

Randomized Prospective
Multicenter Oscillator ARDS Trial
(MOAT 2)
SensorMedics model 3100B HFOV

October 1997

rev: 2/98

rev: 2/99

rev: 11/99

Sponsor:

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A. 3100B INSTALLATION - Clinical Investigational Plan

1. Personnel and Location

These activities will take place at the SensorMedics approved investigational site. This may occur prior to IDE and IRB approval at the discretion of the site principal investigator and the sponsor.

These activities will be conducted by the SensorMedics field application specialist. Clinicians from the site who will be participating in the investigation will participate along with appropriate biomedical engineering personnel.

2. Objectives

The purpose of this introductory phase is to provide a basic in-service in the proper operation of the 3100B and a complete review of the Clinical Investigational Plan (CIP).

3. Procedure

A complete copy of the Operators Manual and CIP will be given to the site principal investigator prior to the meeting. All those participating in the investigation are required to thoroughly review this material prior to the meeting. The SensorMedics field application specialist will review all aspects of the CIP; highlighting entry criteria, treatment strategies as well as record keeping and monitoring requirements.

The SensorMedics field application specialist will review the correct operation of the 3100B using the operator's manual as a guide. Various aspects of operation will be demonstrated using a standard patient simulator.

B. CLINICAL TRAINING - Clinical Investigational Plan

1. Personnel and Location

These activities will take place primarily at the SensorMedics approved investigational site, though in a few cases may include participation in a SensorMedics sponsored training seminar. This may occur prior to IDE and IRB approval at the discretion of the principal investigator at the site and the sponsor.

Clinicians from the site who will be participating in the investigation will participate with appropriate biomedical engineering personnel.

2. Objectives

The purpose of this training phase is to provide practical experience in the proper operation of the 3100B and related clinical strategies.

3. Procedure

Clinicians and support personnel not already familiar with the 3100 will be required to utilize the 3100 Video In-service program. The program covers operation, maintenance and clinical strategies and includes tests and laboratories.

For those sites without animal laboratories or experience treating ARDS with the 3100, a seminar featuring an animal laboratory will be conducted.

C. CLINICAL TRIAL - Clinical Investigation Plan

1. Personnel and Location

This study is to be performed only at FDA and SensorMedics approved institutions by the authorized investigational team. The team will consist of physicians, respiratory therapists and nurses acting under the direction of the authorized site principal investigator(s).

2. Intended Use

Consistent with the clinical investigational plan, the 3100B is intended for the ventilatory support and treatment of ARDS in adults and large children (16 years or older).

3. Objectives

The objective of this prospective randomized clinical study is to demonstrate the safety and effectiveness of the 3100B for the ventilatory support and treatment of ARDS in adults and large children.

4. Study Design

This is a multicenter prospective, randomized trial. Study entry and exclusionary criteria have been selected which should encourage entry early in the ARDS process, thus insuring a reasonable opportunity for the alternative study therapies to be effective. Exit from the treatment strategies is permitted only after 30 days of treatment, successful weaning from mechanical ventilation, death, or withdrawal of informed consent. . This is a non-crossover study, however patients who are assigned to the experimental therapy (HFOV) and meet specific

treatment failure criteria can be offered the conventional therapy, if in the opinion of their physician, they would benefit from it.

5. Patient Population

- Entry Criteria - Any patient greater than 35 kg and 16 years or older will be eligible if they have ARDS associated with a PaO₂/FiO₂ less than 200 in two consecutive ABG's at least 30 minutes and not more than 4 hours apart. and a PEEP of 10 or greater (see ARDS in 12. Definitions)
- Entry Exclusion - patients otherwise eligible for entry will be excluded if : 1) FiO₂ has been greater than .80 for 48 hours, or 2) grade 3 or 4 airleak, or 3) non pulmonary terminal prognosis, or 4) intractable shock, or 5) severe COPD or asthma, or 6) enrollment in another investigational protocol for ARDS or septic shock within 30 days. (see 12. Definitions)
- Physiological Measurement Requirements - The measurement of gas exchange and cardiac output are required as part of this study. While no measurements are to be made unless clinically appropriate, patients should not be enrolled if these measurements can not be made. An arterial blood gas assessment is necessary prior to study entry to determine eligibility and should be necessary at least every 8 hours during the first 72 hours of treatment. All patients must be monitored with a pulmonary artery catheter at least during the first 48 hours on study. The catheter, while not necessary to determine eligibility, should be in place no later than 2 hours after study entry and remain in place for at least 48 hours.

6. Informed Consent

Informed consent must be obtained prior to entering patients in the study. This procedure is required by federal laws regulating both investigational devices and related clinical studies. Its purpose is to

protect the patient from harm and to insure that the patient or their legal representative understands fully the nature of the potential risks and benefits of participation in the study. It is an aid to help facilitate a voluntary choice regarding participation in the study.

Requirements for the information provided in a consent form are described in detail in 21 CFR, Part 812 (Investigational Device Exemptions). The suggested Consent Form that satisfies all the requirements is included with the other Study Data Forms. No other Consent Form may be used for this study without the prior approval of SensorMedics and the Food and Drug Administration.

After the information in the Consent Form has been explained to the patient's legal representative, it is vital that the authorizing representative, the investigator and a witness all sign the Consent Form.

7. Exit Criteria

Patients will be exited from the study for the following reasons:

1. Withdrawal of informed consent
2. Death
3. Weaned from mechanical ventilation
4. 30 days from entry
5. HFOV treatment failure - physician determination that cv rescue of potential benefit to patient
6. HFOV unanticipated adverse event - physician determination that continued HFOV jeopardized patient
7. Inappropriate enrollment

8. Data Collection

Data will be collected on all patients entered into the study which describes the patient before entry to the study, defines the course of treatment during the study and documents the status of the patient 30 days and 6 months after entry into the study.

The data to be collected on each patient is summarized below, all forms contain the patient ID number, site and responsible investigator. (see Case Report Forms for details)

The study time will begin one hour following randomization for the conventionally treated patients and at the initiation of HFOV for the HFOV treated patients. (see 12. Definitions for clarification) The specific date and time for all data will be recorded.

