every 2-4 seconds, the other uses several very small breaths per second. We do not know which is best, so we are treating half the patients in intensive care with conventional (slow) breaths, and half with the very rapid breaths (high frequency oscillatory ventilation). When the study finishes we will compare many aspects of the patients' recovery to find out which ventilator leads to the fastest recovery.

**Why have you sent me a questionnaire?**

When you were in the Intensive Care Unit agreement to participate in the study was obtained, and you were treated with one of the two types of ventilators above. As we are interested in your long term wellbeing, we have sent you the enclosed questionnaire so that you can tell us how your breathing is now, and how it affects your day-to-day living. Asking you to complete a questionnaire is the best way to do this without inconveniencing you with further hospital visits.

Over 1,000 other patients like yourself from hospitals across the UK will also be followed up by questionnaire. You, and they, are helping to find out which of the two types of ventilators are more effective at aiding breathing both in the short and longer term.

We would also like to send you another questionnaire in six months time, to see if there is any change in your breathing. We may also send up to three more questionnaires, again spaced six month apart, if this is agreeable to you.

**How do I fill in the questionnaire?**

Guidance is provided on the questionnaire itself. A pen is provided for ease of completion and most questions require a 'tick' response. It should take you about 10 minutes to complete. If you require any help completing the questionnaire please telephone the study office.

**What do I do when I've completed the questionnaire?**

Please check that you have answered ALL the questions and the front sheet of the questionnaire. Then place the questionnaire in the freepost envelope provided (no stamp required). You can then place it in the post in the usual way.

**Who regulates the study?**

The OSCAR study started in many hospitals around the United Kingdom (UK) in 2007. Before any patients could be recruited we were required to go through a variety of reviews to ensure that the study was ethically and scientifically worthwhile. Researchers at the University of Oxford co-ordinate the study and it is funded by the Health Technology Assessment Programme.

**Consenting to the study**

We enclose a copy of the study information your friend, relative or person representing you was given in the Intensive Care Unit. They considered the information presented and agreed that you were unlikely to have any objections to entering the study. We would now like to ask for your formal consent.

A consent form is attached and we would be grateful if you would sign this if you are agreeable. If you would like further information before signing the form, please contact us in the OSCAR study office on telephone: 01865 857613.

The form can be placed in the envelope with your completed questionnaire.

Thank you very much for your time.

Dr Duncan Young, Chief Investigator OSCAR Study, Consultant in Adult Critical Care,

**Centre No.**
**Xxx**

**Trial number: xxx**


Sent with 6m Q to those who had not regained capacity in ICU

## PATIENT CONSENT SLIP

*Version 1 – 3 September 2007*
*REC reference: 07/H0502/98*

*Title of project: OSCAR: A study to investigate whether high frequency oscillatory ventilation or conventional positive pressure ventilation is of benefit to patients in the Intensive Care Unit.*

1 I confirm that I have read and understand the summary information leaflet dated [date and version here] for the above study.

2 I understand that I am voluntarily agreeing to participate in the study and that I am free to withdraw at any time, without giving any reason.

3 I confirm:

- That the study office can contact me by post to find out how I am in six months time, or, if necessary they can contact my family doctor. I understand that I may be sent a further three questionnaires six months apart.
- That sections of my medical record can be looked at by responsible individuals involved with the study and transcribed onto an anonymised study form
- That appropriate personal identifying information will be collected, stored and used by the study office to enable follow up of my health status. This is on the understanding that any information will be treated with the strictest security and confidentiality.
- That the Office of National Statistics will be used to help keep in touch with me or to help follow up my health (and that for this purpose my details may be sent, in confidence, to the study office).
- That my family doctor records may be looked at by my general practitioner to identify my location or health status in the future. These details may be shared with, and held at, the study office.
- That this consent form will be stored at the study office for monitoring purposes.
- That Members of the University of Oxford or Health Technology Assessment monitoring/auditing team may require access to my details. Confidentiality of personal details will be maintained throughout this process.

**If you would like further information before signing this form please contact the OSCAR Trial Office: telephone 01865 857613.**

| Name (PRINT) | Date | Signature |
|---|---|---|

**PATIENTS FOLLOW UP QUESTIONNAIRE**

OSCAR

Conventional positive pressure ventilation
or
high frequency oscillatory ventilation?

# [x] MONTH QUESTIONNAIRE

Ref: MRECxxxx / V2 – 4 March 08

Study Number: xxxx

We would be grateful if you would complete this OSCAR study questionnaire. We would like to understand how your health is since you left the Intensive Care Unit.

There are no right or wrong answers. We have found that the best way to answer the questions is to go with your first instinct, whatever you think is the correct response for you.

A pen is provided along with a freepost envelope for return of the questionnaire. Please contact the study office if you have any questions (details on the Summary provided).

**If you are reading this on behalf of the addressee, we would still very much like to hear about the health of the addressee. In this case, please fill in the questionnaire on their behalf and tick (√) this box ☐ to indicate you have completed the questionnaire. Please also state your relationship to the addressee below.**

**I am the patients:** _____

If you have any questions please contact the study office on 01865 220614.

