NIH ARDS NETWORK

KETOCONAZOLE AND RESPIRATORY MANAGEMENT IN ALI/ARDS

CASE REPORT FORM INSTRUCTIONS
Version 2

October 24, 1996

Table of Contents

Form **Page**

Introduction....2
ALI SCREENING FORM....3
INCLUSION CRITERIA (Enrollment)....6
EXCLUSION CRITERIA (Enrollment)....7
APACHE III DEMOGRAPHICS (Enrollment)....11
APACHE III PHYSIOLOGY (Enrollment)....13
APACHE - ARTERIAL BLOOD GASES (Enrollment)....15
VITAL SIGNS Day 0....16
BASELINE VENTILATOR PARAMETERS (Enrollment)....19
CHEST X-RAY / BAROTRAUMA (Enrollment)....21
MEDICATION REPORT (Enrollment)....22
GLASGOW COMA SCORE: DAY 0....23
ON STUDY VITAL SIGNS (Day 1, 2, 3, 4, 7, 14, 21, 28)....24
ON STUDY VENTILATOR PARAMETERS (Day 1, 2, 3, 4, 7, 14, 21, 28)....27
CHEST X-RAY / BAROTRAUMA (Day 1, 2, 3, 4, 7, 14, 21, 28)....29
MEDICATION REPORT (Day 1, 2, 4, 7)....30
GLASGOW COMA SCORE (Day 7, 14, 21, 28)....31
WEANING / VENTILATOR MONITORING (Days 1-28)....32
BRUSSELS TABLE (Days 1-28)....35
STUDY TERMINATION....36
ADVERSE EVENT....38

This manual contains instructions for completing the case report forms on patients enrolled In the ARDS Network study entitled "Prospective, Randomized, Multicenter Trial of 12 ml/kg vs 6 ml/kg Tidal Volume Positive Pressure Ventilation and Ketoconazole vs Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome."

The format of the instructions is similar to the format of the case report form. Each section of the instructions has a title at the top of the first page similar to the title of the corresponding case report form pages. Within each section, the sequence of instructions is identical to the sequence of the questions on the case report form pages.

Some of the case report form pages must be completed only once on each patient (e.g., "INCLUSION CRITERIA" and "BASELINE VENTILATOR PARAMETERS"). For these pages, the corresponding instruction manual pages will be required only once. Other case report form pages must be completed on several dates after enrollment (e.g., "ON STUDY VITAL SIGNS" AND "WEANING/VENTILATOR MONITORING FORM"). For these pages, the corresponding instruction manual pages should be used each time the case report form page is completed.

Most of the questions on the case report form screens are self-explanatory, and the corresponding instructions are brief. For other questions, additional information is provided in the instructions or a reference to a specific protocol section or operating procedure is given.

Reminder about the use of the dot (.) missing value. The missing value can be entered Into any field, but the coordinator should only use it to indicate that **the data will never be available**. For some of the questions, a value will not be available when the case report orms are being completed. This may occur because a value is pending or the chart was unavailable. In these instances, the coordinator should leave the field blank until the data can be obtained.

The designation "+" appears next to some of the items on the case report form screen. This indicates that there are important instructions for data coordinators that should be reviewed and understood before data are entered. The specific instructions for these items can be viewed by pressing the F2 key when the cursor is over the data field.

ALI SCREENING FORM

This form should be completed on all patients meeting the study inclusion criteria in regularly screened ICUs. It should also be completed for patients meeting the inclusion criteria identified in other ICUs.

Inclusion Criteria

Acute onset of:

1. $PaO_2/FiO_2 \leq 300$. If altitude > 1000m, use $(PaO_2/FiO_2) \leq (300) * (B.P./760)$
2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogenous, or asymmetric.
3. Requirement for positive pressure ventilation via endotracheal tube.
4. No evidence of left atrial hypertension (if measured, pulmonary arterial wedge pressure < 18 mmHg.

If a patient meets all inclusion criteria and no exclusion criteria AND it has been < 36 hours since all inclusion criteria were first met, she/he is eligible for study enrollment.

ITEM	DEFINITION	DATA RULES
1. Acute Onset	Enter "1" (Yes) or "2" (No). Acute onset is defined as follows: PaO_2/FiO_2 ratio ≤ 300 (corrected for altitude) and bilateral infiltrates must be present for ≤ 28 days. If either is present continuously for > 28 days, the condition is not considered "acute", and the patient is not eligible for enrollment.	Required field.
	THE FOLLOWING INCLUSION CRITERIA (2a-c,3) MUST OCCUR WITHIN A SINGLE 24 HOUR INTERVAL (PROTOCOL SEC. 4.2).	
2a. $PaO_2/FiO_2 \leq 300$ (corrected for altitude)	Example PaO_2/FiO_2 calculation: If PaO_2=89 and FiO_2=.50, then PaO_2/FiO_2=89/.50 = 178.	Required field.
2b. Bilateral infiltrates consistent with pulmonary edema	The infiltrates may be patchy, diffuse, homogeneous, or asymmetric. Infiltrates must not be caused solely by atelectasis, effusions, mass, plump or indistinct vessels, or shadows known to be chronic.	Required field.
2c. Receiving positive pressure ventilation via endotracheal tube	"Positive pressure ventilation" is defined as ventilation assistance wherein airway pressure is raised during inspiration and lowered during expiration. This excludes CPAP but includes Pressure Support, Pressure Control, and Assist/Control modes. "Endotracheal tube" may be an orotracheal, nasotracheal, or tracheostomy tube.	Required field.
3. No clinical evidence of left atrial hypertension. If measured, pulmonary arterial wedge pressure $\leq$ 18 mmHg.	Enter "1" if there is **NO** evidence of left atrial hypertension; enter "2" if there **IS** evidence of left atrial hypertension.	Required field.
4. PaO_2	Enter the PaO_2 used to calculate the P/F ratio in 2a above	Required field.

ALI SCREENING FORM

(Continuation)

5. FiO_2	Enter the FiO_2 used to calculate the P/F ratio in 2a above. Enter as a decimal (e.g., 50% should be entered as .50).	Required field.
6. Enter the first date that all these criteria exist simultaneously	Enter the first calendar date when ALL inclusion criteria (2a-c, 3) first occur together. Example: If the P/F criterion was first met on 1/30/96 but the chest x-ray did not show bilateral infiltrates until 2/1/96 and the patient STILL met the P/F criterion on 2/1/96, then the first date both were met would be 2/1/96	Required field.
7. Patient Hospital ID #	Enter the unique number used by the hospital to identify the patient for medical record purposes.	Required field.
8. Gender	Enter "1" if the patient is male, "2" if the patient is female.	Required field. (required to calculate IBW)
9. Ethnicity	1=White, not of Hispanic Origin, 2=Black, not of Hispanic Origin, 3=Hispanic, 4=Asian/Pacific Islander, 5=American Indian/Alaskan Native, 6=Other.	Required field.
10. Age	Enter patient's age in years at last birthday.	Required field.
11. Location	Enter number code to indicate patient's current location: MICU, SICU, Cardiac SICU, CCU, NeuroICU, Burn, Trauma, Cancer Unit, MICU/SICU, Other.	Required field.
12. Regularly Screened ICU	Enter "1" (Yes) if this ICU is screened at least 5 days each week.	Required field.
13a. Primary Reason for Exclusion	Enter the number from the list that indicates the most important condition that led to exclusion (if any). Refer to protocol section 4.3 and Appendix A for definitions of specified exclusion criteria such as chronic lung disease, terminal illness, chronic liver disease, acute liver disease, morbid obesity.	Required field.
13 b. Comment	If not excluded but not eligible at the time of study entry, complete this section	Required field if 13a = not excluded.
14. Lung Injury Category	Enter one primary and 0-4 secondary causes of lung injury: Trauma, Aspiration, Sepsis, Multiple Transfusions, Other. The "primary" category should be the most immediate cause. E.g., a patient with multiple trauma who develops sepsis and then ALI: primary category = sepsis; secondary category = trauma.	Required field.
Question 15 Optional	If CCTG has indicated it will collect this information, then it is a required field.	