- Enrollment/Pretreatment - Entry Category (OI < >40), confirmation of no exclusions, randomization number, assigned ventilator, triggering etiology associated with ARDS, hours on CV prior to study, ET Tube length and diameter, air leak score, APACHE 2 score and pretreatment clinical indicators (arterial blood gases, ventilator settings, and cardiovascular measurements) (faxed within 24-48 hours of entry)
- Treatment Data - treatment clinical indicators while on mechanical ventilator (arterial blood gases, ventilator settings, cardiac output, heart rate and blood pressure), plus notation of changed ET Tube and air leak score as well as identification of reaching Treatment Failure benchmarks. Data will be recorded: 1) after entry when the patient is stable or two hours after entry if not stable, 2) subsequently every eight hours for the first three days on the assigned ventilator, 3) following 3 days of treatment, once per day while on mechanical ventilation and additionally 4) ventilator settings and prior gas exchange data will also be recorded for every ventilator change during the first three days (submitted within 45 days of entry)
- Study Exit - reason for exit along with supporting details if exit due to death (submitted within 45 days of entry)
- Outcome 30 days - survival and respiratory status 30 days from entry, (submitted within 45 days of entry)

- Outcome 6 months - survival and respiratory status 6 months from entry, (submitted within 7 months of entry)
- Unanticipated Adverse Events - report of device failures, protocol violations or unanticipated events. (faxed within 24 hours of event)
- Eligibility Log - daily log of all patients in the unit with P/F <200 and if not in study, reason not entered. (reviewed during monthly site visit)

9. Treatment Strategies

The general physiological targets and philosophy for the two ventilator treatment arms is the same. The oxygenation goal is to maintain an O₂ saturation equal to or greater than 88% by normalizing lung volume. The treatment priority is to maintain lung volume and wean FiO₂ to < .60 after which mean airway pressure and FiO₂ are given equal priority for reduction. The respiratory goal is to maintain the pH > 7.15 while minimizing peak pressures and treating metabolic acidosis. There is no PCO₂ target, but a range of 40 - 70 Torr is anticipated. In the case of malignant air leaks lower lung volumes, higher FiO₂'s and lower O₂ saturations are acceptable.

The HFOV treatment strategy is what is referred to as a high volume or open lung strategy. Initial oscillations will be at 5 Hz with the amplitude (ΔP) set for adequate chest wall vibration. Inadequate ventilation will be initially addressed by increasing the ΔP . Once ΔP is maximized, frequency can be reduced in 1 Hz steps. The initial mean airway pressure will be set 5 cmH₂O higher than the previous setting on CV and then adjusted to achieve and maintain optimum inflation. When mean airway pressure is weaned to less than 30 cmH₂O and lung volume normalized or there is no progress in weaning on HFOV, ventilator weaning can be continued on conventional ventilation. Patients assigned to the HFOV must continue in that ventilator

strategy until they exit the study (consent is withdrawn, death or weaned from mechanical ventilation) or have been ventilated on study for 30 days or meet defined treatment failure criteria and would, in the opinion of their physician, benefit from the conventional ventilation strategy .

The conventional ventilation strategy will be what is commonly referred to as a pressure limited, volume maintenance strategy with permissive hypercapnia. Tidal volumes of 6-10 ml/kg will be used. PEEP will be increased in increments of up to 5 cmH₂O to improve oxygenation. If oxygenation is inadequate with a PEEP of 18 cmH₂O or greater, %IT may also be increased incrementally from an initial setting of approximately 33%. Patients assigned to conventional ventilation must continue in that ventilator strategy until they exit the study (consent is withdrawn, death or weaned from mechanical ventilation) or have been ventilated on study for 30 days. Conventional ventilators are limited to Siemens 300, Siemens 900c and PB 7200.

10. Statistical Considerations

- Randomization Procedure - Within each institution, randomization will be accomplished using a sequentially numbered randomization scheme provided by the sponsor. It will be of a balanced block design such that, at each institution, a difference of no more than two can occur in the number of patients with an oxygenation index suggesting poor prognosis (OI>40) assigned to each device.
- Descriptive Statistics - Descriptive characteristics of the patients assigned to the two treatment ventilators will be tabulated. Differences in pretreatment demographics (gender, weight, age), air leak score, APACHE2 score and clinical indicators (blood gases, ventilator settings, and blood pressure) will be evaluated using chi square and t tests as appropriate. In addition to evaluation with chi square and t tests as appropriate, differences in outcomes such as treatment failure criteria , and endotracheal care which relate to potential clinical risk will

be further evaluated by constructing 95% confidence limits. Differences in the primary outcome, survival without chronic lung disease, will be evaluated using the chi square test based on intention to treat.

Differences in gas exchange, cardiac output and blood pressure over the first 3 days of treatment will be evaluated utilizing repeated measures analysis of variance. Important nonparametric time related events such as survival and length of respiratory support will be analyzed using the Kaplan-Meier survival model.

To explore possible limits of effectiveness of the ventilatory capability of HFOV, two approaches will be used. First scatter plots of the HFOV controls that most effects ventilation (power amplitude control and frequency), and PCO₂ and pH will be evaluated. Second, the difference in frequency of treatment failure 2 (intractable respiratory acidosis) between HFOV and the conventional ventilator group will also be an indication of relative ventilatory effectiveness.

- Hypotheses

Rationale - These hypotheses were selected based on the clinical experience of the principal investigators with regard to both the treatment population, as well as their own experience using the the 3100 HFOV. To validate the statistical practicality of the primary hypothesis for sample size calculations we utilized the outcomes from a similarly designed study of HFOV in children. (Prospective, randomized comparison of HFO and conventional ventilation in pediatric respiratory failure. Arnold JH et al. Critical Care Medicine 1994, 22:1530-1539)

Primary null hypothesis

The primary outcome measure of this study is survival without chronic lung disease. Chronic lung disease is defined as requiring

respiratory support (O₂ , CPAP or mechanical ventilation) 30 days after entry in the study.

The null hypothesis is that the patients assigned to conventional ventilation will have a success rate equal to or greater than the success rate of those assigned to the experimental treatment with the 3100B HFOV, plus 0.1.

The two ventilator treatment interventions begin soon after the diagnosis of ARDS and are based on a common goal of normalizing lung volume and minimizing peak ventilator pressures. The experimental HFOV treatment strategy is being compared to a defined conventional ventilation strategy. Both treatments continue until ventilator weaning, or death or the 30 day end point is reached, though some HFOV patients may be offered rescue CV therapy if treatment failure criteria are met.