Thank you. Now please turn the page to start the questionnaire ⟹

If you do not wish to complete this questionnaire, please return the unanswered questionnaire in the freepost envelope to the trial office.

# OSCAR STUDY QUESTIONNAIRE

## *SECTION ONE*

## Your Health

This section of the questionnaire is designed to help us learn much more about how your breathing is troubling you (or not troubling you), and how it affects your life.

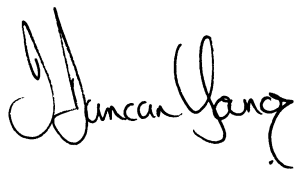
We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

There are no right or wrong answers. We have found that the best way to answer the questions is to go with your first instinct, whatever **you** think is the correct response for you.

Some of the questions appear very similar; however we would be grateful if you could answer every question in order that we have an overview of your health.

Please read the instructions carefully.

Thank you.



Duncan Young
Chief Investigator
OSCAR Study

**Before you start the questionnaire, please write today's date below:**

I completed this questionnaire on _____/_____/_____
Day month year

# Your Health

1 Please tick (√) one box below to show how you describe your current health:

*(Tick (√) only **one** box)*

| Very good | Good | Fair | Poor | Very Poor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## Questions about how much chest trouble you have had over the past 4 weeks

*Please tick (√) **one** box for **each** question*

| | Most days a week | Several days a week | A few days a month | Only with chest infections | Not at all |
|---|---|---|---|---|---|
| *Example: Over the past 4 weeks, I have coughed:* | ☐ | √ | ☐ | ☐ | ☐ |
| 2 Over the past 4 weeks, I have coughed: …….. | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3 Over the past 4 weeks, I have brought up phlegm (sputum): …… | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4 Over the past 4 weeks, I have had shortness of breath: …… | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5 Over the past 4 weeks, I have had attacks of wheezing: …… | ☐ | ☐ | ☐ | ☐ | ☐ |

6 During the past 4 weeks, how many severe or very unpleasant attacks of **chest trouble** have you had?

*Please tick (√) **one***

- *More than 3 attacks* ☐
- *3 attacks* ☐
- *2 attacks* ☐
- *1 attack* ☐
- *No attacks* ☐

7 How long did the worst attack of **chest trouble** last?
*(Go to question 8 if you had no severe attacks)*

*Please tick (√) **one***

- *A week or more* ☐
- *3 or more days* ☐
- *1 or 2 days* ☐
- Less than a day ☐

8 Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

*Please tick (√) **one***

- *No good days* ☐
- *1 or 2 good days* ☐
- *3 or 4 good days* ☐
- *Nearly every day is a good day* ☐
- *Every day is a good day* ☐

9 If you have a wheeze, is it worse in the morning?

*Please tick (√) **one***

- *No* ☐
- *Yes* ☐

10 How would you describe your chest condition?

*Please tick (√) **one***

- *The most important problem I have* ☐
- *Causes me quite a lot of problems* ☐
- *Causes me few problems* ☐
- *Causes no problem* ☐

11 If you have ever had paid employment:

*Please tick (√) **one***

- *My chest trouble made me stop work altogether* ☐
- *My chest trouble interferes with my work or made me change my work* ☐
- *My chest trouble does not affect my work* ☐

12 What activities usually make you feel breathless <u>these days</u>:

*Please tick (√) **in each box** that applies to you **these days**:*

| | TRUE | FALSE |
|---|---|---|
| *Sitting or lying still* | ☐ | ☐ |
| *Getting washed or dressed* | ☐ | ☐ |
| *Walking around the home* | ☐ | ☐ |
| *Walking outside on the level* | ☐ | ☐ |
| *Walking up a flight on stairs* | ☐ | ☐ |
| *Walking up hills* | ☐ | ☐ |
| *Playing sports or games* | ☐ | ☐ |

13 Some more questions about your **cough and breathlessness** these days:

*Please tick (√) **in each box** that applies to you **these days**:*

| | TRUE | FALSE |
|---|---|---|
| *My cough hurts* | ☐ | ☐ |
| *My cough makes me tired* | ☐ | ☐ |
| *I am breathless when I talk* | ☐ | ☐ |
| *I am breathless when I bend over* | ☐ | ☐ |
| *My cough or breathing disturbs my sleep* | ☐ | ☐ |
| *I get exhausted easily* | ☐ | ☐ |

14 Questions about other effects that **your chest trouble** may have on you these days:

*Please tick (√) **in each box** that applies to you **these days**:*

| | TRUE | FALSE |
|---|---|---|
| *My coughing or breathing is embarrassing in public* | ☐ | ☐ |
| *My chest trouble is a nuisance to my family, friends or neighbours* | ☐ | ☐ |
| *I get afraid or panic when I cannot get my breath* | ☐ | ☐ |
| *I feel that I am not in control of my chest problem* | ☐ | ☐ |
| *I do not expect my chest to get any better* | ☐ | ☐ |
| *I have become frail or an invalid because of my chest* | ☐ | ☐ |
| *Exercise is not safe for me* | ☐ | ☐ |
| *Everything seems too much of an effort* | ☐ | ☐ |

