Summary of Protocol Amendments

The study had a total of 6 amendments submitted to and approved by the IRB. All were minor and received expedited approval.

The original protocol was approved on 8/20/12. Patients were to be enrolled and randomized ***at the time of intubation***. However, the logistical issue of obtaining informed consent around the time of intubation made it impossible to enroll ***any*** patients. Since the majority of patients with hypoxemic respiratory failure initially were treated with face mask NIV, we amended the protocol (Amendment # 1, approved on 2/11/2013) to enroll patients while they were receiving noninvasive ventilation. This allowed adequate time so that all patients in the trial were enrolled before endotracheal intubation, while they were receiving face mask NIV.

Amendment #2 intended to broaden the study population from hypoxemic to all types of respiratory failure (i.e. hypoxemic, ventilator and shock). This amendment was approved on 5/22/2013. However, over the complete course of the study, the ***only*** patients ever enrolled in the trial had hypoxemic respiratory failure, specifically ARDS.

Amendment #3 involved personnel changes that reflected supportive staff that had left our institution and therefore were no longer involved in the study. This amendment was approved on 6/27/2013.

Amendment #4 involved personnel changes that reflected supportive staff that had left our institution and therefore were no longer involved in the study. This amendment was approved on 7/10/2013.

Amendment #5 involved personnel changes that reflected supportive staff that had left our institution and therefore were no longer involved in the study. This amendment was approved on 2/27/2015.

Amendment #6 corrected a mathematical error in the statistical analysis plan. This amendment was approved on 4/28/2015.

ORIGINAL PROTOCOL

Title: Mechanical Ventilation in Patients with Shock and/or Hypoxemic Respiratory Failure: A Comparison of Endotracheal Intubation and Non Invasive Ventilation via a Helmet Device

Date: August 20, 2012

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Background:

Respiratory failure characterized by acute deterioration of gas exchange is often treated with endotracheal intubation and mechanical ventilation (figure 1). Similarly, the classic teaching in the treatment of patients with shock required intubation to "take away the work of breathing." Although, the institution of mechanical ventilation is considered life saving, the associated complications of tracheal stenosis,[i] ventilator associated pneumonia,[ii] barotrauma[iii], and neuromuscular weakness[iv] are not without considerable morbidity and mortality.

Over the past years non-invasive ventilation delivered by facemask (figure 2) has become an attractive option to improve gas exchange without an artificial airway, thus preserving airway defense mechanisms, speech and swallow capabilities, and allowing interaction between patients and care providers while avoiding the complications of endotracheal intubation. This strategy of non-invasive ventilation has demonstrated significant mortality benefit in patients with hypercapnic respiratory failure from COPD,[v,vi] acute cardiogenic pulmonary edema,[vii,viii] and hypoxemic respiratory failure in immunocompromised patients.[ix,x] In addition to successfully avoiding endotracheal intubation, non-invasive ventilation has been used to successfully liberate patients from mechanical ventilation via an endotracheal tube to extubation and transition to non-invasive mechanical ventilation. As such non-invasive ventilation has been a standard therapy for certain types of respiratory failure for more than 15 years.

Despite the advantages of non-invasive ventilation, up to forty percent of patients fail facemask trials in part because of mask intolerance and severity of disease.[xi] Some common complications contributing to mask intolerance include claustrophobia, nasal bridge skin necrosis, acneiform rash, and conjunctivitis and if present prompt premature

discontinuation of non-invasive ventilation and endotracheal intubation. Further limitation to facemask non-invasive ventilation is that the seal integrity is lost when higher pressures are required. For example, non-invasive ventilation via a nasal or full face mask typically begins to demonstrate leaks when the pressures required exceed 15-20 cm H2O. Unfortunately, certain types of respiratory failure such as that due to hypoxemia or shock may require such higher pressures. In an attempt to improve patient tolerability and deliver higher pressures, a transparent helmet has been proposed as a novel interface for non-invasive ventilation. The helmet is made of transparent latex-free PVC with a soft collar that adheres to the neck ensuring a seal when inflated (figure 3). It encloses the entire head and neck of the patient and is secured by two armpit braces. The design of the helmet confers some important advantages: 1) the transparency allows the patient to interact with the environment; 2) the lack of contact to the face lowers the risk of skin necrosis; 3) the helmet avoids problems of leaking with higher airway pressures that are seen with the face mask. Accordingly, it can be used to deliver airway pressures up to 40 cm H2O without leaking. Such higher pressures are more often needed to provide effective mechanical ventilation to patients with hypoxemic respiratory failure and/or shock; 4) it can be applied to any patient regardless of facial contour.[xii]

The helmet interface has been compared to face mask in small case control studies for the treatment of hypoxemic respiratory failure (AHRF). While both interfaces have similar improvement of oxygenation, intubation rates, and mortality, the helmet had good tolerability that allowed for longer continuous application of noninvasive ventilation and in some cases sustained improvement of gas exchange even after discontinuation of therapy in immunocompromised patients,[xiii,xiv] non-cardiogenic acute hypoxemic respiratory failure,[xv] and acute cardiogenic pulmonary edema[xvi]. Given this initial experience and success with helmet ventilation, larger randomized studies comparing this intervention to endotracheal intubation in patients with AHRF and shock need to be done to understand the potential benefits of helmet ventilation.

Purpose:

The objective of our study is to evaluate the efficacy of helmet ventilation as compared with endotracheal intubation in patients with acute hypoxemic respiratory failure and evidence of shock, specifically assessing improvement of oxygenation, need for mechanical ventilation, and rates of ICU complications.

Hypothesis:

Noninvasive positive pressure ventilation delivered by helmet will improve oxygenation and avoid the need for endotracheal intubation in some patients with hypoxemic respiratory failure and shock. This may result in improved outcomes with decreased rates of ICU related complications.

Methods:

Study Design

We propose a single center randomized controlled trial studying the efficacy of noninvasive ventilation delivered via helmet in patients with acute hypoxemic respiratory failure

(AHRF) and shock. All patients admitted to the adult medical intensive care unit at the University of Chicago will be screened for eligibility.

Subject Inclusion

Patients aged ≥18 years of age who require endotracheal intubation and mechanical ventilation for non-cardiogenic acute hypoxemic respiratory failure (AHRF) and/or shock will be eligible for enrollment. Additional inclusion criteria include:

- Intact airway protective gag reflex
- Able to follow instructions (e.g. squeeze hand on command, eye contact with care provider, stick out tongue on command)

Acute hypoxemic respiratory failure will be defined as moderate to severe dyspnea, pulmonary infiltrates, and PaO2/FIO2 ratio less than 300.

Shock will be defined as mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite administration of intravenous fluids (at least 1000 ml of crystalloids or 500 ml of colloids, unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter)[xvii].

Subject exclusion

The criteria for exclusion include:

- Cardiopulmonary arrest
- Glascow coma scale <8
- Absence of airway protective gag reflex
- Elevated intracranial pressure
- Tracheostomy
- Upper airway obstruction
- Pregnancy.
- Patients who refuse to undergo endotracheal intubation, whatever the initial therapeutic approach

Helmet group

Patients randomized to the intervention group will receive noninvasive ventilation delivered via a latex-free helmet connected to the ventilator by conventional tubing. The helmet contains the head and the neck of the patient, has a rigid ring and is secured by two armpit braces; a soft collar adheres to the neck and ensures a sealed connection once the helmet is inflated. The rigid ring has an opening for the passage of nasogastric tube (if needed).

Patients randomized to helmet ventilation will either be connected immediately to this device de novo or extubated within the first 24 hours of their respiratory failure. In this latter case they will have mechanical ventilation via the endotracheal tube substituted

immediately with mechanical ventilation via the helmet. The ventilator delivers pressure through the helmet inlet tubing and exhaled breaths are released though the helmet outlet tubing. The positive end-expiratory pressure (PEEP) will be increased in increments of 2-3 cmH_20 to improve peripheral oxygen saturation of at least 90% at an inspired oxygen requirement (FiO2) of ≤ 60%. Pressure support will be increased in increments of 2-3cmH_20 to obtain respiratory rate <25 breaths/min, disappearance of accessory muscle activity, and exhaled tidal volume of 6-8mL/kg of ideal body weight. After application of the helmet, arterial blood gas sampling will be utilized to follow gas-exchange; this is a part of usual care for the management of patients with acute hypoxemic respiratory failure and/or shock. Noninvasive support will be reduced progressively in accordance to clinical improvement and will be discontinues if patient maintains respiratory rate <30breaths/min and PaO2 >75mm Hg with FiO2 0.5 without ventilatory support. If endotracheal intubation is required, the helmet will be removed and the patient will be intubated without delay.