Analysis: This hypothesis will be tested using chi square (single tailed, alpha <.05 for statistical significance), based on the intention to treat (assigned ventilator).

Adverse effects hypothesis

This null hypothesis is that there will be no significant difference in the incidence of development of air leak or treatment failure from intractable hypotension or death between the patients assigned to treatment with HFOV and those assigned to conventional ventilation.

Analysis: In addition to testing this hypothesis using chi square (two tailed, alpha <.05 for statistical significance), the relative risk of these adverse effects will be explored by construction of 95% confidence limits of the odds ratio. These tests will be based on the intention to treat (assigned ventilator).

• Patient Sample Requirements - Outcome data from the randomized pediatric trial is shown in the table below, specifically: survival without chronic lung disease (nCLD), death, develop air leak(AL) and treatment failure from intractable hypotension (IH).

	<u>Survival noCLD</u>	<u>DIED</u>	<u>AL</u>	<u>IH</u>
CV	25%	41%	32%	3%
HFOV	52%	34%	25%	10%

If this study experiences the difference seen in the pediatric study in nCLD (25% vs 52%), only 21 patients would be needed in each treatment group to disprove the null hypothesis and conclude that CV success rate is not at least .1 better than HFOV (i.e., HFOV > .15 and CV =.25, p=.05, power =.80, single tail assumption). However, if we assume that the difference in nCLD experienced in our trial is half that seen in the pediatric trial (CV=31.5%, HFOV=45%) 54 patients would be needed in each treatment arm to disprove the null hypothesis.

Assuming the CV incidence rates of the three adverse outcomes from the pediatric trial (shown in the table above) we calculated the smallest difference that could be detected with the two alternative sample sizes (alpha< 0.05, power =.80, two tailed assumption). Those differences are shown below.

Smallest Difference Detectable

	<u>21/21</u>	<u>54/54</u>
Death	-36% +41%	-25% +27%
AL	-32% +42%	-22% +27%
IH	na +34%	na +17%

We request that the study be approved for 148 patients. The larger sample size will further reduce the uncertainty associated with differences in adverse effects and insure there is sufficient opportunity to evaluate the primary hypothesis, if the differences seem in this

study are less than those projected from the pediatric study (i.e., 60% success with HFOV and 50% with CV).

11. Risk Analysis

- Possible Risks - Several potential theoretical risks of HFV therapy have been identified. The first is overdistention of the pulmonary system or gas trapping which could lead to barotrauma or cardiovascular compromise. The second is packing of mucus in the airways leading to ineffective ventilation or blocked endotracheal tube. The third is necrotizing tracheobronchitis (NTB). The final is over or under ventilation or oxygenation associated with improper setting or weaning of ventilator controls or a limit of effectiveness.

- Minimization of Risks - Measures have been taken in the design of the 3100 HFOV and in this study to minimize these potential risks. These device safety features are standard on all 3100 HFOV models. In addition, the patient monitoring requirements in this study are consistent with those used in routine patient care as well as in other HFOV studies.

- The 3100 has several features which reduce the likelihood of inadvertent pulmonary overdistention or gas trapping. Pressures in the patient circuit are continuously monitored and displayed, and several key parameters are tied to automatic safety features and alarms. Besides an automatic dump valve which actuates at high mean airway pressure, the operator sets a mechanical mean airway pressure limit slightly above the set therapeutic level. In addition, attempts to set inappropriately large oscillatory pressures (compared to the mean airway pressure) which might cause gas trapping, are overridden. Patient oxygenation (pulse oximeter), blood pressure and quite often direct cardiovascular status (pulmonary artery catheter) will be monitored to provide appropriate clinical indicators of cardiovascular compromise or air leak. Periodic chest radiographs, as clinically indicated, will also identify

proper lung inflation. Interestingly several trials of the 3100 have identified a trend toward reduced barotrauma. As in other studies the incidence of new air leaks and degree of chronic lung disease, as well as ventilator associated cardiovascular compromise (intractable hypertension) will be recorded to further study this risk.

- Mucus plugging has been associated with inadequate humidification in high frequency and conventional ventilation. The rain out in the conventional bias flow circuit used in all models of the 3100 provided visual indication of adequate humidification. Significant differences in the incidence of plugged endotracheal tubes and frequency of suctioning have not occurred in previous controlled HFOV trials. Compromised ventilation or oxygenation associated with mucus plugging will be identified via compromised gas exchange measurements. The incidence of plugged endotracheal tubes and frequency of suctioning will be recorded to further study this risk.

- An increased risk of necrotizing tracheobronchitis (NTB) has also been associated with inadequate humidification and high peak airway pressures in some modes of high frequency ventilation. As indicated above adequate humidification can be readily monitored with the 3100. Peak tracheal pressure during HFOV are substantially lower than conventional ventilation, unlike with jet ventilation. NTB has never been reported in any of the controlled HFOV trials. All clinically significant cases of tracheal damage associated with ventilation, including NTB, will be reported to further study this risk.

- The risk of over and under ventilation associated with HFOV operation will be minimized several ways. All clinicians will receive a level of training which has been found to be satisfactory for neonatal and pediatric applications. Of course, monitoring of gas exchange using continuous pulse oximetry and periodic arterial blood gases is required, as are clinically indicated chest radiographs. In pediatric and neonatal populations, effective

ventilation and oxygenation have not been a problem. However, in the pilot ARDS study ineffective ventilation was a common mode of HFOV treatment failure. Because of some concern about a possible limit of effectiveness, three actions have been taken. First the treatment strategy for HFOV has been modified to be more aggressive in adjusting the oscillatory pressure, the primary parameter effecting CO₂ removal. Second, many of the patients who failed HFOV treatment in the pilot study were believed to have had irreversible lung damage, so the entry requirements have been set to limit inclusion of these patients. Finally the 3100 model to be used in this study has more ventilatory capability, which ought to provide a wider range of effectiveness. Gas exchange will be recorded in this study so that any limits of HFOV effectiveness can be identified.

- Possible Benefits - The sponsor of this study believes that HFOV can benefit patients with ARDS, by improving oxygenation and reducing acute barotrauma. They hope that this study will demonstrate an improved outcome associated with HFOV treatment. It is further anticipated that this study will provide insight into which factors (i.e., severity at intervention, length of conventional ventilation, ARDS triggers) are associated with more effective treatment.