15 Questions about your medication:

*(Go to question 16 if you are not receiving any medication):*

*Please tick (√) **in each box** that applies to you **these days**:*

| | TRUE | FALSE |
|---|---|---|
| *My medication does not help me very much* | ☐ | ☐ |
| *I get embarrassed using my medication in public* | ☐ | ☐ |
| *I have unpleasant side effects from my medication* | ☐ | ☐ |
| *My medication interferes with my life a lot* | ☐ | ☐ |

16 These are questions about how your activities might be affected **by your breathing**:

*Please tick (√) **in each box** that applies to you **because of your breathing:***

| | TRUE | FALSE |
|---|---|---|
| *I take a long time to get washed or dressed* | ☐ | ☐ |
| *I cannot take a bath or shower, or I take a long time* | ☐ | ☐ |
| *I walk slower than other people, or I stop for rests* | ☐ | ☐ |
| *Jobs such as housework take a long time, or I have to stop for rests* | ☐ | ☐ |
| *If I walk up one flight of stairs, I have to go slowly or stop* | ☐ | ☐ |
| *If I hurry or walk fast, I have to stop or slow down* | ☐ | ☐ |
| *My breathing makes it difficult to do things such as walk up hills, carrying things upstairs, light gardening such as weeding, dance, play bowls or play golf* | ☐ | ☐ |
| *My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim* | ☐ | ☐ |
| *My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports* | ☐ | ☐ |

17 We would like to know how **your chest** usually affects your daily life:

*Please tick (√) **in each box** that applies to you **because of your chest trouble:***

| | TRUE | FALSE |
|---|---|---|
| *I cannot play sports or games* | ☐ | ☐ |
| *I cannot go out for entertainment or recreation* | ☐ | ☐ |
| *I cannot go out of the house to do the shopping* | ☐ | ☐ |
| *I cannot do housework* | ☐ | ☐ |
| *I cannot move far from my bed or chair* | ☐ | ☐ |

18 Here is a list of other activities that **your chest trouble** may prevent you doing:
*(You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you.)*

- *Going for walks or walking the dog*
- *Doing things at home or in the garden*
- *Sexual intercourse*
- *Going out to church, pub, club or place of entertainment*
- *Going out in bad weather or into smoky rooms*
- *Visiting family or friends or playing with children*

*Please **write in** any other important activities that your chest trouble may stop you doing below:*

19 Now would you tick (√) in the box (**one** only) which you think best describes how **your chest** affects you:

*Please tick (√) **one** only*

- *It does not stop me doing anything I would like to do* ☐
- *It stops me doing one or two things I would like to do* ☐
- *It stops me doing most of the things I would like to do* ☐
- *It stops me doing everything I would like to do* ☐

**Below are some simple questions about your health in general. By ticking (√) one answer in each group below, please indicate which statements best describe your own health state TODAY.**

20 Mobility

*Please tick (√) **one***

- *I have no problems in walking about* ☐
- *I have some problems in walking about* ☐
- *I am confined to bed* ☐

21 Self-care

*Please tick (√) **one***

- *I have no problems with self-care* ☐
- *I have some problems washing or dressing myself* ☐
- *I am unable to wash or dress myself* ☐

22 Usual Activities

*Please tick (√) **one***

- *I have no problems with performing my usual activities (e.g. work, study,housework, family or leisure activities)* ☐
- *I have some problems performing my usual activities* ☐
- *I am unable to perform my usual activities* ☐

23 Pain/Discomfort

*Please tick (√) **one***

- *I have no pain or discomfort* ☐
- *I have moderate pain or discomfort* ☐
- *I have extreme pain or discomfort* ☐

24 Anxiety/Depression

*Please tick (√) **one***

- *I am not anxious or depressed* ☐
- *I am moderately anxious or depressed* ☐
- *I am extremely anxious or depressed* ☐

**Q 25 to Q 31 = SF-12 v 2**
**NEEDS APPROVAL BY MREC**

25 In general, would you say your health is:

*(Tick (√) only **one** box)*

| Excellent | Very Good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

26 The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| *Moderate activities such as moving a table, pushing a Vacuum cleaner, bowling or playing golf* | ☐ | ☐ | ☐ |
| *Climbing several flights of stairs* | ☐ | ☐ | ☐ |

27 During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| *Accomplished less than you would like* | ☐ | ☐ | ☐ | ☐ | ☐ |
| *Were limited in the kind of work or other activities* | ☐ | ☐ | ☐ | ☐ | ☐ |

28 During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| *Accomplished less than you would like* | ☐ | ☐ | ☐ | ☐ | ☐ |
| *Did work or other activities less carefully than usual* | ☐ | ☐ | ☐ | ☐ | ☐ |

29 During the last 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

*(Tick (√) only **one** box)*

| Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

30 These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

| How much of the time during the past 4 weeks: | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| *Have you felt calm and peaceful?* | ☐ | ☐ | ☐ | ☐ | ☐ |
| *Did you have a lot of energy?* | ☐ | ☐ | ☐ | ☐ | ☐ |
| *Have you felt downhearted and depressed?* | ☐ | ☐ | ☐ | ☐ | ☐ |

31 During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

*Thank you for filling in the questions in this section. Before you continue over the page would you please **check** to see that you have answered **all** the **questions** in Section 1.*

## *SECTION TWO*

## Your use of health and support services

If you are in your own home or are in a community-based care facility please complete section two.