ALI SCREENING FORM

(Continuation)

15. Date of unassisted breathing if unassisted breathing sustained for greater than 48 hours	Enter the date that unassisted breathing began (first episode) if it continued for > 48 hours.	Required field if CCTG has indicated that this data will be collected on screened patients.
16. Date of Hospital Discharge	Enter the date patient was discharged from Study Hospital (alive or dead).	Required field for all CCTGs for patients who are screened but not enrolled in study.
17. Status at Hospital Discharge	Indicate whether patient was alive or dead at discharge from Study Hospital.	Required field for all CCTGs for patients who are screened but not enrolled in study.

N.B. Occasional patients meet all inclusion criteria and no exclusion criteria but are not enrolled because they improve quickly or die quickly within the 36 hour enrollment window. For these patients, proceed to the next 2 forms (Inclusion Criteria and Exclusion Criteria) and complete items 1-3 (Inclusion Criteria) and items 1-21 (Exclusion Criteria).

INCLUSION CRITERIA
Enrollment

Complete this form on all patients who are being enrolled in the study.

ITEM	DEFINITION	DATA RULES
1. Acute Onset	Enter "1" (Yes) if both the PaO_2/FiO_2 and chest radiograph inclusion criteria (items 2a and 2b below) are of $\leq$ 28 days continuous duration.	Required field.
2. $PaO_2/FiO_2 \leq 300$, bilateral infiltrates ..., receiving positive pressure ventilation....	Enter "1" (Yes) if the ratio $PaO_2/FiO_2 \leq 300$ (corrected for altitude) **AND** there are bilateral infiltrates consistent with pulmonary edema on chest radiograph (qualifying x-rays must be interpreted by the Center Principal Investigator or designee) **AND** if the patient is receiving positive pressure ventilation via endotracheal tube. "Positive pressure ventilation" is defined as ventilation assistance wherein airway pressure is raised during inspiration and lowered during expiration. This excludes CPAP alone but includes Pressure Support, Pressure Control, and Assist/Control modes. "Endotracheal tube" may be an orotracheal-, nasotracheal-, or tracheostomy tube.	Required field.
3. No clinical evidence of left atrial hypertension (if measured, pulmonary arterial wedge pressure $\leq$ 18 mmHg.	Enter "1" (Yes) if there is **NO** clinical evidence of left atrial hypertension (if measured, pulmonary arterial wedge pressure $\leq$ 18 mmHg). Enter "2" (No) if there **IS** evidence of left atrial hypertension (if measured, pulmonary arterial wedge pressure > 18 mmHg.	Required field.

EXCLUSION CRITERIA
Enrollment

Complete this form on all patients who are being enrolled in the study.

ITEM	DEFINITION	DATA RULES
1. Attending physician unwilling to participate?	Enter "1" (Yes) or "2" (No).	Required field.
2. Patient/family unwilling to participate?	Enter "1" (Yes) or "2" (No).	Required field.
3. Patient unable/Family unavailable to obtain informed consent?	Enter "1" (Yes) or "2" (No).	Required field.
4. Is patient < 18 years old?	Enter "1" (Yes) or "2" (No).	Required field.
5. Has patient participated in other intervention trials in ALI, ARDS or Sepsis within the past 30 days?	Enter "1" (Yes) or "2" (No).	Required field.
6. Has it been > 36 hours since all the inclusion criteria were met?	A patient must be enrolled, randomized, and initial ventilator changes made and first dose of study drug given within 36 hours of when all the inclusion criteria were first met. Enter "1" if the answer to the question is "Yes"; enter "2" if the answer is "No".	Required field.
7. Does the patient have neuromuscular disease that impairs the ability to ventilate spontaneously?	Enter "1" (Yes) or "2" (No). Ability to ventilate may be impaired by C_5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barre syndrome, myasthenia gravis, or other neuromuscular disease.	Required field.
8. Is patient pregnant?	Enter "1" (Yes) or "2" (No). If patient is female of reproductive age, obtain appropriate laboratory test for pregnancy (e.g. urine HCG).	Required field.
9. Does the patient have elevated intracranial pressure, tricyclic antidepressant overdose, HgbSS, HgbSC, or other conditions where hypercapnia would be contraindicated?	Enter "1" (Yes) or "2" (No). Refer to Protocol Appendix A for definitions of elevated intracranial pressure. If tricyclic overdose and level not elevated, enter "2"; if no level available or level elevated, enter "1".	Required field.
10. Does patient have severe chronic respiratory disease?	Enter "1" (Yes) or "2" (No). Severe chronic respiratory disease is defined in Protocol Appendix A.	Required field.

EXCLUSION FORM
(Continuation)

11. Does patient have burns greater than or equal to 30% total body surface area?	Enter "1" (Yes) or "2" (No).	Required field.
12. Does patient have a malignancy or other chronic irreversible disease or condition for which 6 month mortality is estimated at greater than 50%.	Enter "1" (Yes) or "2" (No).	Required field.
13. Has the patient had either a bone marrow transplant or lung transplant.	Enter "1" (Yes) or "2" (No).	Required field.
14. Not committed to full support?	Enter "1" if the health-care team is **NOT** committed to full support; enter "2" if the health-care team **IS** committed to full support. N.B.: Enter "2" if a patient would receive all treatments and supportive measures except for attempts at resuscitation from cardiac arrest (chest compressions, defibrillation).	Required field.
15. Has the patient been treated with ketoconazole, itraconazole, fluconazole within the past 7 days?	Enter "1" (Yes) or "2" (No).	Required field.
16. Has the patient been treated with astemizole, terfenadine, or cisapride within the past 3 days?	Enter "1" (Yes) or "2" (No).	Required field.
17. Does patient have suspected severe, chronic liver disease?	Enter either "1" (Yes) or "2" (No). If "1", then fields A-E are required. If the sum of the values entered in A, B, C, D, and E below $\geq$ 10, the patient has severe chronic liver disease. Enter "1" if sum $\geq$ 10; enter "2" if sum < 10.	If answer to 17 is "1" (Yes) then fields A-E below are required. . Otherwise, skip to item 18.
A. Ascites	Enter "1" if there are no ascites on clinical examination, "2" if ascites are present on clinical examination but not tense, or "3" if there are tense ascites.	Required field only if item 17 ="1" .
B. Encephalopathy	Use the system shown on the computer screen to assess the grade of encephalopathy. Enter "1" for No abnormality, "2" for Grade I or II encephalopathy, or "3" for Grade III or IV encephalopathy.	Required field only if item 17 = "1".

EXCLUSION FORM
(Continuation)

C. Bilirubin (mg/dl)	Enter "1" if Total Bilirubin < 2 mg/dl; enter "2" if Total Bilirubin = 2-3 mg/dl; enter "3" if Total Bilirubin > 3 mg/dl.	Required field only if item 17 = "1".
D. Albumin (g/L)	Enter "1" if serum albumin concentration > 3.5 gm/dl; enter "2" if albumin concentration = 2.8-3.5 gm/dl; enter "3" if albumin concentration < 2.8.	Required field only if item 17 =1.
E. Prothrombin time (sec prolonged).	Enter "1" if prothrombin time is prolonged < 4 seconds above control; enter "2" if prothrombin time is prolonged 5-10 seconds above control; enter "3" if prothrombin time is prolonged >10 seconds above control.	Required field only if item 17 = "1".
18. Does patient have evidence of acute viral, ischemic, or toxic hepatitis with moderate or severe hepatocellular injury?	Enter "1" if "Yes" or "2" if "No". "Acute hepatitis" is defined in Protocol Appendix B as either of the following: AST or ALT $\geq$ 500, or Alkaline phosphatase > 240	Required field.
19. Does patient have known allergy to imidazole or its derivatives?	Enter "1" (Yes) or "2" (No).	Required field.
20. Is patient morbidly obese?	Enter "1" if actual (not ideal) body weight (kg) > body height (cm, heel to crown). Enter "2" if actual weight in kg < height in cm.	Required field.
21. Has informed consent been obtained?	Informed consent must be obtained before any study procedures are initiated. Enter "1" if informed consent has been obtained. Enter "2" if informed consent has not been obtained.	If any item 1-20 = "1" (Yes), then do not complete items 21-24. Otherwise, 21-24 are required fields.
22. Enter study number # _____.	Enter the seven digit study number assigned by the coordinating center voice randomization system.	If any item 1-20 = "1" (Yes), then do not complete items 21-24. Otherwise, 21-24 are required fields.
23. Patient randomized to	Enter "1" if the patient was randomized to the 6 ml/kg group. Enter "2" if the patient was randomized to the 12 ml/kg group.	If any item 1-20 = "1" (Yes), then do not complete items 21-24. Otherwise, 21-24 are required fields.