12. Definitions

- ARDS - Acute respiratory distress syndrome is a process of non hydrostatic pulmonary edema and hypoxemia with acute onset which results in high morbidity and mortality. It is associated most often with sepsis syndrome, aspiration, primary pneumonia or multiple trauma. Much less common associations include cardiopulmonary bypass, multiple transfusions, fat embolism, pancreatitis and others.

Defined as PaO₂/FiO₂ < 200 (regardless of PEEP), and radiographic evidence of bilateral infiltrates, with pulmonary artery wedge

pressure of <18 mmHg or no clinical evidence of left atrial hypertension (The American-European Consensus Conference on ARDS. Am J Crit Care Med vol 149 pp 818-824, 1994)

- Cardiac Output - measurements are to be made using a pulmonary artery catheter and commercial injector and computer. Care is to be taken to minimize artifact from respiratory cycles during conventional ventilation by averaging three different measurements spaced throughout the respiratory cycle. One thermodilution injection should be made at the beginning of inspiration, one injection at one third of the respiratory cycle after the beginning of inspiration, and one injection at two thirds of the respiratory cycle after the beginning of inspiration.

- GROSS AIR LEAK SCORE -

Grade 0: no air leak

Grade 1: isolated pneumomediastinum without tension

Grade 2: uni or bilateral pneumothorax requiring only a single chest tube per hemithorax, without recurrence

Grade 3: recurrence of pneumothorax requiring additional chest tubes or replacement/repositioning of existing chest tubes (< 5 occurrences), or air leak continuing for 72-120 hours

Grade 4: unstable air leak with multiple recurrences (>4), or air leak requiring more than 2 chest tubes per hemithorax, or air leak continuing longer than 120 hours, or pneumopericardium/peritoneum (due to pulmonary air leak)

- INTRACTABLE SHOCK or HYPOTENSION - Entry Exclusion and Treatment Failure Criteria defined to occur when, despite maximum support, the mean arterial pressure is < 60 Torr for 4 hours or < 50 Torr for 1 hour. Generally maximum support would include adequate ventricular preload (pulmonary wedge pressure > 16 Torr after correction for PEEP) and aggressive inotropic support (ie. up to

15 micrograms/kg/min of dopamine or 4 micrograms/kg/min of levophed or equivalent)

- NONPULMONARY TERMINAL PROGNOSIS - Severe chronic systemic disease or other condition with anticipated survival less than 6 months (e.g., irreversible central nervous system disease, rapid fatal malignancy, AIDS, chronic left ventricular failure, chronic organ failure)
- RESPIRATORY SUPPORT REQUIRED - is deemed necessary if any of the three conditions below are met. These criteria are used to determine the respiratory status of the surviving patients at 30 days and 6 months following treatment.
 - OXYGEN REQUIRED - defined as requiring supplemental O₂ administration to maintain an oxygen saturation of at least 90% awake without CPAP. The need for supplemental O₂ may be tested by gradually reducing FiO₂ until O₂ saturation drops to less than 90% or a FiO₂ of .209 is reached.
 - CPAP REQUIRED - defined as CPAP required to maintain an oxygen saturation of 90% or greater, awake breathing room air. This may be tested by eliminating CPAP for one hour or until the O₂ saturation drops to less than 90%.
 - MECHANICAL VENTILATION REQUIRED - Ventilatory support is defined as being required if necessary to maintain a PaCO₂ of ≤ 50 Torr during spontaneous breathing with metabolic acidosis treated (HCO₃[>] 19 meq/L). This may be tested by lowering the ventilator rate until the PaCO₂ increases to above 50 or assumed if the minute volume is greater than 10 L/m and PaCO₂ greater than 40 Torr with of tidal volume at least 8 ml/Kg.
- SEPSIS - Positive blood culture for bacterial or fungal microorganism, or positive latex test, or other equivalent test.

- **STUDY ENTRY TIME** - The separation of the time of randomization and time of study entry occur to partially compensated for the inevitable delay associated with transition of HFOV randomized patients from CV to HFOV. The intent is as follows. Patients randomized to CV treatment will have a study entry time one hour after randomization. The study entry time for HFOV randomized patients will be when they are placed on HFOV. (This needs to be within 2 hours of randomization, failure to do so would constitute a protocol violation. Such a protocol violation should be reported on the “Unanticipated Adverse Events/Deviations” form). Once on study, the initial treatment clinical indicator data is to be recorded when the patient is stable or at two hours after entry, even if the patient is not stable.

- **TREATMENT FAILURE** - is defined as meeting any of the following criteria in concert with compliance with the ventilator strategy and indicated cardiovascular support.
 1. Intractable Hypotension despite maximum support (see above)
 - a. MAP <60 for 4 hours or
 - b. MAP <50 for 1 hours

 2. Intractable Respiratory Acidosis
(pH <7.15 and HCO₃ >19 meq/l for 6 hours)

 3. Oxygenation Failure
after 48 hours of treatment, 2 consecutive readings (at least 30 minutes and not more than 2 hours apart) equal to or worse than those in the following table:

Failing PaO₂ at different mPaw and FiO₂

mPaw 20 25 30 35 40

FiO2

0.60	28	35	42	49	56
0.65	30	38	45	53	60
0.70	33	41	49	57	65
0.75	35	44	52	61	70
0.80	37	47	56	65	74
0.85	40	49	59	69	79
0.90	42	52	63	73	84
0.95	44	55	66	77	88
1.00	47	58	70	81	93

Intentionally blank

Consent Form - Clinical Investigation of High Frequency Oscillatory Ventilation for the Treatment of Acute Respiratory Distress Syndrome