If you are *not* at home or in community-based care you do not need to complete Section 2. Please go directly to Section 3 (page 18). Thank you.

This section of the questionnaire asks about health and support services you have **used** and anything you have had to **buy** since you left the Intensive Care Unit. We know that once patients have been discharged from hospital they may make use of other health and support services (for example, their family doctor, counselling, district nurse, or other hospital based services). This questionnaire asks you whether you have used any of these other health and support services, how often, and the costs to you (in terms of time and personal expenses). Your responses to these questions will give us a clearer idea of the actual costs involved.

When answering the following questions please think only about the time you were in the Intensive Care Unit **that led to you being entered in the OSCAR trial**.
If you need help completing this section please ask someone to assist you who cares for you and who knows which services and care you have had.

**The information you give us will be confidential and will only used for the OSCAR study.** Your answers will not affect any treatment you may be receiving now or any treatment you might receive in the future.

Please answer the questions that follow. Some questions will seem more relevant to you than others, but please try to answer all the questions.

Thank you.

## Your use of primary and community based health and social services

32 Have you used any of the following services **since you left hospital** because of your stay in the Intensive Care Unit that led to your entry into the OSCAR study?

| Have you visited/used any of these services: | In the last 6 months: Please tick (√) yes or no box on each line depending whether you **physically attended** a service | In last 6 months: Write the total number of **face-to-face** contacts for each service | In last 6 months: Write the total number of contacts by **telephone or email** for each service |
|---|---|---|---|
| a) GP, surgery visit | Yes ☐ No ☐ | | |
| b) GP, home visit | Yes ☐ No ☐ | | |
| c) District nurse | Yes ☐ No ☐ | | |
| d) Health visitor | Yes ☐ No ☐ | | |
| e) NHS Walk-in centre | Yes ☐ No ☐ | | |
| f) Social worker | Yes ☐ No ☐ | | |
| g) Physiotherapist | Yes ☐ No ☐ | | |
| h) Occupational Therapist | Yes ☐ No ☐ | | |
| i) Home help or care worker | Yes ☐ No ☐ | | |
| j) Citizens advice or welfare rights advisor | Yes ☐ No ☐ | | |
| k) NHS Direct | Yes ☐ No ☐ | | |
| l) Lunch or social club organised by your local authority | Yes ☐ No ☐ | | |
| m) Food, medicine or laundry delivery service | Yes ☐ No ☐ | | |
| n) Medical supplies | Yes ☐ No ☐ | | |
| o) Family or patient support or self help groups | Yes ☐ No ☐ | | |
| p) Respite care | Yes ☐ No ☐ | | |
| q) Other (please specify): | Yes ☐ No ☐ | | |

## Your use of hospital and residential care services

33 We would like to know whether you have used other hospital or residential care services since you were discharged from the hospital following your entry into the OSCAR study.

| Have you used any of these services: | Since you left hospital: Please tick (√) 'yes' or 'no' box on each line depending whether you used a service | Since you left hospital: Give the total number of days **you were in** each service: *Number of days:* | Since you left hospital: Give total number of **visits made to** each service: *Number of visits:* |
|---|---|---|---|
| a. Hospital inpatient stay | Yes ☐ No ☐ | | |
| b. Hospital day centre | Yes ☐ No ☐ | | |
| c. Hospital outpatient clinic | Yes ☐ No ☐ | | |
| d. Hospital accident and emergency visit | Yes ☐ No ☐ | | |
| e. Day centre run by your local authority | Yes ☐ No ☐ | | |
| f. Residential care home | Yes ☐ No ☐ | | |
| g. Rehabilitation centre | Yes ☐ No ☐ | | |
| h. Warden controlled residence | Yes ☐ No ☐ | | |

34 If you answered 'Yes' to using one or more of the services in question 33, please give us the name of the service and the area it is located in (see example in table below):

| Type of service | Name of service used | Name of hospital/day centre/rehabilitation centre or care home | Town or city |
|---|---|---|---|
| ***Example:*** *Hospital outpatient clinic* | *Back clinic* | *John Radcliffe Hospital* | *Oxford* |
| a. Hospital inpatient stay | | | |
| b. Hospital day centre | | | |
| c. Hospital outpatient clinic | | | |
| d. Hospital accident and emergency visit | | | |
| e. Day centre run by your local authority | | | |
| f. Residential care home | | | |
| g. Rehabilitation centre | | | |
| h. Warden controlled residence | | | |

## Use of equipment and aids to help you after your stay in the Intensive Care Unit

35 Since you left hospital, have you used any special equipment or aids to help you (for example a toilet frame, a grab rail for your bed or a walking frame) due to your stay in the Intensive Care Unit that led to your entry into the OSCAR study?