Predetermined criteria for intubation will include:

- Inability to achieve an arterial oxygen saturation by pulse oximetry or arterial blood gas ≥ 88%
- Respiratory rate > 36 breaths/min
- Loss of ability to maintain ventilation to keep arterial blood pH ≥ 7.20
- Loss of protective airway gag reflex (seizure disorder, severe encephalopathy, Glascow Coma Scale <8)
- Respiratory or cardiac arrest
- Intolerance of the helmet
- Development of airway bleeding, persistent vomiting, and development of copious tracheal secretions.

If an enrolled patient is randomized to helmet noninvasive ventilation after intubation, they will undergo interruption of sedation and extubation with immediate placement of the helmet and initiation on noninvasive ventilation. Early initiation of noninvasive ventilation in patients who do not meet start criteria for extubation to facilitate early extubation has been associated with decreased mortality, ventilator associated pneumonia, and ventilator days.[xviii]

Control Group

Patients assigned to the conventional ventilation group will undergo intubation with cuffed endotracheal tubes. The initial ventilator setting will be assist-control mode with delivery of tidal volumes of 6-8mL/kg of ideal body weight, and titration of PEEP to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). Daily interruption of sedation, awakening and breathing trials will be performed per primary team.

Data Collection:

All study patients during hospitalization will have:

1. General Data collection:

- Demographic information, including medical history number, age, race, gender
- Details of current illness, including diagnosis, interventions, radiology imaging, laboratory results. Severity of illness scoring will occur (APACHE II – see Appendix 1) as well as daily serial organ function assessments (see Appendix 2).
- Baseline medical/surgical/functional status history
- Dates of mechanical ventilation, ICU and hospital length of stay
- Discharge Location

2. Daily Data Collection
    - Daily mental status evaluations, including the Richmond-Agitation-Sedation Scale (Appendix 3) and the Confusion Assessment Method (Appendix 4)
    - Muscular strength testing by physical therapists on ICU admission, ICU discharge and hospital discharge

3. All patients after discharge
    - Telephone interviews at 1, 3, 6, and 12 months after discharge (Appendix 7)
        - Lasting approximately 5 minutes in duration
        - Assessing self-reported performance of ADL's
        - Reviewing need for medical care, including re-hospitalization, rehabilitation, physician outpatient visits
        - Current weight and nutritional status

Endpoints:

Primary

- Improvement of oxygenation (defined as $PaO_2/FiO_2 \geq 200$ or increase from baseline by 100)
- Duration of mechanical ventilation via endotracheal tube
- Percentage of patients requiring endotracheal intubation
- ICU length of stay
- Hospital Mortality

Secondary

- Duration of mechanical ventilation via either endotracheal tube or non-invasive helmet
- ICU complications
    - Ventilator associated pneumonia
    - Barotrauma
    - Gastrointestinal hemorrhage
    - Pulmonary embolism
    - Sacral Decubitus ulcer
    - Delirium
    - ICU acquired weakness
- Hospital length of stay
- Readmission to intensive care unite

- Discharge location (home, skilled nursing facility, nursing home, rehabilitation

Risks and Benefits

The risks of this study are limited beyond those experienced during routine critical care of an intubated, mechanically ventilated patient.

- Non-invasive mechanical ventilation may be associated with failure to stabilize respiratory gas exchange. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with failure to stabilize circulatory shock. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with aspiration. Accordingly, only patients with an intact airway protective gag reflex will be eligible for enrollment. Aspiration is also known to occur in patients who have an endotracheal tube. Care will be taken to monitor all patients in this study for this occurrence.

Figure 1: Endotracheal Tube

Figure 2: Facemask

Figure 3: Helmet

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Appendix 1: ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORING SYSTEM[xix]

			+4	+3	+2	+1	0	+1	+2	+3	+4	MINIMUM	MAXIMUM	SCORE
PHYSIOLOGY	VITAL SIGNS	temp °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9			
		BPs/d												
		mean	≥160	130-159	110-129		70-109		50-69		≤49			
		HR(vent)	≥180	140-179	110-139		70-109		55-69	40-54	≤39			
		RR(total)	≥50	35-49		25-34	12-24	10-11	6-9		≤5			
	OXYGENATION	*ABC $Fi0_2$	IF $Fi0_2$ <50 USE $Pa0_2$ ONLY. IF $Fi0_2 \geq 50$ DO NOT USE $Pa0_2$ CALCULATE $AaD0_2$											
		$Pa0_2$					>70	61-70		55-60	<55			
		$PaC0_2$												
		pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15			
		$AaD0_2$	≥500	350-499	200-349		<200							
		serum $C0_2$	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15			
	LABS	Na+	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110			
		K+	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5			
		**Creat	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6					
		Hct	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20			
		WBC	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1			

GLASGOW COMA	NEURO	APACHE	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	SCORE
		GC SCORE	15	14	13	12	11	10	9	8	7	6	5	4	3	
		(Circle appropriate score for each category)	EYE: 4 SPONTANEOUS; 3 VERBAL COMMAND; 2 PAINFUL STIMULI; 1 NO RESPONSE			VERBAL NON-INTUBATED: 5 ORIENTED AND TALKS; 4 DISORIENTED & TALKS; 3 INAPPROPRIATE WORDS; 2 INCOMPREHENSIBLE SOUNDS; 1 NO RESPONSE			VERBAL INTUBATED: 5 SEEMS ABLE TO TALK; 3 QUESTIONABLE ABILITY TO TALK; 1 GENERALLY UNRESPONSIVE			MOTOR: 6 VERBAL COMMAND; 5 LOCALIZES TO PAIN; 4 WITHDRAWS TO PAIN; 3 DECORTICATE; 2 DECEREBRATE; 1 NO RESPONSE			

AGE & HEALTH	AGE		0	+2	+3	+5	+6	SCORE
		Age Score	≤44	45-54	55-64	65-74	≥75	
	CHRONIC HEALTH							SCORE
		CH Score						
		CH Scale	+5			+2		
			NON-OP or EMERGENCY-OP			ELECTIVE POST-OP		

WITH ANY 1 OF THE FOLLOWING CHRONIC CONDITIONS PRIOR TO THIS ILLNESS:

IF APPLIES, CIRCLE THE NUMBER CORRESPONDING TO THE CONDITION.

1 LIVER – CIRRHOSIS WITH PORTAL HYPERTENSION or ENCEPHALOPATHY
2 CVASC – CLASS IV ANGINA or AT REST or MIN SELF-CARE ACTIVITIES
3 PULM – CHRONIC HYPOX or HYPERCAP or POLYCYTHEMIA or PHT >40 MMHG or RESPIRATOR DEPENDENT
4 KIDNEY – CHRONIC PERITONEAL or HEMODIALYSIS
5 IMMUNE – IMMUNO COMPROMISED HOST

*IF NO ABG USE SERUM CO_2

**IF IN ARF DOUBLE THE CREATININE POINT SCORE

APACHE II	
Physiology Points	
Glasgow points	
Chronic Health Points	
Age Points	
APACHE SCORE (TOTAL)	

Appendix 2: Serial Organ Function Assessment[18][xx]

SOFA score	1	2	3	4
			Respiration with respiratory support	
Respiration with respiratory support PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
Coagulation Platelets $x10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dl	1.2-1.9	2-5.9	6-11.9	> 12
Cardiovascular Hypotension >15 or (doses in ug/kg·min) cathecolamines> 0,1	MAP < 70mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine > 5 or cathecolamines ≤ 0.1	Dopamine
Neurologic Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal Creatinine mg/dl or Urine output ml/zi	1.2-1.9	2-3.4	3.5-4.9 (200-500)	> 5 (< 200)

Appendix 3. Richmond agitation–sedation scale[xxi]

TABLE 1. RICHMOND AGITATION–SEDATION SCALE

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under DESCRIPTION)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1).
   Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2).
   Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score −4).
   Patient has no response to voice or physical stimulation (score −5).