1. I (or my legal representative) hereby give permission for me to participate as a test subject in this research study. The purpose of the study is to determine if the use of a new type of ventilator (breathing machine) called a high frequency oscillatory ventilator (HFOV), is safe and effective for the treatment of acute respiratory distress syndrome (ARDS) a serious lung disease that makes it difficult for me to breathe normally. The HFOV will breathe for me at a much faster rate than a standard ventilator. It may produce more normal gas exchange than a standard ventilator and may speed my recovery. Up to 8 centers across the country will ultimately be participating in this study, which will last approximately 18 months. Up to 105 patients will be treated as part of this study, approximately half with HFOV.
2. I (or my legal representative) understand that I require the use of a ventilator to treat my lung disease. I am currently being ventilated using a standard ventilator and based on a random assignment will either be left on this ventilator or placed on the high frequency oscillatory ventilator (HFOV). Treatment on both ventilators will be according to a prewritten protocol or procedure. If my condition markedly improves while on HFOV, I will be returned to standard ventilation as part of my recovery process. If my condition deteriorates on HFOV I will also be returned to standard ventilation.
3. The intended benefit of this study protocol is to improve the ventilatory management of patients with acute respiratory distress syndrome. However, I (or my legal representative) understand that this use of HFOV is experimental. It has not been shown whether HFOV is more or less effective, or if it is more or less safe, for patients with this condition. I also understand that ventilation (breathing) by this technique could potentially improve, worsen, or not change my condition. No guarantees have been made to me regarding the safety or effectiveness of this ventilation technique with regards to this lung condition.
4. I (or my legal representative) understand that the risks of HFOV for the treatment of acute respiratory distress syndrome are not entirely known. However these risks include: 1) over inflation of the lungs that could result in air leaks in or around the lungs, or compromised pumping capacity of the heart, 2) packing of mucous in or damage to the upper airways from the oscillatory pressures, and 3) under inflation of the lungs resulting in abnormally low blood gas readings.
5. I (or my legal representative) understand that I should experience no discomfort from the use of HFOV. It is understood that I may receive no benefit from the technique and that, if I decline to participate in the study, I will receive all currently acceptable and available alternative forms of treatment for my problem including, but not limited to, standard ventilation therapy. It is also understood that I require other standard intensive care procedures because of the serious nature of my illness and that these treatments will be given regardless of whether or not I participate in the study.
6. I (or my legal representative) understand that records of my participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 USC 552a, and its implementing regulations. The records may be reviewed by the sponsor and

appropriate government agencies, including the U.S. Food and Drug Administration when authorized by law.

7. I (or my legal representative) understand that no compensation will be provided for participation in this study. If the research procedure results in injury or death, and the injury or death is not a result of negligence, no monetary compensation will be provided, although immediate essential medical care as determined by the hospital will be supplied.

8. It is understood that any clinical or medical misadventure will immediately be brought to the attention of me or my legal representative.

9. The decision to participate in this study is completely voluntary on my part (or on the part of my representative). No one has coerced or intimidated me into participating in this program. I am participating because I want to.

10. Dr. _____ has adequately answered all questions that I (or my legal representative) have about this study, my participation, and procedures involved. It is understood that Dr. _____ will be available to answer any questions about the procedure throughout the study. It is understood that if significant new findings develop during the course of the study, I or my legal representative will be informed.

It is further understood that I or my legal representative may withdraw this consent at any time and discontinue further participation in this study without prejudice to entitlements or care. Should I (or my legal representative) choose to withdraw, my medical condition will continue to be treated in accordance with accepted standards of medical treatment. I also understand that the investigator of this study will be monitoring care during the course of the study and may terminate participation in the study at any time if he believes it is in my best interests.

patient name _____

patient address _____

signature of patient or legal representative (date)

signature of advising physician (date)
advising physician telephone # _____

signature of witness to both signatures above (date)

H. E. Record Keeping Requirements

Two tables follow which delineate the record keeping and notification requirements of this study according to 21 CFI, Part 812 federal regulations associated with investigational devices.

The Case Report Forms designed for data collection in the study also follow.

F. INVESTIGATIONAL SITES -

Study Principal Investigators

Stephen Derdak D.O.
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Associate Director
Multidisciplinary ICU
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Additional Sites

Additional sites will be recruited consistent with the number approved as part of this IDE.

SensorMedics Critical Care will maintain a file, available to the FDA, including the following site specific information:

1. Name and address of site and Principal Investigator
2. Name and address of the chairperson of the IRB
3. Copy of the IRB approval letter
4. Copy of the signed Investigator's Agreement
5. Copy of the CV of each Investigator

The clinical trial will not be permitted to begin at any site or Investigator changed until the all the items above are in SensorMedics possession.

MULTICENTER HFOV ARDS TRIAL INVESTIGATORS AGREEMENT

This is to certify that I have read the sections of the Medical Device Procedures for Investigational Device Exemptions, 21CFR Part 812, concerning Responsibilities of Investigators (Sub-part E) and Records and Reports (Sub-part G). I have also read and reviewed with the sponsor the Clinical Investigational Plan and the Report of Prior Investigations. I concur with the Risk/ Benefit Analysis and the justification of this study.

As an investigator, I agree to the following conditions with regard to the clinical investigation.

1. Conduct the investigation in accordance with this agreement and the approved Clinical Investigational Plan. If I feel, in my medical judgment, that reasonable alternatives and deviations from the protocol are required, I will document these alternatives and the reason(s) required on the Unanticipated Adverse Events Form. I will report the protocol deviation to SensorMedics Critical Care within 24 hours and to my Institutional Review Board (IRB) within 5 days of its occurrence.
2. In the event that the investigational device produces an adverse patient reaction which is not anticipated in the Risk Analysis, I will document the effect and the corrective action on the Unanticipated Adverse Events Form. I will report the protocol deviation to SensorMedics Critical Care within 24 hours and to my IRB within 10 days of its occurrence.
3. Conduct the investigation in accordance with 21CFR, Part 812 - Medical Devices - Medical Device Procedures for Investigational Device Exemptions, as issued (and as revised) by the Food and Drug Administration (FDA), Department of Health and Human Services.
4. Conduct the investigation in accordance with other applicable FDA/DHRS regulations, and conditions of approval imposed by the reviewing IRB and FDA.
5. Upon the request of a SensorMedics Critical Care Clinical Monitor, or the FDA, with reasonable notice, I will make records required by Part 812 available for inspection and copying. Progress reports and a final report of the investigation will be furnished to SensorMedics Critical Care according to the approved schedule.
6. It is understood that I retain the right of publication of the clinical work I perform, though I am encouraged to cooperate jointly in publications with other investigators on this subject in order that the data and results may be as complete as possible. I agree that SensorMedics Critical Care has the right of review and comment on any proposed publications, and that I will not submit any articles for publication on this investigation prior to my completion of the Clinical Investigational Plan.
7. I certify that I will obtain Informed Consent from any and all patients used in this investigation according to the Informed Consent Form included in the Clinical Investigational Plan. Upon request each signed Informed Consent Form will be made available to a SensorMedics Critical Care or FDA representative. I understand that the only exceptions to obtaining informed patient consent prior to use of the investigational device on the patient are those listed in Part 812.123 of the Investigational Device Exemptions regulations.
8. SensorMedics Critical Care is responsible for presenting documentation that may be required to the FDA at appropriate intervals.
9. SensorMedics Critical Care retains the right to suspend or terminate this investigation at any time.
10. This investigation may be extended by SensorMedics Critical Care upon establishing clinical need or in order to comply with federal law.
11. I certify that the device(s) will be used only on subjects under my personal supervision or under the supervision of investigators (listed below) responsible to me, and that the device(s) received by me for this investigation will not be supplied to any other investigators or to any institution for use on humans or for other study.
12. It is understood that knowledge of product development and marketing introduction is commercially valuable information and considered confidential in nature. I therefore agree not to disclose to any persons other than those involved in this study the details of the undertaking of the study or its parts. I further agree not to disclose any other proprietary development, materials, or other information that SensorMedics Critical Care made known to me by virtue of my participation in this study, provided that SensorMedics Critical Care identifies that information which it considers proprietary and confidential.