Yes ☐ No ☐

36 If you answered 'yes' to question 35, who provided the equipment or aids following your stay in the Intensive Care Unit that led to your entry into the OSCAR study?

Provided by social services Yes ☐ No ☐

Borrowed from friend/family Yes ☐ No ☐

Bought by you Yes ☐ No ☐

Provided by voluntary organisation Yes ☐ No ☐

Provided by hospital Yes ☐ No ☐

Other: Yes ☐ No ☐

If 'yes' please specify here: _____

37 If you answered 'yes' to question 36, please indicate below each type of equipment or aid you have used since you left the hospital following your stay in the Intensive Care Unit that led to your entry into the OSCAR study. If **you** purchased any of the aids yourself, please indicate which ones, and enter the amount paid for them:

| Type of aid | **Tick (√) if you USED** the aid since you left hospital | **Tick (√) if you PURCHASED** the aid used since you left hospital | If you purchased, please enter the cost to you (£'s) |
|---|---|---|---|
| Commode | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Mowbray Frame | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Combiframe | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Free standing toilet frame | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Raised toilet seat | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |

| **Type of aid** | **Tick (√) if you USED** the aid since you left hospital | **Tick (√) if you PURCHASED** the aid used since you left hospital | If <u>you</u> purchased, please enter the cost to you (£'s) |
|---|---|---|---|
| Urine bottle | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Bed pan | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Chair raisers | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Bed sitting support | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Bed leaver/grab rail | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Transfer board | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Banana board | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Slide sheet | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Walking frame | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Mobilator | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Walking frame with wheels | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Walking stick | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Quad stick | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Perching stool | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Leg lifter | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Bottom wipers | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Buckingham caddy | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Hospital bed | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Splints | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |
| Any other equipment you listed | Yes ☐ | Yes ☐ | £ ☐☐☐☐ |

## Your major expenses

38 Since you left hospital have there been any MAJOR one-off expenses (items costing over £50), that **you** have had to meet because of your stay in the Intensive Care Unit that led to your entry into the OSCAR study?

Yes ☐ No ☐

39 If you answered '**Yes**' to question 39, please describe the MAJOR one-off expense item(s) costing over £50 that **you** have had to purchase because of your stay in the Intensive Care Unit that led to your entry into the OSCAR study.

| Description of Item (please write below): | Cost to you since you left hospital **because of your stay in the Intensive Care Unit** £ |
|---|---|
| i. | £ ☐☐.☐☐ |
| ii. | £ ☐☐.☐☐ |
| iii. | £ ☐☐.☐☐ |
| iv. | £ ☐☐.☐☐ |

*Thank you for filling in the questions in this section. Before you continue over the page would you please **check** to see that you have answered **all** the **questions** in Section 2.*

## *SECTION THREE*

## Your employment or usual activities

In this section we would like to know how your stay in the intensive Care Unit that led to your entry into the OSCAR study has affected the work and other activities that you do on a regular basis.

We first ask about your work or activities in the month BEFORE your stay in the Intensive Care Unit, and then about your work or activities AFTER your stay.

---

## **Before** your stay in the Intensive Care Unit

## Your employment or usual activities

40 In the **month before** your stay in the Intensive Care Unit that led to your entry into the OSCAR study, which of the following describe how you were employed.

If you tick **'Yes'** in any category please write the **number of years** you spent in that category prior to your stay in the intensive care unit in the right hand column.

You may answer '**Yes'** in more than one category. For example, you may have been in part-time employment and in part-time education before your stay in the Intensive Care Unit, in which case you should answer 'yes' in both categories and put the number of years spent in each of those categories in the right hand column.

| **In the month before** your stay in the Intensive Care Unit, what was your Employment Status? | Tick (√) one 'yes' in each box that applies to your employment status in the month **before** your stay in the Intensive Care Unit | Enter the number of years spent in each category you said '**Yes**' to before your stay in the intensive care unit<br>*Number of years:* |
|---|---|---|
| Retired and not in paid employment | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Retired | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Not in paid employment due to long standing illness or disability | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Employee, full time (more than 30 hours/ week) | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Employee, part time (less than 30 hours/week) | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Self-employed | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| In full or part time training or education | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Employee on sick leave | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |
| Not in paid employment (but not due to illness or disability) | Yes ☐ No ☐ | ☐☐<br>If Yes, number of years |

## <u>After</u> your stay in the Intensive Care Unit

## Your employment or usual activities

41 Since your stay in the Intensive Care Unit that led to your entry into the OSCAR study, which of the following describes how you are employed now.