324 APPENDIX 4: Confusion Assessment Method (CAM-ICU)[xxii]

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course*		
A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?		
II. Inattention†		
Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?		
III. Disorganized thinking		
Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up this many fingers. (Examiner holds 2 fingers in front of the patient.) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)		
IV. Altered level of consciousness		
Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environment and interacts appropriately Vigilant: hyperalert Lethargic: drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4): Yes___ No___		

*The scores included in the 10-point RASS range from a high of 4 (combative) to a low of −5 (deeply comatose and unresponsive). Under the RASS system, patients who were spontaneously alert, calm, and not agitated were scored at 0 (neutral zone). Anxious or agitated patients received a range of scores depending on their level of anxiety: 1 for anxious, 2 for agitated (fighting ventilator), 3 for very agitated (pulling on or removing catheters), or 4 for combative (violent and a danger to staff). The scores −1 to −5 were assigned for patients with varying degrees of sedation based on their ability to maintain eye contact: −1 for more than 10 seconds, −2 for less than 10 seconds, and −3 for eye opening but no eye contact. If physical stimulation was required, then the patients were scored as either −4 for eye opening or movement with physical or painful stimulation or −5 for no response to physical or painful stimulation. The RASS has excellent interrater reliability and intraclass correlation coefficients of 0.95 and 0.97, respectively, and has been validated against visual analog scale and geropsychiatric diagnoses in 2 ICU studies.[37,38]

†In completing the visual ASE, the patients were shown 5 simple pictures (previously published[34]) at 3-second intervals and asked to remember them. They were then immediately shown 10 subsequent pictures and asked to nod "yes" or "no" to indicate whether they had or had not just seen each of the pictures. Since 5 pictures had been shown to them already, for which the correct response was to nod "yes," and 5 others were new, for which the correct response was to shake their heads "no," patients scored perfectly if they achieved 10 correct responses. Scoring accounted for either errors of omission (indicating "no" for a previously shown picture) or for errors of commission (indicating "yes" for a picture not previously shown). In completing the auditory ASE, patients were asked to squeeze the rater's hand whenever they heard the letter *A* during the recitation of a series of 10 letters. The rater then read 10 letters from the following list in a normal tone at a rate of 1 letter per second: *S, A, H, E, V, A, A, R, A, T*. A scoring method similar to that of the visual ASE was used for the auditory ASE testing.

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Appendix 5: Telephone Survey

We would like to ask you (the PATIENT) some questions about your (the PATIENT'S) health:

- In general, how would you say your health is now?

☐ Excellent
☐ Very good
☐ Good
☐ Fair
☐ Poor

- Sometimes it is necessary to spend most of the day in bed. Is this true for you now?

☐ Yes
☐ No
☐ Don't know

- Have you fallen since discharge/since the last time our team talked with you by phone?

☐ Yes
☐ No
☐ Don't know

- If you have fallen since discharge/since the last time our team talked with you by phone, did you see a doctor or go to an emergency department to get checked out after the fall?

☐ Yes
☐ No
☐ Don't know

- Have you been admitted to a hospital since your hospital discharge/the last time our team spoke with you by phone?

☐ Yes
☐ No
☐ Don't know

- Since discharge or the last time our team spoke with you, have you spent any time living in a nursing home, group home/assisted living facility, or rehabilitation facility?

☐ Yes
☐ No
☐ Don't know

- Did (you/PATIENT) need help washing or bathing (yourself/HIMSELF/HERSELF)?

□ Yes
□ No
□ Don't know

- Do you need help dressing and undressing?

□ Yes
□ No
□ Don't know

- Do you need help eating, including cutting food?

□ Yes
□ No
□ Don't know

- Do you need help getting in and out of the bed and a chair?

□ Yes
□ No
□ Don't know

- Do you need help cleaning yourself for either bowel or bladder functions?

□ Yes
□ No
□ Don't know

- Do you sometimes have an accident with your bowels either during the day or night?

□ Yes
□ No
□ Don't know

- Do you sometimes wet yourself either during the day or night?

□ Yes
□ No
□ Don't know

Do you do the following on your own (NO HELP), with some help, or are you unable to:

- Use the telephone, including looking up and dialing numbers, and answering the phone?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Get to places out of walking distance by using public transportation or driving your car?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Shop for groceries or clothes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Prepare, serve and provide meals for yourself?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do light housework, such as dusting or doing dishes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Take pills or medicines in the correct amounts and at the correct times?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Handle your own money, including writing checks and paying bills?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do your laundry?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Walk across the room either on your own or with a cane or walker?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

The following questions are about your living situation.

- Where do you currently live?
  - ☐ Your (the PATIENT'S) own apartment or house
  - ☐ A relative or friend's apartment or house
  - ☐ A nursing home, group home/assisted living facility, or long-term care facility
  - ☐ A homeless shelter
  - ☐ Other_____

- How many people live with you (the PATIENT)? _____

- What is your current weight? _____

- If you (the PATIENT) need extra help when you get home from the hospital, is there someone who can help you (the PATIENT)?

☐ No
☐ Yes

If "Yes", what is this person's relationship to you (the PATIENT)?

Spouse	1	Neighbor or landlord		7
Other partner	2	Other friend	8	
Child	3	Floor nurse	9	
Parent	4	Visiting nurse	10	
Brother or sister	5	Home attendant or health aide	11	
Other relative	6	Some other person	12	
(specify)		(specify)		

- What does this person do during the day if he/she is not helping you (the PATIENT)?
  - ☐ Work outside the home without pay
  - ☐ Work outside the home for pay
  - ☐ Work in the home without pay
  - ☐ Work in the home for pay
  - ☐ Other (specify) _____

- How old is this person?

☐ Under 18	☐ 75-84
☐ 18-49	☐ 85-89
☐ 50-64	☐ 90 or greater
☐ 65-74	

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PROTOCOL AMENDMENT 1

Title: Noninvasive Ventilation in Patients with Shock and/or Hypoxemic Respiratory Failure: A Comparison of Face mask versus Helmet interface

Date: January 16, 2013

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Background:

Respiratory failure characterized by acute deterioration of gas exchange is often treated with endotracheal intubation and mechanical ventilation (figure 1). Similarly, the classic teaching in the treatment of patients with shock required intubation to "take away the work of breathing." Although, the institution of mechanical ventilation is considered life saving, the associated complications of tracheal stenosis,[xxii] ventilator associated pneumonia,[xxii] barotrauma[xxii], and neuromuscular weakness[xxii] are not without considerable morbidity and mortality.

Over the past years non-invasive ventilation delivered by facemask (figure 2) has become an attractive option to improve gas exchange without an artificial airway, thus preserving airway defense mechanisms, speech and swallow capabilities, and allowing interaction between patients and care providers while avoiding the complications of endotracheal intubation. This strategy of non-invasive ventilation has demonstrated significant mortality benefit in patients with hypercapnic respiratory failure from COPD,[xxii,xxii] acute cardiogenic pulmonary edema,[xxii,xxii] and hypoxemic respiratory failure in immunocompromised patients.[xxii,xxii] In addition to successfully avoiding endotracheal intubation, non-invasive ventilation has been used to successfully liberate patients from mechanical ventilation via an endotracheal tube to extubation and transition to non-invasive mechanical ventilation. As such non-invasive ventilation has been a standard therapy for certain types of respiratory failure for more than 15 years.

Despite the advantages of non-invasive ventilation, up to forty percent of patients fail facemask trials in part because of mask intolerance and severity of disease.[xxii] Some common complications contributing to mask intolerance include claustrophobia, nasal bridge skin necrosis, acneiform rash, and conjunctivitis and if present prompt premature

discontinuation of non-invasive ventilation and endotracheal intubation. Further limitation to facemask non-invasive ventilation is that the seal integrity is lost when higher pressures are required. For example, non-invasive ventilation via a nasal or full face mask typically begins to demonstrate leaks when the pressures required exceed 15-20 cm H2O. Unfortunately, certain types of respiratory failure such as that due to hypoxemia or shock may require such higher pressures. In an attempt to improve patient tolerability and deliver higher pressures, a transparent helmet has been proposed as a novel interface for non-invasive ventilation. The helmet is made of transparent latex-free PVC with a soft collar that adheres to the neck ensuring a seal when inflated (figure 3). It encloses the entire head and neck of the patient and is secured by two armpit braces. The design of the helmet confers some important advantages: 1) the transparency allows the patient to interact with the environment; 2) the lack of contact to the face lowers the risk of skin necrosis; 3) the helmet avoids problems of leaking with higher airway pressures that are seen with the face mask. Accordingly, it can be used to deliver airway pressures up to 40 cm H2O without leaking. Such higher pressures are more often needed to provide effective mechanical ventilation to patients with hypoxemic respiratory failure and/or shock; 4) it can be applied to any patient regardless of facial contour.[xxii]

The helmet interface has been compared to face mask in small case control studies for the treatment of hypoxemic respiratory failure (AHRF). While both interfaces have similar improvement of oxygenation, intubation rates, and mortality, the helmet had good tolerability that allowed for longer continuous application of noninvasive ventilation and in some cases sustained improvement of gas exchange even after discontinuation of therapy in immunocompromised patients,[xxii,xxii] non-cardiogenic acute hypoxemic respiratory failure,[xxii] and acute cardiogenic pulmonary edema[xxii]. Given this initial experience and success with helmet ventilation, larger randomized studies comparing this intervention to face mask in patients with AHRF and shock need to be done to understand the potential benefits of helmet ventilation.