13. I agree to assign to SensorMedics Critical Care all patent rights to inventions resulting from work on this study.

I have attached my curriculum vita, including the extent and type of my relevant experience with pertinent dates and locations. If I have been involved in any investigation that was terminated for noncompliance at the insistence of the sponsor, IRB, or FDA, an explanation of the circumstances follow.

I understand that this agreement entails my cooperation with authorized FDA employees and monitors appointed by the SensorMedics Critical Care in any inspections or investigations conducted in a reasonable manner and at reasonable times.

_____ Principal Investigator	_____ title	_____ date
_____ Additional Investigator	_____ title	_____ date
_____ Additional Investigator	_____ title	_____ date
_____ Additional Investigator	_____ title	_____ date
_____ Additional Investigator	_____ title	_____ date
_____ Additional Investigator	_____ title	_____ date

notes: - The CV of each Investigator must be submitted

- Each investigator added at a later date must sign a separate Investigator Agreement.

G. CLINICAL MONITORING PROCEDURE - Clinical Investigational Plan

SensorMedics Critical Care Corporation, as sponsor of this clinical investigation, is required by 21 CFR, Part 812, of the Food and Drug Administration regulations to monitor and oversee the progress of the investigation. The individuals assigned by SensorMedics Critical Care to this task may be a direct employee or consultant.

Clinical Monitor

Initially, Thomas E. Bachman (P.O. Box 2 Crest Park CA 92326, 909 337-0828), a long term clinical consultant to SensorMedics, has been designated to be the Clinical Monitor of this study.

Specific responsibilities of the Clinical Monitor include:

1. IRB Approval - Confirmation that the IRB approval letter and signed Investigators agreements are on file in the Regulatory Affairs office of SensorMedics, before commencement of human studies.
2. Site Visits - During the course of the human studies phase of this investigation the Clinical Monitor will supervise regular site visits. The site visits will be conducted by a SensorMedics Critical Care Field Applications Specialists, or if unavailable the Clinical Monitor. In either case the site visit will be highly structured and result in a written report to be filed within 48 hours of the visit. The first site visit will be conducted prior to entering any patients into the study, to confirm readiness for same. Readiness assessment will include not only clinical training, but also a understanding of the clinical protocol and record keeping requirements. The second visit will occur during treatment of the first patient with HFOV and will be long enough to ensure proper implementation of the clinical protocol and associated record keeping across multiple shifts (minimum of 24 hours to 72 hours). Subsequent visits will be made every 4-6 weeks. Each visit will address the following: 1) short case summary of all patients entered since the last visit (confirmation of adherence to treatment strategy and protocol and identification of adverse effects), 2) review of Eligibility Log (confirmation of proper randomization and sufficient patient enrollment), 3) status of transfer of study data to the sponsor, 4) clarification of previously submitted data, and if necessary, 5) discussion of any anticipated or unanticipated adverse effects experience at any of the sites. The visit will be a formal meeting and be conducted at the site in an office or conference room with attendance of at least one of the investigators and as many involved clinicians as deemed necessary by the investigator.

3. Study Data Review - Upon receipt of the FAXed Enrollment Form the enrollment will be recorded in a study enrollment database. Within 7 days of receipt of the complete data for each patient (excluding 6 month follow-up), the Clinical Monitor will review it for completeness, and confirmation of adherence to protocol. Individual Site Status Reports will be prepared before each site visit and sent to the site and site monitor. However, any clinical or procedural problems noted upon review of the data which require immediate attention (prior to the next site visit) will trigger a telephone call to the investigator.
4. Safety Vigilance - All occurrences of unanticipated adverse effects or device failures will be reported to the Clinical Monitor within 24 hours of the event via FAX. These will be shared with the Sponsor and the two Study Principal Investigators for recommendation as to disposition within 48 hours.

Safety Monitoring Committee

An independent Safety Monitoring Committee comprised of two physicians not involved in the study and a biostatistician will be formed.* A Study Meeting including the Principle Investigators, sponsor, Clinical Monitor and Safety Monitoring Committee will be convened by the Clinical Monitor every 12 months (or when 50 and 100 patients have completed treatment, if sooner). The biostatistician on the Safety Committee will monitor the data and also convene a meeting if any of the four outcome measures reach significance (these interim statistical significance tests will be determined according to alpha spending function approach of DeMets {Statistics in medicine, Volume 13; 1341-1352, 1994})

All Safety Committee meetings will be comprised of two sessions. In the first session individual deviations from protocol, individual unanticipated adverse effects and data summarizing pretreatment demographics, pretreatment clinical indicators, as well as the four outcomes (mortality, new air leak, intractable hypotension and survival without chronic lung disease [nCLD]) will be presented, all blinded as to assigned ventilator.