EXCLUSION FORM
(Continuation)

24. Date/Time (military) of initial ventilator changes.	Enter the date and time (24 hour clock) of initial study ventilator changes, if any. If no ventilator changes were necessary to initiate study, enter time that ventilator changes would have been made if they were necessary.	If any item 1-20 = "1" (Yes), then do not complete items 21-24. Otherwise, 21-24 are required fields.

APACHE III - DEMOGRAPHICS
Enrollment

Complete this form on all patients enrolled into the study.

ITEM	DEFINITION	DATA RULES
1. Hospital Admission Date	Enter the date the patient was admitted to the study hospital.	Required field.
2. ICU Admission Date	Enter the date of the current ICU admission.	Required field.
3. Time of ICU Admission	Enter the time the patient was admitted to the current ICU.	Required field.
4. Patient Admitted Directly From:	Enter where the patient was **immediately prior** to this ICU admission (OR, Recovery Room, ER, Floor, Another Special Care Unit, Another Hospital, Direct Admit, Step-down Unit).	Required field.
5. Is the patient immediately post-operative from elective surgery?	Answer this question with "1" (Yes) or "2" (No).	Required field.
6. ICU Readmit?	During this hospitalization, was the patient in an ICU prior to this current ICU admission?	Required field.
7. ICU Readmit within 24 hours?	If item 6 is answered "yes", was the readmission to the ICU within 24 hours of a previous ICU discharge?	Required field.
8a. Chronic Health Information Available?	Enter "1" (Yes) or "2" (No). Chronic health information may be updated at any time during the admission. If any of the following chronic health items (items 8b-9h) are diagnosed during the hospital admission AND **PRIOR** to study entry, record the item as present on study entry.	Required field. If item 8a = "2" (No), then skip 8b-9h.
8b. Is the patient on chronic dialysis or peritoneal dialysis?	Enter "1" (Yes) or "2" (No) to indicate if the patient required dialysis prior to hospitalization.	Required field only if 8a = "1" (Yes).
9a. AIDS?	Enter "1" (Yes) or "2" (No). Enter "2" (No) if HIV positive but without other AIDS criteria.	Required field only if 8a = "1" (Yes).

APACHE III - DEMOGRAPHICS
Enrollment (Continuation)

9b. Leukemia (AML, CML, all lymphocytic leuk., multiple myeloma)	Enter "1" (Yes) or "2" (No).	Required field only if 8a = "1" (Yes).
9c. Non-Hodgkins Lymphoma	Enter "1" (Yes) or "2" (No).	Required field only if 8a = "1" (Yes).
9d. Solid Tumor with metastasis	Enter "1" (Yes) or "2" (No).	Required field only if 8a = "1" (Yes).
9e. Immune Suppression	Enter "1" (Yes) or "2" (No) to indicate if the patient is immunocompromised secondary to chemotherapy, radiation therapy, use of anti-rejection drugs taken after organ transplant, or the daily use of high doses of steroids (0.3 mg Prednisone kg/day or equivalent therapy) within part of or the entire previous six months.	Required field only if 8a = "1" (Yes).
9f. Hepatic Failure	Enter "1" (Yes) or "2" (No) to indicate if the patient has decompensated cirrhosis (Hepatic Failure) as evidenced by one or more episodes of jaundice and ascites, upper gastrointestinal bleeding or hepatic encephalopathy or comas.	Required field only if 8a = "1" (Yes).
9g. Compensated cirrhosis.	Enter "1" (Yes) or "2" (No) to indicate if the patient has cirrhosis without the stigmata indicated above in 9f. If the patient has a functioning liver transplant, this chronic health item would not apply.	Required field only if 8a = "1" (Yes).
9h. Diabetes Mellitus	Enter "1" (Yes) or "2" (No).	Required field only if 8a = "1" (Yes).

APACHE III PHYSIOLOGY
Enrollment

COMPLETE ON DAY 0. ALL DATA SHOULD BE TAKEN FROM THE 24 HOURS PRECEDING INITIAL VENTILATOR CHANGES (IF ANY). DO NOT INCLUDE INTRAOPERATIVE VALUES OR VALUES RELATED TO DEATH OR CARDIO/RESPIRATORY ARREST SITUATIONS.

For items on this table indicated with "*" (items 8-18), if no values were obtained for clinical purposes during the 24 hours preceding initial study procedures, the lab tests must be obtained before initiating study procedures.

ITEM	DEFINITION	DATA RULES
1. Temperature	Enter the highest and lowest temperatures in Centigrade or Fahrenheit. Add 1 degree Centigrade or 2 degrees Fahrenheit if axillary temperatures.	Required field.
2. Systolic BP	Enter the highest and lowest.	Required field.
3. Mean Arterial Pressure	Enter the highest and lowest.	Required field.
4. Heart Rate	Enter the highest and the lowest.	Required field.
5. Respiratory Rate	Enter the highest and the lowest.	Required field.
6a. Was patient ventilated when the lowest respiratory rate occurred?	Enter "1" (Yes) or "2" (No).	Required field.
6b. Was patient ventilated when the highest respiratory rate occurred?	Enter "1" (Yes) or "2" (No).	Required field.
7. Urine Output 24 hr	Enter the amount of urine output (ml) in the 24 hrs prior to initial ventilator changes (if any). E.g., if initial ventilator changes occur on 2/1/96 at 1400, then the urinary output listed should be from 1/31/96 at 1400 to 2/1/96 at 1400). If a large volume of urine was inadvertently spilled or the urine was not measured, leave the field blank. A urine output value of zero indicates that the patient produced no urine.	Required field.
8 Hematocrit*	Enter highest and lowest values as "00.0" (e.g., "35.2", not " .352"). If only one value present for 24 hour period, enter this value as both the highest and lowest.	Required field.

9. WBC* (White Blood Cell count).	Enter highest and lowest as "00000" (e.g., a WBC of 14,200 should be entered as "14200" Do not add comma.). If only one value present for 24 hour period, enter it as both the highest and lowest.	Required field.
10. Platelets*	Enter only the lowest value during the 24 hours. Enter as "000" (e.g., a platelet count of 258,000 should be entered as "258".	Required field.
11. Serum Sodium*	Enter highest and lowest. If only one value present for 24 hour period, it should be entered as both the highest and lowest.	Required field.
12. Serum Potassium*	Enter highest and lowest. If only one value present for 24 hour period, it should be entered as both the highest and lowest.	Required field.
13. Serum BUN*	Enter only highest value.	Required field.
14. Serum Creatinine*	Enter highest and lowest. If only one value present for 24 hour period, it should be entered as both the highest and lowest.	Required field.
15. Serum Glucose*	Enter highest and lowest. If only one value present for 24 hour period, it should be entered as both the highest and lowest.	Required field.
16. Serum Albumin*	Enter highest and lowest. If only one value present for 24 hour period, it should be entered as both the highest and lowest.	Required field.
17. Serum Bilirubin*	Enter only highest value.	Required field.
18. Serum Bicarbonate*	Enter only lowest value.	Required field.

APACHE ARTERIAL BLOOD GASES
Enrollment

Record ALL ABG's in the 24 hours preceding initial study ventilator changes, if any. Record "Yes" or "No" if the patient was intubated (with or without positive pressure ventilation) when each ABG was obtained.

FiO_2	PaO_2	$PaCO_2$	pH	Intubated?	DATA RULES
1.					Required field.
2.					Record values, if available.
3.					Record values, if available.
4.					Record values, if available.
5.					Record values, if available.
6.					Record values, if available.
7.					Record values, if available.
8.					Record values, if available.
9.					Record values, if available.
10.					Record values, if available.

VITAL SIGNS DAY-0

VALUES FOR ITEMS 2-5 SHOULD BE OBTAINED IN THE 4 HOUR INTERVAL THAT PRECEDES INITIAL STUDY VENTILATOR CHANGES, IF ANY. IF MORE THAN ONE VALUE IS AVAILABLE DURING THIS INTERVAL, RECORD THE VALUE CLOSEST TO THE TIME THAT STUDY PROCEDURES WERE INITIATED.