You may answer '**Yes'** in more than one category (if you are in part-time employment and in part-time education you should answer 'yes' in both categories).

| What was your Employment Status now? | Tick (√) one 'yes' in each box that applies to your employment status |
|---|---|
| Retired and not in paid employment | Yes ☐ No ☐ |
| Retired | Yes ☐ No ☐ |
| Not in paid employment due to long standing illness or disability | Yes ☐ No ☐ |
| Employee, full time (more than 30 hours/ week) | Yes ☐ No ☐ |
| Employee, part time (less than 30 hours/week) | Yes ☐ No ☐ |
| Self-employed | Yes ☐ No ☐ |
| In full or part time training or education | Yes ☐ No ☐ |
| Employee on sick leave | Yes ☐ No ☐ |
| Not in paid employment (but <u>not</u> due to illness or disability) | Yes ☐ No ☐ |

42 Have you lost any earnings because of your stay in the Intensive Care Unit that led to your entry into the OSCAR study?

Yes ☐ No ☐

43 If you answered ‘yes’ to question 43, please estimate the gross amount lost since your stay in the Intensive Care Unit (i.e. before tax and national insurance has been deducted) and write the amount here:

£ ☐☐☐☐☐

44 Thinking about your usual activities, have you experienced any of the following changes since your stay in the Intensive Care Unit that led to your entry into the OSCAR study?

| **Changes to your activities:** | Please tick (√) ‘yes’ or ‘no’ for each question. |
|---|---|
| Changed to less demanding or less intensive activities | Yes ☐ No ☐ |
| Changed to more demanding or more intensive activities | Yes ☐ No ☐ |
| Spend less time on activities | Yes ☐ No ☐ |
| Spend more time on activities | Yes ☐ No ☐ |
| Opportunities for taking on new activities decreased | Yes ☐ No ☐ |
| Opportunities for taking on new activities increased | Yes ☐ No ☐ |
| Other (If yes, specify below):<br>_____ | Yes ☐ No ☐ |

## *SECTION FOUR*

## Support from others

In this section we ask you about any support or help you receive from others.

We know that some people have support and help from people they know. This may be someone who you have a close relationship with, such as a family member, partner or close friend. This may also be an acquaintance or neighbour.

---

45 Have you had any support or assistance from someone since you left hospital (the stay related to your time in the Intensive Care Unit which led to your entry into the OSCAR study)?

Yes ☐ No ☐ If no, please go to question 48

46 If you answered 'yes' to question 46, which one of the following best describes your relationship with the person who has been <u>most involved</u> in providing support or help:

*Please tick (√) **one** only*

*Spouse or partner* ☐

*Other family member* ☐

*Close friend or companion* ☐

*Acquaintance, colleague or neighbour* ☐

*Carer paid for by the NHS* ☐

*Carer paid for privately* ☐

*Other* ☐

*If 'other' please specify below:*

_____

47 It would be very useful to us to have some information from the person who has helped you the most since you left hospital. If you are happy for them to complete the enclosed questionnaire entitled 'Carers Questionnaire', please pass this on to them. You are under no obligation to pass on this questionnaire and whatever you do it will not affect any treatment you might be receiving or might need to receive in the future.

*Please tick (√) **one** only*

| | |
|---|---|
| *I chose not to ask anyone to complete the questionnaire* | ☐ |
| *I have given the questionnaire to someone and they have **agreed** to fill it in* | ☐ |
| *I have given the questionnaire to someone but they have decided **not** to fill it in* | ☐ |
| *I indicated in question 46 that I have not had any support or assistance since I left hospital* | ☐ |

**Thank you for filling in this questionnaire.**

The information you provide and the information given by the person who has given you support will be confidential and only used for the OSCAR study.

If you have any further comments you would like to make about the OSCAR study or your health, please do so on the back of this page..

**Before placing the questionnaire in the freepost envelope please check that all the questions have been answered.**

No stamp is required when returning the questionnaire as postage is pre-paid by the study.

Thank you for your time.

*Q32-47 Adapted from ACT NoW Study, University of Manchester*

# Appendix 6:

# DATA MONITORING AND ETHICS COMMITTEE MEMBERSHIP

1. Chair (Vacant)
2. Professor David Menon
3. Dr Peter Nightingale

# Appendix 7:
# TRIAL STEERING COMMITTEE MEMBERSHIP

Professor Deborah Ashby (CHAIR)
Professor of Medical Statistics
Wolfson Institute of Preventive Medicine
Barts and The London, Queen Mary's School of Medicine and Dentistry
London

Dr Brian H Cuthbertson
Clinical Senior Lecturer and Honorary Consultant
Health Services Research Unit
University of Aberdeen
Aberdeen

Dr Kathy Rowan
Director
Intensive Care National Audit & Research Centre (ICNARC)
London

Professor Sallie Lamb
Director
Warwick Clinical Trials Unit
University of Warwick
Coventry

Dr Steve Drage
Consultant in Intensive Care Medicine
Royal Sussex County Hospital
Brighton