Following appropriate discussion in the first session, the second session will be convened. The second session will include only the Safety Monitoring Committee which will review the unblinded results and consider the following: 1) whether the protocol violations compromise the scientific validity of the potential results and 2) whether the mortality, air leak, intractable

hypotension and nCLD data suggest undo patient risk associated with continuation of the study, and 3) based on the projected trends in the data, whether continuation of the study is unlikely to yield statistically significant results. Decisions regarding the potential effect of protocol violations on the validity of the study will have to be subjective, based on the experience of the committee members. In contrast, trends in outcome variables will only be considered important if they reach statistical significance (these interim statistical significance tests will be determined according to alpha spending function approach of DeMets {Statistics in medicine, Volume 13; 1341-1352, 1994}). However statistical significance alone would be insufficient information to stop the trial. Rather the Committee should only then consider other factors (e.g., uncertainty in the comparability of the treatment groups, inconsistencies between sites, potential effect on credibility/acceptability of the limited results). Finally the projection of results to determine if there is a reasonable likelihood of reaching statistically significant results.

The statistical tests to evaluate these outcomes will be as outlined in the hypotheses section of the Statistical Considerations section of the protocol. The threshold for determining whether continuation of the study is futile will be a probability of .1 or less that statistical significance will be reached if the current frequency is projected to 148 patients. (ref. Lan K, Wittes J, The beta-value: a tool for monitoring data, Biometrics 1988, 44:579-585). The significance level for interim tests will be determined according to alpha spending function approach of DeMets, Statistics in Medicine, Volume 13; 1341-1352, 1994.

Three actions are in place to avoid potential problems of interim analysis. First, for the interim analyses the significance level is being adjusted according to the method of DeMets to control for the potential of errors associated with multiple analyses. Second each of the four blinded outcomes will be individually scrambled, to minimize the chance of inference of ventilator in the first session. Finally the unblinded results will only be reviewed by the independent Safety Committee.

* The Biostatistician will be James Ashurst Ph.D., Research Support Services, Irvine, CA 92714-500. The two physicians will be selected after the trial is underway, approximately 3-6 months before the first meeting.

APPENDIX

Multicenter HFOV for ARDS Trial (MOAT2) 2/6/98

24 hr clinical support: Terry Blansfield
(beeper 800 759-7243 1268365)

Inclusions:

- Age \geq 16 years **and**
- Weight \geq 35 kg **and**
- P/F ration $<$ 200 (with PEEP \geq 10 cm H₂O)
on two consecutive ABG's $>$ 30 min. apart but $<$ 4 hrs apart **with**
- bilateral infiltrates **and**
- PA wedge $<$ 18 mmHg **or**
- no evidence of LA hypertension **and**
- ability to gain Informed Consent (surrogate)

Exclusions:

- FiO₂ $>$ 80% for 24 hrs **or**
- Air Leak grade 3 or 4 (see below) **or**
- Non-pulmonary terminal prognosis **or**
- Intractable shock (see below) **or**
- other experimental tx for ARDS or Sepsis \leq 30 days

HFOV Strategy:

- initial: - meanPaw set 5 cmH₂O $>$ CV setting
- set rate 5 Hz, 33% I-time
- set Δ P for adequate chest wiggle
- if SO₂ $<$ 88% : - increase mean Paw (3-5 cm H₂O incr.) (max 45 cmH₂O)
- if high pCO₂ (pH $<$ 7.15) : - increase Δ P (5- 10 cm H₂O incr.) **then**
- decrease rate (1 Hz incr., to 3 Hz) **then**
- induce ETT cuff leak (maintain mean Paw)
- wean: - FiO₂ to 40%- 50%, if SO₂ $>$ 90% **then**
- mean Paw to 20 (decr. 3 cm H₂O Q 4-6 hrs) **then**
- switch to PCV (TV 6-10 ml/kg, 1:1 with PEEP 10), adjust for meanPaw same as HFOV, then wean as below

CMV Strategy:

- initial: - PCV with TV of 6-10 ml/kg
- set PEEP \geq 10 cm
- set I:E= 1:2
- if SO₂ $<$ 88% : - increase PEEP to 15-18 cm (5 cm increments) **then**
- increase I-time (0.5sec. increments) to max 2:1
- if high pCO₂ (pH $>$ 7.15) : - increase rate or TV (max 10 ml/kg)
- wean: FiO₂ to 40%-50%, **then**
I:E to 1:2 (0.5 sec. ecrements), **then**
PEEP 5 (5 cm decrements) **then**
spontaneous breathing trials

Method:

- contact _____
- randomize: must commit to random assignment to HFOV or CMV
- if HFOV, begin $<$ 2 hrs - if CMV, change strategy $<$ 1 hr
- compute P/F and APACHE 2
- suggest: ABG at 30 min, 2 hrs, **then**
every 8 hrs for 72 hrs, then every 24 while on MV
- suggest: chest Xray (with air leak score) every 24 hrs
- APACHE 2 score every 24 hrs (use study computer or other system)

Helpful HFOV Hints:

- keep ambu bag with PEEP valve and O₂ hooked up at the head of bed
- insert in-line O₂ analyzer in the bias flow gas, before HFOV calibration. Use the analyzer to fine tune blender for FiO₂
- HFOV circuit must smoothly interface with the ET tube
- avoid kinks in the ET tube and HFOV circuit
- do not place right angle ET tube adaptors in circuit until confirmed satisfactory PCO₂
- if obvious secretions in ET tube, briefly interrupt HFOV to allow suctioning with ambu bagging (new in-line suctioning may preclude this in the future)

Definitions:

- Gross Air Leak Score:
 - grade 0: no air leak
 - grade 1: isolated pneumomediastinum, without tension
 - grade 2: pneumothorax requiring one chest tube per hemithorax, without recurrence
 - grade 3: recurrent pneumothorax requiring additional tubes or replacement/repositioning of existing tubes ($<$ 5 occurrences) or continuing air leak for 72-120 hrs
 - grade 4: unstable air leak with multiple recurrences (.4), or air leak requiring $>$ 2 tubes per hemithorax, or air leak continuing $>$ 120 hrs or pneumopericardium/peritoneum (due to gross air leak)
- P/F ratio = (PaO₂) / (FiO₂)
- Oxygenation Index: OI = (mean Paw * FiO₂ * 100) / PaO₂
- Intractable hypotension (shock)
 - MAP $<$ 60 for 4 hours **or**
 - MAP $<$ 50 for 1 hour (average) **and**
 - PAwedge $>$ 16 (PEEP corrected) **and**
 - aggressive vasopressor support

G. Study Background and Rationale

Respiratory failure in patients admitted to the intensive care unit is triggered by a number of different clinical problems (e.g., pulmonary infection, aspiration, inhalation, trauma, sepsis). While the pathophysiologic mechanisms for each are quite different, acute lung injury mediated by oxygen toxicity, infection, biochemically active mediators and volutrauma can lead to the development of acute respiratory distress syndrome (ARDS). (1) The pathologic evolution of ARDS is marked by the development of increased permeability of the alveolar-capillary membrane that results in pulmonary edema. The clinical appearance is that of increasing respiratory distress, increasing hypoxia, decreased lung compliance and a chest radiograph that demonstrates diffuse pulmonary infiltrates. The mortality and morbidity of patients who develop ARDS is extremely high. (1) The likely mortality of patients meeting entry criteria for this study will likely range between 40-80%, depending on the specific underlying etiology and severity at entry.