Values for other items may be obtained during the 24 hour interval preceding initial study ventilator changes, if any. If no values were obtained for clinical purposes during this interval, a blood specimen or measurement should be drawn and sent prior to study initiation. If more than one value is available, use the most recent value before study initiation.

ITEM	DEFINITION	DATA RULES
1. Date and Time of current intubation	Enter the date and time (24 hour clock) that indicates when positive pressure ventilation was initiated via endotracheal tube.	Required field.
2. Heart Rate	Use last value prior to study initiation.	Required field.
3. Systolic BP	Use last value prior to study initiation.	Required field.
4. Diastolic BP	Use last value prior to study initiation. If diastolic BP cannot be obtained (e.g. when BP is palpable but not audible or when doppler is used to measure systolic pressure), enter "."	Required field.
5. Temperature	Use last value prior to study initiation. Prefer rectal, tympanic, or core temperature. If axillary used, add 1 degree Centigrade or 2 degrees Fahrenheit.	Required field.
6. Height	Record patient's height from heel to crown. Patient should be supine with legs straight (no flexion or extension of hips and knees, if possible), during measurement.	Required field.
7. IBW	Value for Ideal Body Weight in kilograms will be computed based on gender and height. Males: IBW = 50 + 2.3(inches - 60) Female: IBW = 45.5 + 2.3(inches - 60)	Computer generated. Must have entered both gender and height in order for computer to generate number.
8. Weight	Enter most recent measured body weight. If weight not available during preceding 24 hours, enter most recent weight. Note technique for weighing patient (bed-scale, lift, etc.) on medical record.	Collect data, when available

VITAL SIGNS DAY-0
(Continuation)

9. Fluid Intake	Enter total amount of fluids (parenteral and enteral) measured/recorded during the 24 hours that preceded study initiation.	Collect data, when available.
10. Urine Output	Enter total amount of urine output measured/recorded during the 24 hours that preceded study initiation.	Collect data, when available.
11. Hct	Enter value as "00.0" (e.g., 39.3).	Required field.
12. WBC	Enter value as "00000" (e.g., if WBC = 14,200, enter "14200". Do not use comma.	Required field.
13. Total Bilirubin	Record most recent value (mg/dl). If none in 24 hours prior to study initiation, send blood specimen.	Required field.
14. AST (SGOT)	Record most recent value. If none in 24 hours prior to study initiation, send blood specimen.	Required field.
15. ALT (SGPT)	Record most recent value. If none in 24 hours prior to study initiation, send blood specimen.	Required field.
16. Alkaline Phosphatase	Record most recent value. If none in 24 hours prior to study initiation, send blood specimen.	Required field.
17. Urinary Thromboxane Metabolite	Collect urine for thromboxane metabolite as follows: 1. Collect 6 ml of freshly voided urine. If urinary catheter in place, obtain from catheter tubing port. 2. Place 2 ml in each of 3 microtubes. 3. Attach appropriate bar-coded label on specimen. 4. Place on ice until able to freeze at -70 ° C (ASAP). 5. Comment on any deviation from protocol, such as late sampling.	Required field.

VITAL SIGNS DAY-0
(Continuation)

18. Blood Cytokines	Collect plasma for blood cytokines as follows: 1. Draw blood from patient via arterial line, venous line, or by venipuncture. Use at least an 18 gauge needle for venipuncture and when instilling blood into the purple top vacutainer to prevent hemolysis of the specimen. Hemolyzed samples should be redrawn if possible. 2. Gently invert the vacutainer 2-3 times to mix. 3. Place on ice if unable to centrifuge immediately. 4. Centrifuge for 10 minutes at approximately 1500-3000 rpm (standard table-top centrifuge may be used). 5. Withdraw plasma (do not remove buffy coat) using a pipette or syringe and fill purple top micro tubes (2 ML OF PLASMA IN EACH OF 3 TUBES) with plasma. 6. Attach appropriate bar-coded label which contains an ID number and contents of tube. 7. Place on ice until able to freeze at -70° C (ASAP). 8. Comment on any deviation from protocol, such as late sampling or hemolyzed samples.	Required field.

BASELINE VENTILATOR PARAMETERS
Enrollment

The following information should be taken from the four-hour interval that immediately precedes initial study ventilator changes, if any. If more than one value is available during this four-hour interval, enter the last value prior to initial study ventilator changes, if any.

ITEM	DEFINITION	DATA RULES
1. Ventilator manufacturer and model	Enter the appropriate number to indicate if the patient is on a Puritan 7200, Servo 9000, Servo 300, Hamilton Veolar/Amadeus, Bird 8400, Bear 1000, or other ventilator.	Required field.
2. Ventilator mode	Enter "1" (Yes) or "2" (No) for each of the four modes shown (SIMV, Pressure Support, Assist/Control, Pressure Control, PCIRV, Other. If the patient was on SIMV with PS, enter "1" (Yes) for both "SIMV" and "Pressure Support".	Required field.
3. Calculated delivered tidal volume	Enter the corrected inspired tidal volume (ml) set on the ventilator. Refer to the Standard Operating Procedures for correcting inspired tidal volumes for gas compression/tube expansion on ventilators that do not make this correction automatically.	Required field if item #2, 2.1 or 2.3 = "1" (Yes).
4. Pressure Control Level	Enter the pressure control level (cm H_2O) on the ventilator if the patient is on Pressure Control Ventilation or PCIRV.	Required field if item #2, 2.4 or 2.5 = "1" (Yes).
5. Pressure Support	Enter the level of Pressure Support (in cmH_2O) if the patient is receiving pressure support ventilation either in the Pressure Support or SIMV with Pressure Support mode. The Pressure Support level indicates the increment in airway pressure during inspiration above its level during expiration. For example, if PEEP = 5 and inspired airway pressure = 20, then enter Pressure Support = 15.	Required field if item #2, 2.2 = "1" (Yes.)
6. Set Rate	Enter the rate set on the ventilator if the patient is on the SIMV, SIMV with Pressure Support, Assist/Control, or Pressure Control mode. (This is the minimum rate set on the ventilator, not the patient rate).	Required field if item #2, 2.1, 2.3, 2.4 or 2.5 = "1" (Yes).

7. Total Respiratory Rate	Enter the total respiratory rate, which may exceed the Set Rate above if the patient is making additional inspiratory efforts.	Required field.
8. Total Minute Ventilation	Enter the total minute ventilation in liters per minute. This value is available from a digital report on the ventilator.	Required field.
9. PEEP	Enter the PEEP applied on the ventilator in cmH_2O. This is the external or applied PEEP, not the total PEEP, auto-PEEP, or intrinsic PEEP.	Required field.
10. Plateau Pressure	Enter the values for each of three plateau (Pstat) pressure measurements (cmH_2O) made during the four-hour interval prior to initial ventilator changes, if any. Each plateau pressure measurement should be made with a 0.5 second inspiratory pause.	Required field if item #2, 2.1 or 2.3 = "1" (Yes).
11. Peak Inspiratory Pressure	Enter the peak inspiratory airway pressure (cmH_2O). This should be obtained while the patient is relaxed, not coughing or moving in bed.	Required field if item #2, 2.1 or 2.3 = "1" (Yes).
12. I:E Ratio	Enter the ratio of the duration of inspiration to expiration. Monitor the I:E ratio for at least one minute and enter a representative value.	Required field.
13. Mean Airway Pressure	Enter the mean airway pressure (cmH_2O). This should be obtained while the patient is relaxed, not coughing or moving in bed.	Required field.
14. FiO_2	Enter the fraction of inspired oxygen as decimal (e.g., ".50", not 50%)	Required field.
15,16,17: PaO_2, $PaCO_2$, and Arterial pH	Enter results of the last arterial blood gas prior to initial study ventilator changes, if any.	Required field.
18. SpO_2	Enter pulse oximetry value prior to study ventilator changes, if any. Observe the oximeter values for at least one minute and enter a representative value.	Required field.

CHEST X-RAY/BAROTRAUMA
Enrollment

Use the most recent chest radiograph prior to initial ventilator changes, if any. Qualifying radiographs must be interpreted by a Network Principal Investigator or designee.