Purpose:
The objective of our study is to evaluate the efficacy of helmet ventilation as compared with face mask ventilation in patients with acute hypoxemic respiratory failure and evidence of shock, specifically assessing improvement of oxygenation, need for mechanical ventilation, and rates of ICU complications.

Hypothesis:
Noninvasive positive pressure ventilation delivered by helmet will improve oxygenation and avoid the need for endotracheal intubation in some patients with hypoxemic respiratory failure and shock. This may result in improved outcomes with decreased rates of ICU related complications.

Methods:
Study Design

We propose a single center randomized controlled trial studying the efficacy of noninvasive ventilation delivered via helmet in patients with acute hypoxemic respiratory failure (AHRF) and shock. All patients admitted to the adult medical intensive care unit at the University of Chicago will be screened for eligibility.

Subject Inclusion
Patients aged ≥18 years of age who require noninvasive mechanical ventilation via facemask for ≥ 8 hours for the management of non-cardiogenic acute hypoxemic respiratory failure (AHRF) and/or shock will be eligible for enrollment. Additional inclusion criteria include:

- Intact airway protective gag reflex
- Able to follow instructions (e.g. squeeze hand on command, eye contact with care provider, stick out tongue on command)

Acute hypoxemic respiratory failure will be defined as moderate to severe dyspnea, pulmonary infiltrates, and PaO2/FIO2 ratio less than 300.

Shock will be defined as mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite administration of intravenous fluids (at least 1000 ml of crystalloids or 500 ml of colloids, unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter)[xxii].

Subject exclusion
The criteria for exclusion include:
- Cardiopulmonary arrest
- Glascow coma scale <8
- Absence of airway protective gag reflex
- Elevated intracranial pressure
- Tracheostomy
- Upper airway obstruction
- Pregnancy.
- Patients who refuse to undergo endotracheal intubation, whatever the initial therapeutic approach

Helmet group
Patients randomized to the intervention group will switch from noninvasive ventilation delivered via facemask to a latex-free helmet connected to the ventilator by conventional tubing. The helmet contains the head and the neck of the patient, has a rigid ring and is secured by two armpit braces; a soft collar adheres to the neck and ensures a sealed connection once the helmet is inflated. The rigid ring has an opening for the passage of nasogastric tube (if needed).

Patients randomized to helmet ventilation will have the helmet applied and connected to a ventilator. The ventilator delivers pressure through the helmet inlet tubing and exhaled breaths are released though the helmet outlet tubing. The positive end-expiratory pressure (PEEP) will be increased in increments of 2-3 cmH_20 to improve peripheral oxygen saturation of at least 90% at an inspired oxygen requirement (FiO2) of ≤ 60%. Pressure support will be increased in increments of 2-3cmH_20 to obtain respiratory rate <25 breaths/min and disappearance of accessory muscle activity. After application of the helmet, arterial blood gas sampling will be utilized to follow gas-exchange; this is a part of usual care for the management of patients with acute hypoxemic respiratory failure and/or shock. Noninvasive support will be reduced progressively in accordance to clinical improvement and will be discontinued if patient maintains respiratory rate <30breaths/min and PaO2 >75mm Hg with FiO2 0.5 without ventilatory support. If endotracheal intubation is required, the helmet will be removed and the patient will be intubated without delay.

Control Group
Patients assigned to the control group will continue to wear face mask for delivery of noninvasive ventilation. The expiratory positive airway pressure will be titrated in 2-3cm H20 increments to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). The inspiratory positive airway pressure will be titrated as well to decrease tachypnea (<25 breaths/min) and improve work of breathing. Blood gas analysis will be obtained to determine appropriate gas exchange.

Predetermined criteria for intubation for both groups will include:

- Inability to achieve an arterial oxygen saturation by pulse oximetry or arterial blood gas ≥ 88%
- Respiratory rate > 36 breaths/min
- Loss of ability to maintain ventilation to keep arterial blood pH ≥ 7.20
- Loss of protective airway gag reflex (seizure disorder, severe encephalopathy, Glascow Coma Scale <8)
- Respiratory or cardiac arrest
- Intolerance of the helmet or face mask
- Development of airway bleeding, persistent vomiting, and development of copious tracheal secretions.

Patients who require endotracheal intubation will have initial ventilator settings of assist-control mode with delivery of tidal volumes of 6mL/kg of ideal body weight, and titration of PEEP to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). Daily interruption of sedation, awakening and breathing trials will be performed per primary team.

If an enrolled patient is randomized to helmet noninvasive ventilation after intubation, they will undergo interruption of sedation and extubation with immediate placement of the helmet and initiation on noninvasive ventilation. Early initiation of noninvasive ventilation

in patients who do not meet start criteria for extubation to facilitate early extubation has been associated with decreased mortality, ventilator associated pneumonia, and ventilator days.[xxii]

Data Collection:
All study patients during hospitalization will have:

1. General Data collection:
    - Demographic information, including medical history number, age, race, gender
    - Details of current illness, including diagnosis, interventions, radiology imaging, laboratory results. Severity of illness scoring will occur (APACHE II – see Appendix 1) as well as daily serial organ function assessments (see Appendix 2).
    - Baseline medical/surgical/functional status history
    - Dates of mechanical ventilation, ICU and hospital length of stay
    - Discharge Location

2. Daily Data Collection
    - Daily mental status evaluations, including the Richmond-Agitation-Sedation Scale (Appendix 3) and the Confusion Assessment Method (Appendix 4)
    - Muscular strength testing by physical therapists on ICU admission, ICU discharge and hospital discharge

3. All patients after discharge
    - Telephone interviews at 1, 3, 6, and 12 months after discharge (Appendix 7)
        - Lasting approximately 5 minutes in duration
        - Assessing self-reported performance of ADL's
        - Reviewing need for medical care, including re-hospitalization, rehabilitation, physician outpatient visits
        - Current weight and nutritional status

Endpoints:
Primary

- Percentage of patients requiring endotracheal intubation
- Duration of mechanical ventilation
    - Noninvasive ventilation via face mask or helmet
    - Invasive mechanical ventilation via endotracheal tube
- ICU length of stay
- Hospital Mortality
- Improvement of oxygenation (defined as $PaO_2/FiO_2 \geq 200$ or increase from baseline by 100)

Secondary

- ICU complications
    - Ventilator associated pneumonia
    - Barotrauma
    - Gastrointestinal hemorrhage
    - Pulmonary embolism
    - Sacral Decubitus ulcer
    - Delirium
    - ICU acquired weakness
- Hospital length of stay
- Readmission to intensive care unit
- Discharge location (home, skilled nursing facility, nursing home, rehabilitation

Risks and Benefits

The risks of this study are limited beyond those experienced during routine critical care of an intubated, mechanically ventilated patient.