Dr Ranjit Lall
Warwick Clinical Trials Unit
University of Warwick
Coventry

Professor Tim Walsh *(to be confirmed)*
Consultant in Anaesthesia and Intensive Care
Chairman of the Scottish Critical Care Trials Group
Royal Infirmary
Edinburgh

Professor Chris McCabe
Academic Unit of Health Economics
University of Leeds
Leeds

Mr Barry Williams
*(Critical Care Patient Liaison Committee (CritPal))*

Ms Lesley Morgan
OSCAR Trial Office
Intensive Care Society's Trials Group
University of Oxford
Oxford

Mrs Heather House
University of Oxford's Clinical Trials and Research Governance
Oxford

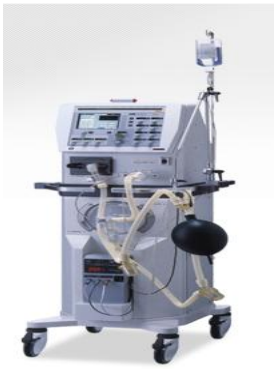
Dr Duncan Young *(Chief Investigator OSCAR Trial)*
OSCAR Trial Office
Intensive Care Society's Trials Group
University of Oxford
Oxford

# Appendix 8:
# TRIAL MANAGEMENT GROUP MEMBERSHIP

| | | |
|---|---|---|
| 1 | Dr Vicki Barber | Trialist |
| 2 | Dr Brian Cuthbertson | Clinician/Trialist |
| 3 | Dr Iain MacKenzie | Clinician/ Trialist |
| 4 | Prof Chris McCabe | Health Economist |
| 5 | Dr Ranjit Lall | Statistician |
| 6 | Prof Sallie Lamb | Trialist |
| 7 | Ms Lesley Morgan | OSCAR Trial Manager |
| 8 | Dr Sanjoy Shah | Clinician |
| 9 | Dr Bill Tunnicliffe | Clinician |
| 10 | Dr Duncan Young | Clinician & OSCAR Chief Investigator |

## Appendix 9: SUMMARY PROTOCOL FOR DOCTORS/NURSES

High Frequency OSCillation in ARDS



# OSCAR Trial: Summary Protocol

*MREC xxxx / Version 3 – 27 June 2011*

**The hypothesis**
Patients with acute respiratory distress syndrome (ARDS) who are treated with high frequency oscillatory ventilation (HFOV) will have a decreased mortality at 30 days (post randomisation) compared with patients treated with conventional positive pressure ventilation.

**The intervention and control groups**
The study arms being compared in this trial are:

*Group 1: High frequency oscillatory ventilation (HFOV)*
*versus*
*Group 2: Conventional positive pressure ventilation*

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

The intervention is high frequency oscillatory ventilation (HFOV) delivered using a Vision Alpha. The management of artificial ventilation with HFOV will be based on a simple algorithm .

Both groups will begin the treatment immediately following randomisation and the patients will remain on the ventilator until the start of weaning from artificial ventilation.

**The setting**
Ten or more ICUs in the NHS in the United Kingdom able to care for Level 3 patients as defined by "Comprehensive Critical Care".

**Outcome measures**

| | |
|---|---|
| Primary outcome measure: | Mortality 30 days after randomisation. |
| Secondary outcome measures: | Mortality rate at first discharge from ICU<br>Mortality rate at first discharge from hospital<br>Mortality rate one year after randomisation<br>Non-pulmonary organ failures whilst treated on an intensive care unit<br>Health-related quality of life six months after randomisation<br>Health-related quality of life one year after randomisation<br>Pulmonary function one year after randomisation |

**Trial design**
OSCAR is a multicentre, open, randomised controlled trial. This is a pragmatic, effectiveness study, where the mode of ventilation is determined randomly, but all other treatment decisions are left to the clinicians managing the patient.

**Population to be studied**
All adult intensive care patients requiring artificial ventilation who meet the inclusion criteria.

**Eligible patients**

Patients are eligible for the trial if they meet the following inclusion criteria:

Patients are eligible for the trial if they meet the following inclusion criteria:

i. Age ≥16 years
ii. Weight ≥35 kg
iii. Receiving artificial ventilation via an endotracheal or tracheostomy tube
iv. Have acute hypoxaemic respiratory failure as defined by:
   - √ 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 $cmH_20$
   - √ Bilateral infiltrates on chest radiograph
v. Will not be extubated by tomorrow evening (predicted by attending clinician)
vi. Have been mechanically ventilated for LESS than 7 consecutive days (≤ 168 hours) at the point of randomisation.

**Clinical management of the 'high frequency oscillatory' ventilation arm**
As HFOV will not have been used previously in most of the intensive care units in the study, before the study starts the clinicians in these units will be trained to operate the HFOV ventilator and follow the treatment algorithm.

**Clinical management of the 'conventional' ventilation arm**
The control patients will be managed using the current best conventional ventilation strategy, which is limited tidal volume, pressure controlled artificial ventilation.