ITEM	DEFINITION	DATA RULES
1. Radiographic Lung Injury Score	Enter a number from 0 through 4 that indicates the number of quadrants with pulmonary infiltrate. Shadows interpreted as infiltrates may not be caused by effusions, atelectasis, masses, indistinct or plump blood vessels, or shadows known to be chronic.	Required field.
2a. Pneumothoraces	Enter the appropriate numerical code to indicate if there is a pneumothorax on the right side (1), on the left side (2), on both sides, bilateral (3), or none (4).	Required field.
2b. Subcutaneous emphysema	Indicate with "1" (Yes) or "2" (No) if there is subcutaneous emphysema apparent on the chest x-ray that is attributed to barotrauma.	Required field.
2c. Pneumomediastinum	Indicate with "1" (Yes) or "2" (No) if the chest x-ray shows air in the mediastinum attributed to barotrauma.	Required field.
2d. Pneumatoceles > 2 cm diameter	Indicate if there are one or more pneumatoceles > 2 cm minimum diameter (a bubble or hole in the parenchyma that is not attributed to a chronic bleb or bullous lesion), on the right side (1), the left side (2), on both sides, bilateral (3), or on neither side.	Required field.
3. Chest Tube	Indicate if there are one or more chest tubes on the right side (1), on the left side (2), on both sides (3), or on neither side (4).	Required field.

MEDICATION REPORT
Enrollment

Complete this form using information pertaining to the 24 hour interval that precedes initial study ventilator changes, if any.

ITEM	DEFINITION	DATA RULES
1. Sedatives/ Tranquilizers (benzo's, narcotics, barbiturates, propofol, or other medications given for sedation.	Enter "1" (Yes) or "2" (No) to indicate if the patient received any amount of the listed medications in the 24 hours prior to study initiation.	Required field.
2. Neuromuscular Blocking Agents	Enter "1" (Yes) or "2" (No) to indicate if patient has received pancuronium, vecuronium, atracurium, succinylcholine, or other medication for neuromuscular blockade within 24 hours prior to study initiation.	Required field.
3. H2 Blockers	Answer "yes or "no" if the patient has received cimetidine, ranitidine, or other H-2 blocking agent within 24 hours prior to study initiation.	Required field.
4. Erythromycin, Clarithromycin or other macrolide antibiotics	Enter "1" (Yes) or "2" (No) to indicate if the patient has received any macrolide antibiotic within the 24 hours prior to study initiation.	Required field.
5. Vasopressors	Enter "1" (Yes) or "2" (No) to indicate if the patient has received any vasopressor within the 24 hours prior to baseline. "Vasopressor" is defined as: Dopamine $\geq$ 6 mcg/kg/min or neosynephrine, epinephrine, or levophed at any rate. Dobutamine is not considered a vasopressor.	Required field.
6. Date and Time of Study Drug	Enter the date and time (24 hour clock) to indicate when the first dose of Study Drug was administered. This should be within 4 hours of the time of randomization and within 36 hours of when the inclusion criteria were first met.	Required field.

GLASGOW COMA SCORE: DAY 0

Complete this form using the worst values for the 24 hour interval preceding **initial study ventilator changes**, if any.

ITEM	DEFINITION	DATA RULES
1. Sedatives or Neuromuscular Blocking Agents.	1. Enter "1" (Yes) or "2" (No) to indicate if the patient received any sedative or any neuromuscular blocking agent during the 24 hour interval preceding initial study ventilator changes, if any. If "Yes", then make best estimates for the values below assuming the patient had not received any of these medications.	Required field.
Glasgow Coma Score (GCS)	Use the worksheet provided to calculate the worst GCS within 24 hours prior to initial study ventilator changes, if any. All three components should originate from the same time point.	
2. Eye Opening Score	Enter a value (1,2,3, or 4) to indicate best response. If patient's eyes are swollen shut, estimate best response.	Required field.
3. Motor Response Score	Enter a value (1,2,3,4,5, or 6) to indicate best response.	Required field.
4. Verbal Response Score	Enter a value (1,2,3,4, or 5) to indicate best response. If patient was intubated for 24 hours prior to initial study procedures, use clinical judgment to estimate best response. If unsure, enter "3".	Required field.
5. GCS (total)	Computer calculated total Glasgow Coma Score.	Computer generated.

ON STUDY VITAL SIGNS

Dates after Date of Enrollment: 1, 2, 3, 4, 7, 14, 21, 28

Complete this form on the dates following the date of enrollment shown above if the patient is alive and receiving mechanical ventilation or is attempting a 48 hour period of unassisted breathing.. Discontinue completing this form after the patient has achieved 48 hours of unassisted breathing.

PARAMETERS INDICATED WITH "*" MUST BE MEASURED DURING THE REFERENCE PERIOD 0600-1000 ON THE CALENDAR DATE. IF MORE THAN ONE VALUE IS AVAILABLE FROM 0600-1000, RECORD THE VALUE CLOSEST TO 0800.

FOR PARAMETERS NOT INDICATED WITH "*", USE VALUES CLOSEST TO 0800, IF AVAILABLE. IF VALUES ARE NOT AVAILABLE FROM 0600-1000, USE VALUES CLOSEST TO 0600-1000 ON THIS CALENDAR DATE.

ITEM	DEFINITION	DATA RULES
1. Heart Rate*	Enter earliest value recorded between 0600-1000.	Required field.
2. Systolic BP*	Enter earliest value recorded between 0600-1000.	Required field.
3. Diastolic BP*	Enter earliest value recorded between 0600-1000. If diastolic pressure not available because pressure is measurable only by palpation or doppler, enter "."	Required field.
4. Temperature*	Rectal, tympanic, or core temperature preferred. If axillary temperature used, add 1° C or 2° F.	Required field.
5. Weight	Enter actual body weight measured on this date, if available.	Required field.
6. Fluid Intake	Record total fluid intake (parenteral and enteral) during 24 hours preceding the reference interval 0600-1000..	Required field.
7. Urine Output	Record total urine output during 24 hours preceding the reference interval 0600-1000.	Required field.
8. Hematocrit	Record Hematocrit if measured on this calendar date. Enter as "00.0".	Required field.
9. WBC	Record white blood cell count if measured on this calendar date. Record as "00000" (e.g., if WBC = 14,300, enter as "14300". Do not use a comma.	Required field.

ON STUDY VITAL SIGNS
(Continuation)

10. AST (SGOT)	Record if measured on this calendar date.	Required field on days 0,4,7,14, 21. If ketoconazole has been discontinued prior to 10 days, measure lft's one additional time. (if keto is discontinued on day 8, measure lft's on day 14)
11. ALT (SGPT)	Record if measured on this calendar date.	Required field on days 0,4,7,14, 21. If ketoconazole has been discontinued prior to 10 days, measure lft's one additional time. (if keto is discontinued on day 8, measure lft's on day 10).
12. Alkaline Phosphatase	Record if measured on this calendar date.	Required field on days 0,4,7,10. If ketoconazole has been discontinued prior to 10 days, measure lft's one additional time. (if keto is discontinued on day 8, measure lft's on day 10).
13. Urinary Thromboxane Metabolite	Collect urine for thromboxane metabolite **only on the first and third calendar dates after the date of enrollment**: 1. Collect 6 ml of freshly voided urine. If urinary catheter in place, obtain from foley catheter tubing port. 2. Place 2 ml in each of 3 microtubes. 3. Attach appropriate bar-coded label on specimen. 4. Place on ice until able to freeze at -70 ° C (ASAP). 5. Comment on any deviation from protocol, such as late sampling.	Required field.