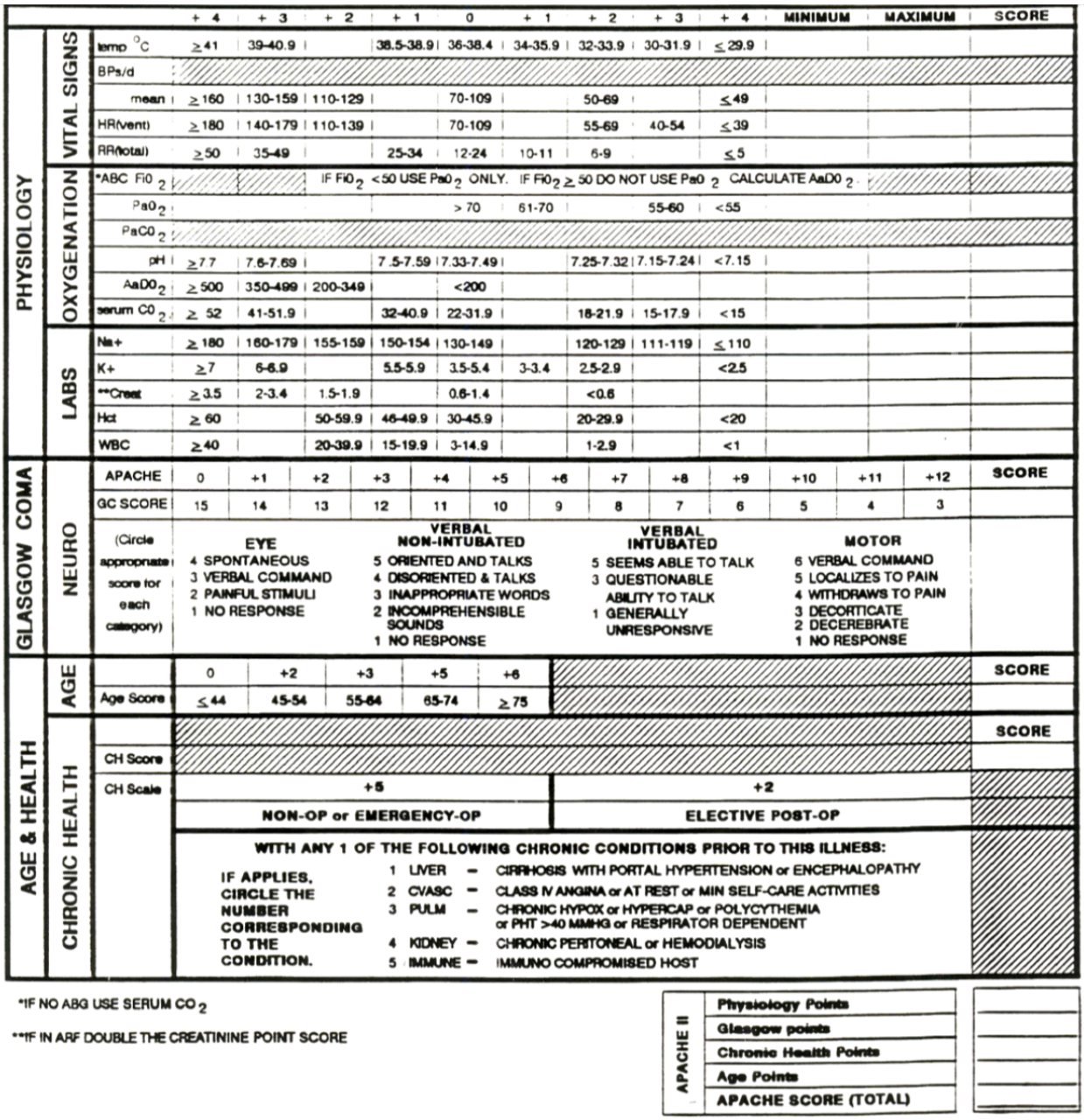
- Non-invasive mechanical ventilation may be associated with failure to stabilize respiratory gas exchange. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with failure to stabilize circulatory shock. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with aspiration. Accordingly, only patients with an intact airway protective gag reflex will be eligible for enrollment. Aspiration is also known to occur in patients who have an endotracheal tube. Care will be taken to monitor all patients in this study for this occurrence.

Figure 1: Endotracheal Tube

Figure 2: Facemask

Figure 3: Helmet

Appendix 1: ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORING SYSTEM[xxii]



			+4	+3	+2	+1	0	+1	+2	+3	+4	MINIMUM	MAXIMUM	SCORE
PHYSIOLOGY	VITAL SIGNS	temp °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9			
		BPs/d												
		mean	≥160	130-159	110-129		70-109		50-69		≤49			
		HR(vent)	≥180	140-179	110-139		70-109		55-69	40-54	≤39			
		RR(total)	≥50	35-49		25-34	12-24	10-11	6-9		≤5			
	OXYGENATION	*ABC FiO_2	IF FiO_2 <50 USE PaO_2 ONLY. IF FiO_2 ≥50 DO NOT USE PaO_2 CALCULATE $AaDO_2$											
		PaO_2					>70	61-70		55-60	<55			
		$PaCO_2$												
		pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15			
		$AaDO_2$	≥500	350-499	200-349		<200							
		serum CO_2	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15			
	LABS	Na+	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110			
		K+	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5			
		**Creat	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6					
		Hct	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20			
		WBC	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1			

		APACHE	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	SCORE
GLASGOW COMA	NEURO	GC SCORE	15	14	13	12	11	10	9	8	7	6	5	4	3	

(Circle appropriate score for each category)

EYE	VERBAL NON-INTUBATED	VERBAL INTUBATED	MOTOR
4 SPONTANEOUS	5 ORIENTED AND TALKS	5 SEEMS ABLE TO TALK	6 VERBAL COMMAND
3 VERBAL COMMAND	4 DISORIENTED & TALKS	3 QUESTIONABLE ABILITY TO TALK	5 LOCALIZES TO PAIN
2 PAINFUL STIMULI	3 INAPPROPRIATE WORDS	1 GENERALLY UNRESPONSIVE	4 WITHDRAWS TO PAIN
1 NO RESPONSE	2 INCOMPREHENSIBLE SOUNDS		3 DECORTICATE
	1 NO RESPONSE		2 DECEREBRATE
			1 NO RESPONSE

			0	+2	+3	+5	+6	SCORE
AGE & HEALTH	AGE	Age Score	≤44	45-54	55-64	65-74	≥75	

			+5	+2	SCORE
AGE & HEALTH	CHRONIC HEALTH	CH Score			
		CH Scale	NON-OP or EMERGENCY-OP	ELECTIVE POST-OP	

WITH ANY 1 OF THE FOLLOWING CHRONIC CONDITIONS PRIOR TO THIS ILLNESS:

IF APPLIES, CIRCLE THE NUMBER CORRESPONDING TO THE CONDITION.

1 LIVER – CIRRHOSIS WITH PORTAL HYPERTENSION or ENCEPHALOPATHY
2 CVASC – CLASS IV ANGINA or AT REST or MIN SELF-CARE ACTIVITIES
3 PULM – CHRONIC HYPOX or HYPERCAP or POLYCYTHEMIA or PHT >40 MMHG or RESPIRATOR DEPENDENT
4 KIDNEY – CHRONIC PERITONEAL or HEMODIALYSIS
5 IMMUNE – IMMUNO COMPROMISED HOST

*IF NO ABG USE SERUM CO_2

**IF IN ARF DOUBLE THE CREATININE POINT SCORE

APACHE II	
Physiology Points	
Glasgow points	
Chronic Health Points	
Age Points	
APACHE SCORE (TOTAL)	

Appendix 2: Serial Organ Function Assessment[18][xxii]

SOFA score	1	2	3	4
			Respiration with respiratory support	
Respiration with respiratory support PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
Coagulation Platelets $x10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dl	1.2-1.9	2-5.9	6-11.9	> 12
Cardiovascular Hypotension >15 or (doses in ug/kg·min) cathecolamines> 0,1	MAP < 70mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine > 5 or cathecolamines ≤ 0.1	Dopamine
Neurologic Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal Creatinine mg/dl or Urine output ml/zi	1.2-1.9	2-3.4	3.5-4.9 (200-500)	> 5 (< 200)

Appendix 3. Richmond agitation–sedation scale[xxii]

TABLE 1. RICHMOND AGITATION–SEDATION SCALE

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under DESCRIPTION)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1).
   Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2).
   Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score −4).
   Patient has no response to voice or physical stimulation (score −5).