**Sample size**
802 patients (401 in each arm).

**Planned recruitment period**
Recruitment started Dec 2007 and will continue until end July 2012.

*For further information please contact the OSCAR Trial on: Email: OSCAR.trial@nda.ox.ac.uk, Tel: 01865 220614.*

# Appendix 10: FAMILY DOCTOR NOTIFICATION OF PATIENT IN TRIAL

## UNIVERSITY OF OXFORD

Telephone 01865 857613
Facsimile 01865 857611
Email: OSCAR.trial@nda.ox.ac.uk

OSCAR Trial Office
ICS Trials Group
Kadoorie Centre for Critical Care
Level 3, John Radcliffe Hospital
Headley Way
Oxford OX3 9DU

Patient's Trial Number: [xxxx]

[Date]
[address]

Ref: MRECxxxx / V1/12 June 07

Dear Dr [name]

**GENERAL PRACTITIONER NOTIFICATION OF PATIENT IN THE OSCAR TRIAL**

This letter is to notify you that one of your patients has been recruited to the OSCAR Trial (Protocol Summary attached).

The patient concerned is:

[name] Date of birth: [xx/xx/xxxx]

S/he was recruited to the study during their admission to the Intensive Care Unit (ICU) at the [hospital name] hospital in [month/year].

Whilst in the ICU, patients with the condition 'acute respiratory distress syndrome' (ARDS) are generally treated on a conventional artificial ventilator. The trial is comparing the use of a conventional ventilator with the use of a high frequency oscillatory ventilator for the treatment of ARDS. As your patient was diagnosed with the condition ARDS consent was obtained and they were entered into the trial.

We are notifying you of their participation in the research as they have now left the ICU. No action is required on your part.

Follow up of your patient

There are no further tests or hospital visits associated with the trial. We will however be contacting the patient by postal questionnaire at intervals of six months (up to 30 months post trial entry). We have obtained consent to do so. The questionnaire will ask how their breathing affects their day-to-day living, and a more generally about their wellbeing. If you would like a copy of the questionnaire please let us know.

We co-ordinate the UK study at the John Radcliffe Hospital and would be pleased to answer any questions you might have.

Yours sincerely,

Dr J Duncan Young
Chief Investigator OSCAR Trial
Consultant in Adult Intensive Care

Enc: Protocol Summary

## Appendix 11:
## POSTER FOR RELATIVES ROOM IN THE INTENSIVE CARE UNIT

(England/Wales/NI sample)


ISRCTN10416500
REC reference: 07/H0502/98
Version 2 – 3 September 07

OSCAR STUDY

This Intensive Care Unit (ICU) supports medical research to improve patient care and is currently involved in the national OSCAR Study, funded by the Health Technology Assessment Programme (a section of the Department of Health).

If the consultant in charge of the care of your relative, friend or person you are representing thinks that it is appropriate, you may be approached by a member of our ICU team to discuss their possible involvement in the OSCAR study.

It is likely that your relative, friend or person you are representing is not well enough to be able to decide for him/herself whether to participate. If this is the case, we will ask you to give your opinion as to whether you think they would have objected to taking part in this research.

The study has been approved by a Main Research Ethics Committee, and the Research and Development Department of this Trust.

If you would like any more information about the OSCAR study, please speak to a member of the ICU team.

Thank you.

# OSCAR: WHY NOT IN TRIAL LOG

Centre Code:
Centre Name:

IF PATIENT MEETS THE INITIAL INCLUSION CRITERIA OF:

- Age ≥16 years of age
- Weight ≥ 35kg
- Receiving artificial ventilation via an endotracheal or tracheostomy tube
- Have acute hypoxaemic respiratory failure as defined by:l
  - Lowest recorded ($PaO_2/FiO_2$) ratio measured between onset of artificial ventilation and time of screening of ≤26.7kPa with a positive end expiratory pressure (PEEP) ≥ 5cm$H_20$.
  - Bilateral infiltrates on chest radiograph.

BUT IS **NOT** ENTERED (RANDOMISED) INTO THE TRIAL, INDICATE REASON BELOW:

| No. | Today's date | Patient's date of birth | Sex (M/F) | The patient was **not entered** into the OSCAR trial because: (tick column that applies) 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 **more than** 7 consecutive days | E: Consultant predicts patient WILL be extubated by tomorrow evening | F: PERSONAL Consultee refused agreement | G: Nominated PROFESSIONAL Consultee refused agreement | H: Other reason (Write reason below): |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | | |
| 2 | | | | | | | | | | | |
| 3 | | | | | | | | | | | |
| 4 | | | | | | | | | | | |

Brief details of patients considered for the trial but not entered will be recorded on this log at each collaborating unit. Recording this information is to establish an unbiased case selection and full reporting according to the CONSORT statement.

References (Nos. 64/65 in Protocol):


- Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *Jama.* 1996; **276:** 637-9.
- Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Clin Oral Investig.* 2003; **7:** 2-7.