14 Blood Cytokines	Collect plasma for blood cytokines **only on the first and third calendar dates after the date of enrollment**: 1. Draw blood from patient via arterial line, venous line, or by venipuncture. Use at least an 18 gauge needle for venipuncture and when instilling blood into the purple top vacutainer to prevent hemolysis of the specimen. Hemolyzed samples should be redrawn if possible. 2. Gently invert the vacutainer 2-3 times to mix. 3. Place on ice if unable to centrifuge immediately. 4. Centrifuge for 10 minutes at approximately 1500-3000 rpm (standard table-top centrifuge may be used). 5. Withdraw plasma (do not remove buffy coat) using a pipette or syringe and fill purple top micro tubes (2 ML OF PLASMA IN EACH OF 3 TUBES) with plasma. 6. Attach appropriate bar-coded label which contains an ID number and contents of tube. 7. Place on ice until able to freeze at -70° C (ASAP). 8. Comment on any deviation from protocol, such as late sampling or hemolyzed samples.	Required field.
15. Ketoconazole Level	Obtain blood sample for ketoconazole level 2 hours after study drug given **only on the third calendar date after enrollment:** 1. Draw 5-10 ml of blood via arterial line, venous line, or venipuncture and fill one 10 ml red-top clot tube. A vacutainer may be used. 2. Allow blood to clot in the tube at room temperature for 15 minutes. 3. Spin the tube at 2500 rpm in a standard table-top centrifuge for 15 minutes. 4. Pipette serum into 2 ml cryotubes; place 1 ml of serum into each of two tubes. 5. Discard the remaining blood and serum. 6. Freeze the cryotubes at -70° C until ready to send in batch. 7. The total time from blood draw to freeze should not exceed 45 minutes.	Required field.

ON STUDY VENTILATOR PARAMETERS

Dates after Date of Enrollment: 1, 2, 3, 4, 7, 14, 21, and 28

Complete this form on the dates after the date of enrollment shown above if the patient is alive and receiving mechanical ventilation or is attempting a 48 hour period of unassisted breathing.. Record data from the Reference Interval from 0600-1000. When more than one value is available during this interval, record the value closest to 0800.. Discontinue this form after the patient has achieved 48 hours of unassisted breathing.

ITEM	DEFINITION	DATA RULES
1. Ventilator manufacturer and model	Enter the appropriate number to indicate if the patient is on a Puritan 7200, Servo 9000, Servo 300, Hamilton Veolar/Amadeus, Bird 8400, Bear 1000, or other ventilator.	Required field.
2. Ventilator mode	Enter "1" (Yes) or "2" (No) for each of the four modes shown (SIMV, Pressure Support, Assist/Control, Pressure Control, PCIRV, Other. If the patient was on SIMV with PS, enter "1" (Yes) for both "SIMV" and "Pressure Support".	Required field.
3. Calculated delivered tidal volume	Enter the inspired tidal volume (ml) set on the ventilator.	Required field if item #2, 2.1 = "1" (Yes).
4. Pressure Support	Enter the level of Pressure Support (in cmH_2O) if the patient is receiving pressure support ventilation either in the Pressure Support or SIMV with Pressure Support mode. The Pressure Support level indicates the increment in airway pressure during inspiration above its level during expiration. For example, if PEEP = 5 and inspired airway pressure = 20, then enter Pressure Support = 15.	Required field if item #2, 2.2 = "1" (Yes).
5. Set Rate	Enter the rate set on the ventilator if the patient is on the SIMV, SIMV with Pressure Support, Assist/Control, or Pressure Control mode. (This is the minimum rate set on the ventilator, not the patient rate).	Required field if item #2, 2.1 = "1" (Yes).
6. Total Respiratory Rate	Enter the total respiratory rate, which may exceed the Set Rate above if the patient is making additional inspiratory efforts.	Required field.
7. Total Minute Ventilation	Enter the total minute ventilation in liters per minute. This value is available from a digital report on the ventilator.	Required field if item #2, 2.1 or 2.2 = "1" (Yes).

ON STUDY VENTILATOR PARAMETERS

8. PEEP	Enter the PEEP applied on the ventilator in cmH_2O. This is the external or applied PEEP, not the total PEEP, auto-PEEP, or intrinsic PEEP.	Required field if item #2, 2.1 or 2.2 = "1" (Yes).
9. Plateau Pressure	Enter the values for each of three plateau (Pstat) pressure measurements (cmH_2O) made during the four-hour interval prior to initial ventilator changes, if any. Each plateau pressure measurement should be made with a 0.5 second inspiratory pause	Required field only if item #2, 2.1 = "1" (Yes).
10. Peak Inspiratory Pressure	Enter the peak inspiratory airway pressure (cmH_2O). This should be obtained while the patient is relaxed, not coughing or moving in bed.	Required field only if item #2, 2.1 = "1" (Yes).
11. I:E Ratio	Enter the "True I:E" if patient is on a ventilator that displays actual I:E ratios with each breath (Puritan Bennett ventilators do this). Enter the "set I:E" if the patient is on a ventilator that does not display actual I:E ratios (Siemens 900 ventilators do not). (On ventilators that do not display actual I:E ratios, the therapist selects a % Inspiratory Time to achieve a Set I:E ratio, assuming the Total Respiratory Rate = Set Rate. If the % Inspiratory Time = 33%, then the Set I:E ratio = 1:2. If % Inspiratory Time = 25%, then the Set I:E ratio = 1:3. If the % Inspiratory Time = 50%, the Set I:E ratio = 1:1	Required field only if item #2, 2.1 = "1" (Yes).
12. Mean Airway Pressure	Enter the mean airway pressure (cmH_2O). This should be obtained while the patient is relaxed, not coughing or moving in bed.	Required field only if item #2, 2.1 = "1" (Yes).
13. FiO_2	Enter the fraction of inspired oxygen as decimal (e.g., ".50", not 50%)	Required item.
14., 15, 16. PaO_2, $PaCO_2$, and Arterial pH	Enter results of arterial blood gas analysis. If no ABG obtained during 0600-1000, record value closest in time to this interval on this calendar date.	Required item.
17. SpO_2:	Enter pulse oximetry value. Observe the oximeter values for at least one minute and enter a representative value.	Required item.

CHEST X-RAY/BAROTRAUMA

Dates after Date of Enrollment: 1, 2, 3, 4, 7, 14, 21, 28

Complete this form on the dates after the date of enrollment shown above if the patient is alive and receiving mechanical ventilation or is attempting a 48 hour period of unassisted breathing. Use the first chest x-ray obtained during the Reference Interval 0600-1000. If no chest x-ray was obtained during this interval, use the first x-ray obtained on this calendar date. If no chest x-ray was obtained on this calendar date, do not complete this form.

ITEM	DEFINITION	DATA RULES
1. Radiographic Lung Injury Score	Enter a number from 0 through 4 that indicates the number of quadrants with pulmonary infiltrate. Shadows interpreted as infiltrates may not be caused by effusions, atelectasis, masses, indistinct or plump blood vessels, or shadows known to be chronic.	Required field.
2a. Pneumo-thoraces	Enter the appropriate numerical code to indicate if there is a pneumothorax on the right side (1), on the left side (2), on both sides, bilateral (3), or none (4).	Required field.
2b. Subcutaneous emphysema	Indicate with "1" (Yes) or "2" (No) if there is subcutaneous emphysema apparent on the chest x-ray that is attributed to barotrauma.	Required field.
2c. Pneumo-mediastinum	Indicate with "1" (Yes) or "2" (No) if the chest x-ray shows air in the mediastinum attributed to barotrauma.	Required field.
2d. Pneumatoceles > 2 cm diameter	Indicate if there are one or more pneumatoceles > 2 cm minimum diameter (a bubble or hole in the parenchyma that is not attributed to a chronic bleb or bullous lesion), on the right side (1), the left side (2), on both sides, bilateral (3), or on neither side.	Required field.
3. Chest Tube	Indicate if there are one or more chest tubes on the right side (1), on the left side (2), on both sides (3), or on neither side (4).	Required field.

MEDICATION REPORT

Dates after the Date of Enrollment: 1, 2, 4, 7

Complete this form on the dates after the date of enrollment shown above if the patient is alive and receiving mechanical ventilation or is attempting a 48 hour period of unassisted breathing.