APPENDIX 4: Confusion Assessment Method (CAM-ICU)[xxii]

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course*		
A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?		
II. Inattention†		
Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?		
III. Disorganized thinking		
Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up this many fingers. (Examiner holds 2 fingers in front of the patient.) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)		
IV. Altered level of consciousness		
Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environment and interacts appropriately Vigilant: hyperalert Lethargic: drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4): Yes___ No___		

*The scores included in the 10-point RASS range from a high of 4 (combative) to a low of −5 (deeply comatose and unresponsive). Under the RASS system, patients who were spontaneously alert, calm, and not agitated were scored at 0 (neutral zone). Anxious or agitated patients received a range of scores depending on their level of anxiety: 1 for anxious, 2 for agitated (fighting ventilator), 3 for very agitated (pulling on or removing catheters), or 4 for combative (violent and a danger to staff). The scores −1 to −5 were assigned for patients with varying degrees of sedation based on their ability to maintain eye contact: −1 for more than 10 seconds, −2 for less than 10 seconds, and −3 for eye opening but no eye contact. If physical stimulation was required, then the patients were scored as either −4 for eye opening or movement with physical or painful stimulation or −5 for no response to physical or painful stimulation. The RASS has excellent interrater reliability and intraclass correlation coefficients of 0.95 and 0.97, respectively, and has been validated against visual analog scale and geropsychiatric diagnoses in 2 ICU studies.[37,38]

†In completing the visual ASE, the patients were shown 5 simple pictures (previously published[34]) at 3-second intervals and asked to remember them. They were then immediately shown 10 subsequent pictures and asked to nod "yes" or "no" to indicate whether they had or had not just seen each of the pictures. Since 5 pictures had been shown to them already, for which the correct response was to nod "yes," and 5 others were new, for which the correct response was to shake their heads "no," patients scored perfectly if they achieved 10 correct responses. Scoring accounted for either errors of omission (indicating "no" for a previously shown picture) or for errors of commission (indicating "yes" for a picture not previously shown). In completing the auditory ASE, patients were asked to squeeze the rater's hand whenever they heard the letter *A* during the recitation of a series of 10 letters. The rater then read 10 letters from the following list in a normal tone at a rate of 1 letter per second: *S, A, H, E, V, A, A, R, A, T*. A scoring method similar to that of the visual ASE was used for the auditory ASE testing.

Appendix 5: Telephone Survey

We would like to ask you (the PATIENT) some questions about your (the PATIENT'S) health:

- In general, how would you say your health is now?

☐ Excellent
☐ Very good
☐ Good
☐ Fair
☐ Poor

- Sometimes it is necessary to spend most of the day in bed. Is this true for you now?

☐ Yes
☐ No
☐ Don't know

- Have you fallen since discharge/since the last time our team talked with you by phone?

☐ Yes
☐ No
☐ Don't know

- If you have fallen since discharge/since the last time our team talked with you by phone, did you see a doctor or go to an emergency department to get checked out after the fall?

☐ Yes
☐ No
☐ Don't know

- Have you been admitted to a hospital since your hospital discharge/the last time our team spoke with you by phone?

☐ Yes
☐ No
☐ Don't know

- Since discharge or the last time our team spoke with you, have you spent any time living in a nursing home, group home/assisted living facility, or rehabilitation facility?

☐ Yes
☐ No
☐ Don't know

- Did (you/PATIENT) need help washing or bathing (yourself/HIMSELF/HERSELF)?

☐ Yes
☐ No
☐ Don't know

- Do you need help dressing and undressing?

☐ Yes
☐ No
☐ Don't know

- Do you need help eating, including cutting food?

☐ Yes
☐ No
☐ Don't know

- Do you need help getting in and out of the bed and a chair?

☐ Yes
☐ No
☐ Don't know

- Do you need help cleaning yourself for either bowel or bladder functions?

☐ Yes
☐ No
☐ Don't know

- Do you sometimes have an accident with your bowels either during the day or night?

☐ Yes
☐ No
☐ Don't know

- Do you sometimes wet yourself either during the day or night?

☐ Yes
☐ No
☐ Don't know

Do you do the following on your own (NO HELP), with some help, or are you unable to:

- Use the telephone, including looking up and dialing numbers, and answering the phone?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Get to places out of walking distance by using public transportation or driving your car?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Shop for groceries or clothes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Prepare, serve and provide meals for yourself?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do light housework, such as dusting or doing dishes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Take pills or medicines in the correct amounts and at the correct times?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Handle your own money, including writing checks and paying bills?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do your laundry?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Walk across the room either on your own or with a cane or walker?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

The following questions are about your living situation.

- Where do you currently live?
  - ☐ Your (the PATIENT'S) own apartment or house
  - ☐ A relative or friend's apartment or house
  - ☐ A nursing home, group home/assisted living facility, or long-term care facility
  - ☐ A homeless shelter
  - ☐ Other_____

- How many people live with you (the PATIENT)? _____

- What is your current weight? _____

- If you (the PATIENT) need extra help when you get home from the hospital, is there someone who can help you (the PATIENT)?
  - ☐ No
  - ☐ Yes

If “Yes”, what is this person’s relationship to you (the PATIENT)?

Spouse	1	Neighbor or landlord	7
Other partner	2	Other friend	8
Child	3	Floor nurse	9
Parent	4	Visiting nurse	10
Brother or sister	5	Home attendant or health aide	11
Other relative	6	Some other person	12
(specify)		(specify)	

- What does this person do during the day if he/she is not helping you (the PATIENT)?
  - □ Work outside the home without pay
  - □ Work outside the home for pay
  - □ Work in the home without pay
  - □ Work in the home for pay
  - □ Other (specify) _____

- How old is this person?

□ Under 18
□ 18-49
□ 50-64
□ 65-74
□ 75-84
□ 85-89
□ 90 or greater

PROTOCOL AMENDMENT 2

Title: Noninvasive Ventilation in Patients with Respiratory Failure: A Comparison of Face mask versus Helmet interface

Date: April 11, 2013

Principle Investigators:

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Background:

Respiratory failure characterized by acute deterioration of gas exchange is often treated with endotracheal intubation and mechanical ventilation (figure 1). Similarly, the classic teaching in the treatment of patients with shock required intubation to "take away the work of breathing." Although, the institution of mechanical ventilation is considered life saving, the associated complications of tracheal stenosis,[xxii] ventilator associated pneumonia,[xxii] barotrauma[xxii], and neuromuscular weakness[xxii] are not without considerable morbidity and mortality.

Over the past years non-invasive ventilation delivered by facemask (figure 2) has become an attractive option to improve gas exchange without an artificial airway, thus preserving airway defense mechanisms, speech and swallow capabilities, and allowing interaction between patients and care providers while avoiding the complications of endotracheal intubation. This strategy of non-invasive ventilation has demonstrated significant mortality benefit in patients with hypercapnic respiratory failure from COPD,[xxii,xxii] acute cardiogenic pulmonary edema,[xxii,xxii] and hypoxemic respiratory failure in immunocompromised patients.[xxii,xxii] In addition to successfully avoiding endotracheal intubation, non-invasive ventilation has been used to successfully liberate patients from mechanical ventilation via an endotracheal tube to extubation and transition to non-invasive mechanical ventilation. As such non-invasive ventilation has been a standard therapy for certain types of respiratory failure for more than 15 years.

Despite the advantages of non-invasive ventilation, up to forty percent of patients fail facemask trials in part because of mask intolerance and severity of disease.[xxii] Some common complications contributing to mask intolerance include claustrophobia, nasal bridge skin necrosis, acneiform rash, and conjunctivitis and if present prompt premature

discontinuation of non-invasive ventilation and endotracheal intubation. Further limitation to facemask non-invasive ventilation is that the seal integrity is lost when higher pressures are required. For example, non-invasive ventilation via a nasal or full face mask typically begins to demonstrate leaks when the pressures required exceed 15-20 cm H2O. Unfortunately, certain types of respiratory failure such as that due to hypoxemia or shock may require such higher pressures. In an attempt to improve patient tolerability and deliver higher pressures, a transparent helmet has been proposed as a novel interface for non-invasive ventilation. The helmet is made of transparent latex-free PVC with a soft collar that adheres to the neck ensuring a seal when inflated (figure 3). It encloses the entire head and neck of the patient and is secured by two armpit braces. The design of the helmet confers some important advantages: 1) the transparency allows the patient to interact with the environment; 2) the lack of contact to the face lowers the risk of skin necrosis; 3) the helmet avoids problems of leaking with higher airway pressures that are seen with the face mask. Accordingly, it can be used to deliver airway pressures up to 40 cm H2O without leaking. Such higher pressures are more often needed to provide effective mechanical ventilation to patients with hypoxemic respiratory failure and/or shock; 4) it can be applied to any patient regardless of facial contour.[xxii]

The helmet interface has been compared to face mask in small case control studies for the treatment of hypoxemic respiratory failure (AHRF). While both interfaces have similar improvement of oxygenation, intubation rates, and mortality, the helmet had good tolerability that allowed for longer continuous application of noninvasive ventilation and in some cases sustained improvement of gas exchange even after discontinuation of therapy in immunocompromised patients,[xxii,xxii] non-cardiogenic acute hypoxemic respiratory failure,[xxii] and acute cardiogenic pulmonary edema[xxii]. Given this initial experience and success with helmet ventilation, larger randomized studies comparing this intervention to face mask in patients with AHRF and shock need to be done to understand the potential benefits of helmet ventilation.