The precise mediators of acute lung injury that produce ARDS are not known. Two important factors are oxygen toxicity and volutrauma. Limiting the patient's exposure to oxygen and large tidal volumes may reduce the severity of the disease progression. (2)

Hyperoxia produces lung injury by promoting the development of oxygen free radicals. (3) Oxygen radicals cause lipid peroxidation with cell membrane disruption, inactivation of enzyme systems, damage to deoxyribonucleic acid, and degradation of structural proteins. Injury to the pulmonary endothelial and parenchyma cells produces pulmonary capillary leak of proteins and fluid with surfactant dysfunction. This results in pulmonary edema, alveolar atelectasis, and leukocyte infiltration. (4, 5) Ventilation-perfusion mismatch is also severe, reducing delivery of oxygenated blood to the arterial circuit. As lung damage progresses, higher levels of inspired oxygen become necessary to prevent

hypoxemia. This cycle of oxygen toxicity potentiated lung injury must be interrupted if irreversible lung injury is to be avoided.

Lung injury caused by volutrauma is also an important mediator in the evolution of ARDS. Animal studies clearly demonstrate that it is not the amount of pressure applied to the lung, but the degree of lung hyperinflation, that produces lung injury. (6) Animals exposed to large tidal volume mechanical ventilation develop pulmonary edema. When animals are exposed to the same pressures but the tidal volume delivered is limited by chest casting, lung injury is avoided. Airleak syndromes (pneumothorax, pneumopericardium, pneumoperitoneum, and pneumomediastinum) are another manifestation of lung overdistention and occur in patients requiring assisted ventilation.

HFOV, with the SensorMedics 3100, has been proven effective as a primary mode of ventilation for neonates with respiratory failure. (7, 8) It has also been shown to improve gas exchange in infants with severe respiratory failure, who have not responded to conventional mandatory ventilation with positive end-expiratory pressure (CMV-PEEP) (9 - 12). In 1994 a multi-center randomized controlled trial of the use of the SensorMedics 3100 HFOV in a lower weight (<35 kg) pediatric population with ARDS reported statistically significant improvements in gas exchange and improved long term pulmonary morbidity and mortality. (13) Several multicenter prospective trials are underway to determine the effectiveness of HFOV as the primary mode of ventilation for patients with ARDS. In a 1997 report, a prospective rescue trial demonstrated the ability of HFOV to rescue patients failing inverse ratio conventional ventilation. (14) Anecdotal rescue experience in more than 50 large patients managed with the 3100 HFOV also support the of management of adult patients and large children with HFOV. (15)

Optimal effectiveness of therapies is tied to patient selection, timing of intervention and timing of alternative, likely more invasive/expensive, interventions. In infants and children long term pulmonary morbidity has been

shown to be associated with extended conventional mechanical ventilation. (8, 13). Several studies of large children and adults with ARDS have shown that mortality is much higher in patients that do not respond with a dramatic improvement in oxygenation with HFOV intervention. (13, 14) Oxygenation derangement at HFOV intervention has not, however, been a consistent predictor of treatment failure. Associated etiologies of ARDS has long been known to dramatically effect mortality. (1) Particularly aspiration pneumonia has been associated with a low mortality and sepsis a high mortality. In addition, a careful analysis of 215 ARDS patients treated in four ICU's, increased age and acuity (APACHE2) were associated with increased mortality. (16)

Management of ARDS with HFOV, because of HFOV's ability to gently recruit lung volume thus improving oxygenation and to ventilate while minimizing tidal volume distention, may prove to be an effective therapy. This trial and others are underway to test this hypothesis.

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CHANGES - October 1996 to August 1997 version

(changes underscored)

7. Exit Criteria

Patients will be exited from the study for the following reasons:

1. Withdrawal of informed consent
2. Death
3. Weaned from mechanical ventilation
4. 30 days from entry
5. HFOV treatment failure - physician determination that cv rescue of potential benefit to patient
6. HFOV unanticipated adverse event - physician determination that continued HFOV jeopardized patient
7. Inappropriate enrollment

note: The Treatment Failure/Exit Report Form also changed to reflect these 7 study exits

ADDED DEFINITION

- STUDY ENTRY TIME - The separation of the time of randomization and time of study entry occur to partially compensated for the inevitable delay associated with transition of HFOV randomized patients from CV to HFOV. The intent is as follows. Patients randomized to CV treatment will have a study entry time one hour after randomization. The study entry time for HFOV randomized patients will be when they are place on HFOV. (This needs to be within 2 hours of randomization, failure to do so would constitute a protocol violation. Such a protocol violation should be reported on the "Unanticipated Adverse Events/Deviations" form). Once on study, the initial treatment clinical indicator data is to be recorded when the patient is stable or at two hours after entry, even if the patient is not stable.

Change from 3/98 Investigators Meeting

5. Patient Population
Entry Criteria
a minimum PEEP of 10 cm H2O required with P/F < 200

Appendix
study QRC including vent management algorithm

Change from 2/99 Investigator Consensus

5.0 Patient Population

- Entry Exclusion - patients otherwise eligible for entry will be excluded if : 1)
FiO₂ has been greater than .80 for 48 hours,
(The original criteria was 24 hours, however, after experience with the
protocol centers felt 24 hours provided and insufficient window to gain
informed consent)

Change from 11/99 Investigators Meeting

Investigators agreed on the need to use a specific CRF for identifying potential confounding therapies. CRF Confounding Therapies included in the CRF section.