ITEM	DEFINITION	DATA RULES
1. Sedatives/ Tranquilizers (benzo's, narcotics, barbiturates, propofol, or other medications given for sedation.	Enter "1" (Yes) or "2" (No) to indicate if the patient received any amount of the listed medications on this calendar date.	Required field.
2. Neuromuscular Blocking Agents	Enter "1" (Yes) or "2" (No) to indicate if patient has received pancuronium, vecuronium, atracurium, succinylcholine, or other medication for neuromuscular blockade on this calendar date.	Required field.
3. H2 Blockers	Answer "yes or "no" if the patient has received cimetidine, ranitidine, or other H-2 blocking agent on this calendar date.	Required field.
4. Ketoconazole, fluconazole, itraconazole	Enter "1" (Yes) or "2" (No) to indicate if the patient received any of these medications (other than study drug) in any amount on this calendar date.	
5. Astemizole (Hismanal), terfenadine (Seldane), or cisapride (Propulsid).	Enter "1" (Yes) and call the study PI at your institution if the patient received any of these three medications on this calendar date. This is a STUDY VIOLATION and requires discontinuation of study drug. Enter "2" if none were given.	
6-7. Nitric Oxide, Surfactant, Liquid Ventilation, ECMO, IVOX, High Frequency Ventilation or Oscillation, Prone Positioning.	Enter "1" (Yes) if the patient received any of these experimental treatments on this calendar date. Enter "2" if none were given.	
8. Erythromycin, Clarithromycin or other macrolide antibiotics	Enter "1" (Yes) or "2" (No) to indicate if the patient has received any macrolide antibiotic within the previous 24 hours.	Required field.

GLASGOW COMA SCORE
Dates after the Date of Enrollment: 7, 14, 21, 28

Complete this form on the 7th, 14th, 21st, 28th calendar date after the date of enrollment. Use the worst values for the date.

ITEM	DEFINITION	DATA RULES
Glasgow Coma Score (GCS)	Use the worksheet provided to calculate the worst GCS for this calendar date. All three components should originate from the same time point.	Required field.
1. Eye Opening Score	Enter a value (1,2,3, or 4) to indicate best response. If patient's eyes are swollen shut, estimate best response.	Required field.
2. Motor Response Score	Enter a value (1,2,3,4,5, or 6) to indicate best response.	Required field.
3. Verbal Response Score	Enter a value (1,2,3,4, or 5) to indicate best response. If patient was intubated for 24 hours prior to initial study procedures, use clinical judgment to estimate best response. If unsure, enter "3".	Required field.
4. GCS (total)	Computer calculated total Glasgow Coma Score.	Calculated value.

WEANING/VENTILATOR MONITORING
Dates after Date of Enrollment: 1-28

Complete this form on all patients on dates 1 through 28 after the date of enrollment if the patient is alive and receiving mechanical ventilation or is attempting a 48 hour period of unassisted breathing. Use information from the calendar date (midnight-midnight) shown on the computer screen.

ITEM	DEFINITION	DATA RULES
1a. Was the patient permanently withdrawn from the ventilator arm of the protocol?	Enter "1" (Yes) or "2" (No) to indicate if the patient was withdrawn from all aspects of the ventilator protocol.with no intention to return to the protocol.	Required field.
1b. Was the patient permanently withdrawn from the keto/placebo arm of the protocol?	Enter "1" (Yes) or "2" (No) to indicate whether the patient was permanently withdrawn from the keto/placebo arm of the protocol.	Required field.
2. Was study drug administered?	Enter "1" (yes) or "2" (no) to indicate if the study drug was administered on this calendar date.	Required field.
3. At 0600 the patient was on:	Indicate the ventilator mode at 0600. Enter "1" if the patient was on Volume Assist/Control or "2" if the patient was on Pressure Support. Enter "3" if the patient was on Unassisted Breathing.	Required field. If answer = "2", go to Weaning History, #5 a-h. If answer = "3", go to #6.
4. Did patient meet weaning evaluation criteria?	(a) $\geq$ 12 hours since initial protocol ventilator changes, if any. (b) $FiO_2 \leq .40$. (c) Values of both PEEP and $FiO_2 \leq$ values from the previous day (comparing reference measurement values). (d) Not receiving neuromuscular blocking agents, and without neuromuscular blockade. (e) Patient exhibiting inspiratory efforts (ventilator rate should be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts if no efforts are evident at baseline ventilator rate.	Required field. If answer = "2" or "3", go to #6, "did patient tolerate trial...."

WEANING/VENTILATOR MONITORING
(Continuation)

4a. If 4 is Yes, did the patient pass the 5 min. CPAP trial?	Enter "1" if a 5-minute CPAP trial was conducted and the patient's respiratory rate remained ≤ 35 breaths/min. Enter "2" if RR > 35 during the CPAP trial. Enter "3" if the CPAP trial was not conducted.	Required field if #4 ="1" (Yes). If answer = "2" (No), go to #8, "FiO_2".
5. Were there attempts to wean PS by 5 cm H_2O?	Enter "1" (Yes), "2" (No), or "3" (Not tried) to indicate if the patient tolerated reductins in Pressure Support to 5 cmH_2O. The criteria for tolerance are in Section 5.1.2.3 of the protocol.	Required field if #4 ="1" (Yes). If answer = "2" (No), go to #8, "FiO_2".
5a-h. Weaning History	Record initial and subsequent pressure supoort levels along with their corresponding starting times (mililitary) each time the Pressure Support Level is changed.	Required field if #5 ="1" (Yes).
6. Did patient tolerate of trial of spontaneous breathing > 2 hours?	Enter "1" (Yes), "2" (No), or "3" (Not tried) to indicate if the patient tolerated a trial of spontaneous breathing > 2 hrs.	Required field.
7. Did patient complete 48 hours of unassisted breathing?	Enter "1" (Yes), "2" (No), or "3" (Not tried) to indicate if patient completed 48 hours of "Unassisted Breathing". See section 5.1.2.6 of the protocol for definition of "Unassisted Breathing".	Required field.
RANDOM VENTILATOR CHECK	FOR ITEMS 9-13 ENTER FIRST VALUE IN FOUR HOUR INTERVAL **ON OR AFTER** THE TIME INDICATED ON THE SCREEN FOR THE RANDOM VENTILATOR CHECK IF NO TIME APPEARS, ITEMS 8-15 NOT REQUIRED	Complete only if selected time not blank. If #8 = No, skip 9-15.
8. Was patient on A/C continuously during hour hours preceding and four hours following selected time of ventilator check?	Enter "1" (Yes) or "2" (No)	
9. FiO_2	Enter the FiO_2 as a decimal (e.g. .50).	Required field.

10. Calculated delivered tidal volume (if on A/C)	Enter the inspired tidal volume (ml) set on the ventilator minus any additional tidal volume added to correct for gas compression and ventilator tube expansion (this should = the tidal volume called for by the protocol; this will not = the volume set on the ventilator unless the ventilator makes automatic adjustments for gas compression/tube expansion). Puritan-Bennett 7200's and some other ventilators make this correction automatically, in which case the tidal volume set on the ventilator should = the tidal volume called for in the protocol. For patients on these ventilators, enter the tidal volume set on the ventilator.	Required field only if patient is on A/C.
11. PEEP	Enter the level of PEEP in cmH_2O.	Required field only if patient is on A/C.
12. Set Rate	Enter the minimum respiratory rate set on the ventilator (not the actual rate, which may exceed the set rate).	Required field only if patient is on A/C.
13. Pplat Mid	Enter the middle of the three values of plateau pressure measured.	Required field only if patient is on A/C.
RANDOM VENTILATOR CHECK	FOR ITEMS 14 AND 15 ENTER THE LAST VALUE IN THE FOUR HOUR INTERVAL IMMEDIATELY BEFORE THE TIME OF THE VENTILATOR SETTING ENTERED IN ITEMS 9-13 ABOVE.	
14 a & b. pH	Enter the most recent value during the four hour interval **PRIOR** to the random ventilator check, if available. If not available, enter "."	Required field.
14b. If pH available, was set rate changed.....	Enter "1" (Yes) or "2" (No)	
15a. SpO_2	Enter the most recent pulse oximetry value **PRIOR** to the time of the random ventilator check.	Required field.
15 b. If SpO2 available was FiO2 or PEEP changed.....	Enter "1" (Yes) or "2" (No)	

BRUSSELS TABLE
Dates After the Date of Enrollment: 1-28

Complete this form using available data on each date after the date of enrollment through Date 28 or until death or discharge, whichever comes first.

In the row labeled "Day 0.5", enter data pertaining to the date of enrollment from the time immediately following initial study procedures until 2359.59 (11:59.59 pm).If no values are available during this interval, enter most recent values from before this interval.