Purpose:
The objective of our study is to evaluate the efficacy of helmet ventilation as compared with face mask ventilation in patients with acute hypoxemic respiratory failure and evidence of shock, specifically assessing improvement of oxygenation, need for mechanical ventilation, and rates of ICU complications.

Hypothesis:
Noninvasive positive pressure ventilation delivered by helmet will improve oxygenation and/or ventilation and avoid the need for endotracheal intubation in more patients with respiratory failure than noninvasive ventilation via face mask. This may result in improved outcomes with decreased rates of ICU related complications.

Methods:
Study Design

We propose a single center randomized controlled trial studying the efficacy of noninvasive ventilation delivered via helmet in patients with respiratory failure (hypoxemic, ventilatory, or failure due to shock). All patients admitted to the adult medical intensive care unit at the University of Chicago will be screened for eligibility.

Subject Inclusion
Patients aged ≥18 years of age who require noninvasive mechanical ventilation via facemask for ≥ 8 hours for the management of respiratory failure including:

1. hypoxemic failure due to cardiac pulmonary edema and non-cardiogenic acute hypoxemic respiratory failure (AHRF) and/or
2. shock and/or
3. Ventilatory failure due to Chronic obstructive Pulmonary disease (COPD)/Asthma,

will be eligible for enrollment. Additional inclusion criteria include:

- Intact airway protective gag reflex
- Able to follow instructions (e.g. squeeze hand on command, eye contact with care provider, stick out tongue on command)

Acute hypoxemic respiratory failure will be defined as moderate to severe dyspnea, pulmonary infiltrates, and PaO2/FIO2 ratio less than 300.

Shock will be defined as mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite administration of intravenous fluids (at least 1000 ml of crystalloids or 500 ml of colloids, unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter)[xxii].

Subject exclusion
The criteria for exclusion include:

- Cardiopulmonary arrest
- Glascow coma scale <8
- Absence of airway protective gag reflex
- Elevated intracranial pressure
- Tracheostomy
- Upper airway obstruction
- Pregnancy.
- Patients who refuse to undergo endotracheal intubation, whatever the initial therapeutic approach

Helmet group
Patients randomized to the intervention group will switch from noninvasive ventilation delivered via facemask to a latex-free helmet connected to the ventilator by conventional

tubing. The helmet contains the head and the neck of the patient, has a rigid ring and is secured by two armpit braces; a soft collar adheres to the neck and ensures a sealed connection once the helmet is inflated. The rigid ring has an opening for the passage of nasogastric tube (if needed).

Patients randomized to helmet ventilation will have the helmet applied and connected to a ventilator. The ventilator delivers pressure through the helmet inlet tubing and exhaled breaths are released though the helmet outlet tubing. The positive end-expiratory pressure (PEEP) will be increased in increments of 2-3 cmH_20 to improve peripheral oxygen saturation of at least 90% at an inspired oxygen requirement (FiO2) of ≤ 60%. Pressure support will be increased in increments of 2-3cmH_20 to obtain respiratory rate <25 breaths/min and disappearance of accessory muscle activity. After application of the helmet, arterial blood gas sampling will be utilized to follow gas-exchange; this is a part of usual care for the management of patients with acute hypoxemic respiratory failure and/or shock. Noninvasive support will be reduced progressively in accordance to clinical improvement and will be discontinued if patient maintains respiratory rate <30breaths/min and PaO2 >75mm Hg with FiO2 0.5 without ventilatory support. If endotracheal intubation is required, the helmet will be removed and the patient will be intubated without delay.

Control Group

Patients assigned to the control group will continue to wear face mask for delivery of noninvasive ventilation. The expiratory positive airway pressure will be titrated in 2-3cm H20 increments to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). The inspiratory positive airway pressure will be titrated as well to decrease tachypnea (<25 breaths/min) and improve work of breathing. Blood gas analysis will be obtained to determine appropriate gas exchange.

Predetermined criteria for intubation for both groups will include:

- Inability to achieve an arterial oxygen saturation by pulse oximetry or arterial blood gas ≥ 88%
- Respiratory rate > 36 breaths/min
- Loss of ability to maintain ventilation to keep arterial blood pH ≥ 7.20
- Loss of protective airway gag reflex (seizure disorder, severe encephalopathy, Glascow Coma Scale <8)
- Respiratory or cardiac arrest
- Intolerance of the helmet or face mask
- Development of airway bleeding, persistent vomiting, and development of copious tracheal secretions.

Patients who require endotracheal intubation will have initial ventilator settings of assist-control mode with delivery of tidal volumes of 6-8mL/kg of ideal body weight, and titration of PEEP to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). Daily interruption of sedation, awakening and breathing trials will be performed per primary team.

If an enrolled patient is randomized to helmet noninvasive ventilation after intubation, they will undergo interruption of sedation and extubation with immediate placement of the helmet and initiation on noninvasive ventilation. Early initiation of noninvasive ventilation in patients who do not meet start criteria for extubation to facilitate early extubation has been associated with decreased mortality, ventilator associated pneumonia, and ventilator days.[xxii]

Data Collection:
All study patients during hospitalization will have:

2. General Data collection:
    - Demographic information, including medical history number, age, race, gender
    - Details of current illness, including diagnosis, interventions, radiology imaging, laboratory results. Severity of illness scoring will occur (APACHE II – see Appendix 1) as well as daily serial organ function assessments (see Appendix 2).
    - Baseline medical/surgical/functional status history
    - Dates of mechanical ventilation, ICU and hospital length of stay
    - Discharge Location

4. Daily Data Collection
    - Daily mental status evaluations, including the Richmond-Agitation-Sedation Scale (Appendix 3) and the Confusion Assessment Method (Appendix 4)
    - Muscular strength testing by physical therapists on ICU admission, ICU discharge and hospital discharge

5. All patients after discharge
    - Telephone interviews at 1, 3, 6, and 12 months after discharge (Appendix 7)
        - Lasting approximately 5 minutes in duration
        - Assessing self-reported performance of ADL's
        - Reviewing need for medical care, including re-hospitalization, rehabilitation, physician outpatient visits
        - Current weight and nutritional status

Endpoints:
Primary
- Percentage of patients requiring endotracheal intubation
- Duration of mechanical ventilation
    - Noninvasive ventilation via face mask or helmet
    - Invasive mechanical ventilation via endotracheal tube
- ICU length of stay
- Hospital Mortality

- Improvement of oxygenation (defined as $PaO_2/FiO_2 \geq 200$ or increase from baseline by 100)

Secondary

- ICU complications
    - Ventilator associated pneumonia
    - Barotrauma
    - Gastrointestinal hemorrhage
    - Pulmonary embolism
    - Sacral Decubitus ulcer
    - Delirium
    - ICU acquired weakness
- Hospital length of stay
- Readmission to intensive care unit
- Discharge location (home, skilled nursing facility, nursing home, rehabilitation

Risks and Benefits

The risks of this study are limited beyond those experienced during routine critical care of an intubated, mechanically ventilated patient.