In the rows for Days 1-28, enter data from the first through the 28th calendar date after the date of enrollment. Each of these calendar dates includes the interval from 0000 (Midnight) until 23:59.59.

Record the worst values for each of the five variables shown at the headings of the columns. If a variable was not measured on a calendar date, enter "."

Worst values are defined below:

Systolic	**Lowest** value for the date.
P/F Ratio	**Lowest** value for the date.
Platelets	**Lowest** value for the date.
Creatinine	**Highest** value for the date.
Total Bilirubin	**Highest** value for the date.

Vasopressors yes/no: Enter "1" to indicate that one or more vasopressors were used on the calendar date. Enter "2" if no vasopressors were used on the calendar date. "Vasopressor" is defined as: Dopamine $\geq$ 6 mcg/kg/min and neosynephrine, epinephrine, or levophed at any rate. Dobutamine is NOT considered a vasopressor. Vasopressors is required all days that patient is in study.

Systolic BP is required except for Day 0.5.

STUDY TERMINATION

Complete this form on each patient enrolled in the study when:

1) **The patient goes home with unassisted breathing or sustains unassisted breathing at home for ≥ 48 hours,**

or

2) **The patient dies, whichever comes first.**

If a patient is alive after day 28 but is not discharged home with unassisted breathing or on unassisted breathing for ≥ 48 hours at home, check on patient status at intervals of ≤ 30 days until condition 1 or 2 above occurs or the patient survives at any location for 180 days with or without assisted breathing.

ITEM	DEFINITION	DATA RULES
1. Patient Status	Enter "1" if the patient went home with unassisted breathing. Enter "2" if the patient died prior to discharge home with unassisted breathing or died prior to achieving unassisted breathing at home for 48 hours. Enter "3" if neither condition "1" nor condition "2" applies. E.g., if the patient went home on assisted breathing and has not achieved unassisted breathing for 48 hours. continues on assisted breathing. Enter "?" if the patient died but continues on assisted breathing!	Required field.
1a,b,c. Dates	Enter date of discharge home with unassisted breathing (if condition 1 above), date of death prior to discharge home with unassisted breathing (if condition 2, above), or of last patient contact (if condition 3 above).	Required field.
2. Was the patient able to sustain unassisted breathing for ≥ 48 hours during the first 28 days after initiation of study procedures?	Enter "1" (Yes) or "2" (No).	Required field.
2a. Date of beginning of unassisted breathing during first 28 days if sustained for ≥ 48 hours.	Enter date.	Required field if #2 = "1" (Yes).

3. Did patient return to assisted breathing during the first 28 days (if answer to #2 above is "Yes").	Enter "1" (Yes) or "2" (No).	Required field if #2 = "1" (Yes)
3a. Enter the number of calendar dates on which the patient required assisted breathing between the date in 2a and day 28.	If the patient achieved 48 hours of unassisted breathing but returned to assisted breathing before day 28, enter the number of calendar dates on which the patient received positive or negative pressure assisted breathing for ANY period of time.	Required field.
4. Was the patient discharged alive from ICU during the first 28 days?	Enter "1" (Yes) or "2" (No) to indicate if the patient was discharged alive from an intensive care unit. If the patient was transferred from one intensive care unit to another but died prior to discharge from the subsequent ICU(s), enter "2".	Required field.
4a. Date of discharge alive from ICU?	If answer to question 4 above is "Yes", enter the date the patient was discharged alive from ICU. If the patient was discharged alive from ICU more than once during the first 28 days, enter the first date.	Required field if #4 = "1" (Yes). .
5. Did the patient return to an ICU during the first 28 days?	Enter "1" (Yes) or "2" (No) to indicate if the patient was re-admitted to an ICU during the first 28 days after enrollment.	Required field.
5a. Enter the number of calendar dates on which the patient received any ICU-care between the date in "4a" and day 28.	If the answer to question "5" was "Yes" (the patient was discharged alive from ICU prior to day 28 but then was readmitted to an ICU prior to day 28), enter the number of calendar dates on which the patient received any ICU-care.	Required field.
6. Was the patient discharged alive from study hospital?	Enter "1" (Yes) or "2" (No).	Required field.
6a. Date of discharge from hospital.	Enter date.	Required field.

ADVERSE EVENT

This form should be used to capture the following events:

- Adverse Events specified by the protocol:
  Increased intracranial pressure: (> 20 mm Hg, if measured)
  GI bleed: (blood or coffee grounds per NG tube)
  Hepatitis: (AST or ALT > 500 or rise in AST or ALT > 8x baseline)
  Arrhythmias: (Episodes of ventricular tachycardia, sustained or unsustained ventricular fibrillation, supraventricular tachycardia other than sinus tachycardia but including atrial fibrillation/flutter, complete heart block or high-grade A-V block, and sinus bradycardias with rate < 50/min.)
- Serious, Unexpected and Drug Related Adverse Events
- Other Adverse Events Not Systematically captured by the protocol
- All Deaths (include cause of death under item 4)

The Adverse Event Form should not be used to report organ failure related to ARDS or the patient's underlying condition as these events are systematically captured by the protocol.

Reporting of expected side effects of Ketoconazole administration is not required as part of this protocol. However, known side effects with an increase in frequency or severity should be captured by this form.

When using this form to report a death, complete items 1-4, 9 and 10. For other fields, enter dots (.).

All serious unexpected, and drug-related adverse events should be reported to the Clinical Coordinating Center within 24 hours by phone. The investigator must submit a detailed, written report to the Clinical Coordinating Center within 5 working days. A printed copy of this form including a narrative description of the AE under item 4 may be sufficient. The Institutional Review Board should be notified based on institutional policy, but no later than 5 working days after the event is discovered.

ITEM	DEFINITION	DATA RULES
1. Date of event	Enter the date the event first occurred	Required field.
2. Time of event	Enter the time the event began	Required field.
3. Specified event	Answer "1"(Yes) or "2" (No) for items 1-5	Required field.
4. Describe event or problem	Give a brief narrative description of problem. If death, give cause.	Required field.
5. Severity of event	Select one: **mild**-Any event that is usually transient, requires no special treatment and does not interfere with the patient's daily activities. **moderate**- Any event that introduces a low level of inconvenience or concern to the patient and may interfere with daily activities. Usually ameliorated by simple measures. **severe**- Any event that if fatal or immediately life threatening, is permanently disabling, or severely incapacitating, or requires or prolongs inpatient hospitalization	Required field. Not required if using form to report a death.
6. Therapeutic intervention?	Answer "1" (Yes) or "2" (No)	Required field. Not required if using form to report a death.

7. Immediate risk of death?	Answer "1" (Yes) or "2" (No)	Required field. Not required if using form to report a death.
8. Death related to event?	Answer "1" (Yes) or "2" (No)	Required field. Not required if using form to report a death.
9. Unexpected or more severe than normally seen in ARDS?	Answer "1" (Yes), "2" (No) or "3"(Unknown) **Unexpected or more severe**- Any experience not identified by type, severity, or frequency in the current study protocol or clinical safety updates or an event unexpected in ARDS or more severe or frequent than expected in ARDS	Required field.
10. Causal relationship to study drug?	Select the answer which best describes the event's relationship to the study drug. **1=Definitely Associated**- The event follows: 1) A reasonable, temporal sequence from drug administration. 2) Cannot be explained by the known characteristics of the patient's clinical state or other therapies. 3) Evaluation of the patients clinical state indicates to the investigator that the experience is definitely related to the study drug. **2=Probably or 3=Possibly Associated:** The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected. **4=Probably Not Associated:** The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patients clinical state or other therapies. **5=Definitely Not Associated:** The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient. **6=Uncertain Association:** The event does not meet any of the criteria previously outlined.	Required field.
11. Study drug discontinued?	Answer "1"(Yes) or "2"(No) if the study drug was discontinued related to this event.	Required field. Not required if using form to report a death.
12. Withdrawn from ventilator?	Answer "1"(Yes) or "2"(No) if the patient was withdrawn from the ventilator because of this event.	Required field. Not required if using form to report a death.

13. Outcome to date	Ongoing assessment. The final answer should be reflective of the status of the event at death, discharge, or study day 28 (whichever comes first). If the answer selected is "1"(recovered), list the date of recovery from the event.	Required field. Not required if using form to report a death.