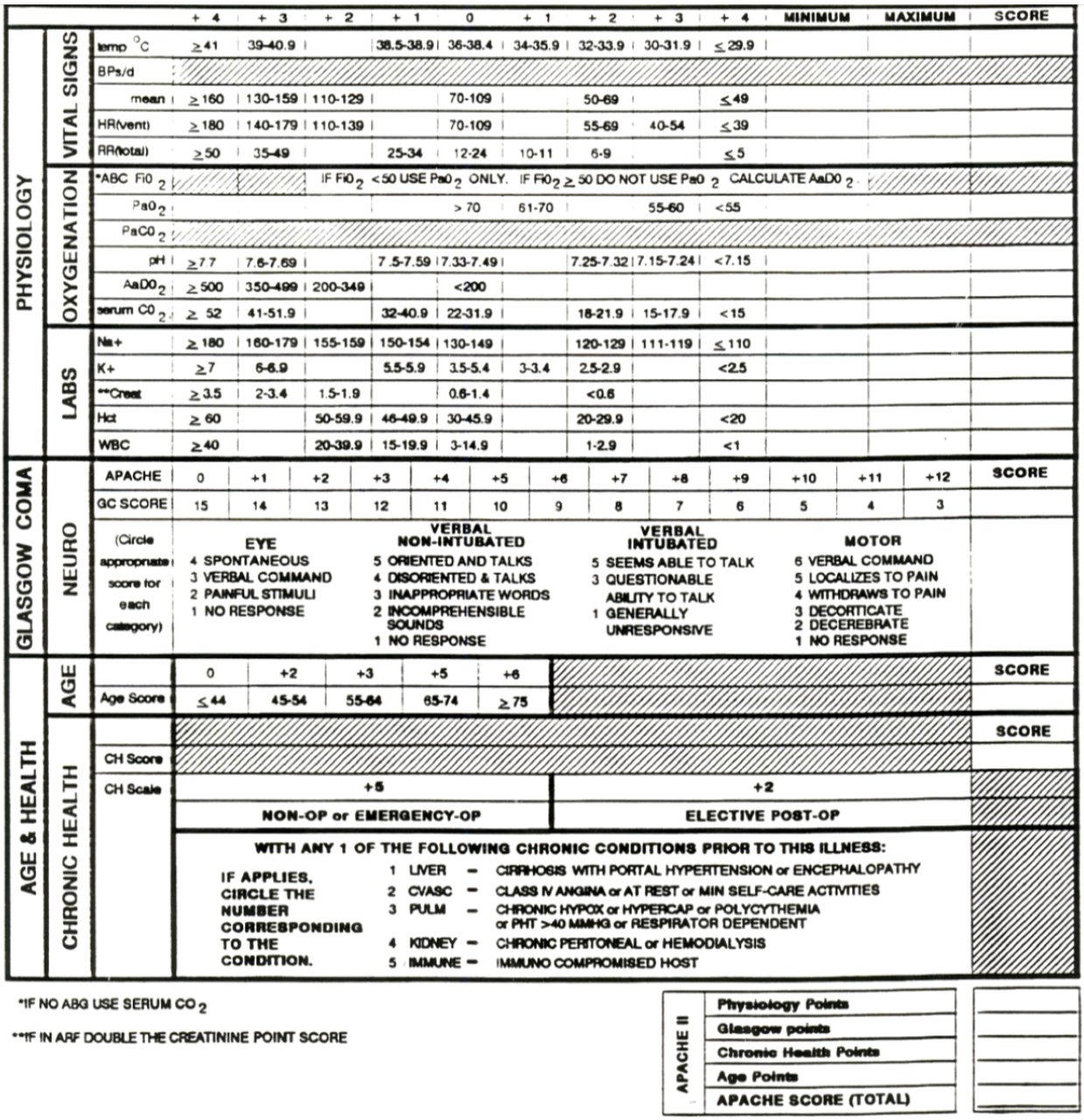
- Non-invasive mechanical ventilation may be associated with failure to stabilize respiratory gas exchange. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with failure to stabilize circulatory shock. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with aspiration. Accordingly, only patients with an intact airway protective gag reflex will be eligible for enrollment. Aspiration is also known to occur in patients who have an endotracheal tube. Care will be taken to monitor all patients in this study for this occurrence.

Figure 1: Endotracheal Tube

Figure 2: Facemask

Figure 3: Helmet

Appendix 1: ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORING SYSTEM[xxii]



			+4	+3	+2	+1	0	+1	+2	+3	+4	MINIMUM	MAXIMUM	SCORE
PHYSIOLOGY	VITAL SIGNS	temp °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9			
		BPs/d												
		mean	≥160	130-159	110-129		70-109		50-69		≤49			
		HR(vent)	≥180	140-179	110-139		70-109		55-69	40-54	≤39			
		RR(total)	≥50	35-49		25-34	12-24	10-11	6-9		≤5			
	OXYGENATION	*ABC FiO_2	IF FiO_2 <50 USE PaO_2 ONLY. IF FiO_2 ≥50 DO NOT USE PaO_2 CALCULATE $AaDO_2$											
		PaO_2					>70	61-70		55-60	<55			
		$PaCO_2$												
		pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15			
		$AaDO_2$	≥500	350-499	200-349		<200							
		serum CO_2	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15			
	LABS	Na+	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110			
		K+	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5			
		**Creat	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6					
		Hct	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20			
		WBC	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1			

		APACHE	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	SCORE
GLASGOW COMA	NEURO	GC SCORE	15	14	13	12	11	10	9	8	7	6	5	4	3	

(Circle appropriate score for each category)

EYE	VERBAL NON-INTUBATED	VERBAL INTUBATED	MOTOR
4 SPONTANEOUS	5 ORIENTED AND TALKS	5 SEEMS ABLE TO TALK	6 VERBAL COMMAND
3 VERBAL COMMAND	4 DISORIENTED & TALKS	3 QUESTIONABLE ABILITY TO TALK	5 LOCALIZES TO PAIN
2 PAINFUL STIMULI	3 INAPPROPRIATE WORDS	1 GENERALLY UNRESPONSIVE	4 WITHDRAWS TO PAIN
1 NO RESPONSE	2 INCOMPREHENSIBLE SOUNDS		3 DECORTICATE
	1 NO RESPONSE		2 DECEREBRATE
			1 NO RESPONSE

			0	+2	+3	+5	+6	SCORE
AGE & HEALTH	AGE	Age Score	≤44	45-54	55-64	65-74	≥75	

			+5	+2	SCORE
AGE & HEALTH	CHRONIC HEALTH	CH Score			
		CH Scale	NON-OP or EMERGENCY-OP	ELECTIVE POST-OP	

WITH ANY 1 OF THE FOLLOWING CHRONIC CONDITIONS PRIOR TO THIS ILLNESS:

IF APPLIES, CIRCLE THE NUMBER CORRESPONDING TO THE CONDITION.

1 LIVER – CIRRHOSIS WITH PORTAL HYPERTENSION or ENCEPHALOPATHY
2 CVASC – CLASS IV ANGINA or AT REST or MIN SELF-CARE ACTIVITIES
3 PULM – CHRONIC HYPOX or HYPERCAP or POLYCYTHEMIA or PHT >40 MMHG or RESPIRATOR DEPENDENT
4 KIDNEY – CHRONIC PERITONEAL or HEMODIALYSIS
5 IMMUNE – IMMUNO COMPROMISED HOST

*IF NO ABG USE SERUM CO_2

**IF IN ARF DOUBLE THE CREATININE POINT SCORE

APACHE II	
Physiology Points	
Glasgow points	
Chronic Health Points	
Age Points	
APACHE SCORE (TOTAL)	

Appendix 2: Serial Organ Function Assessment[18][xxii]

SOFA score	1	2	3	4
			Respiration with respiratory support	
Respiration with respiratory support PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
Coagulation Platelets $x10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dl	1.2-1.9	2-5.9	6-11.9	> 12
Cardiovascular Hypotension >15 or (doses in ug/kg·min) cathecolamines> 0,1	MAP < 70mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine > 5 or cathecolamines ≤ 0.1	Dopamine
Neurologic Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal Creatinine mg/dl or Urine output ml/zi	1.2-1.9	2-3.4	3.5-4.9 (200-500)	> 5 (< 200)

Appendix 3. Richmond agitation–sedation scale[xxii]

TABLE 1. RICHMOND AGITATION–SEDATION SCALE

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under DESCRIPTION)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1).
   Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2).
   Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score −4).
   Patient has no response to voice or physical stimulation (score −5).

APPENDIX 4: Confusion Assessment Method (CAM-ICU)[xxii]

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course*		
A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?		
II. Inattention†		
Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?		
III. Disorganized thinking		
Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up this many fingers. (Examiner holds 2 fingers in front of the patient.) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)		
IV. Altered level of consciousness		
Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environment and interacts appropriately Vigilant: hyperalert Lethargic: drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4): Yes___ No___		

*The scores included in the 10-point RASS range from a high of 4 (combative) to a low of −5 (deeply comatose and unresponsive). Under the RASS system, patients who were spontaneously alert, calm, and not agitated were scored at 0 (neutral zone). Anxious or agitated patients received a range of scores depending on their level of anxiety: 1 for anxious, 2 for agitated (fighting ventilator), 3 for very agitated (pulling on or removing catheters), or 4 for combative (violent and a danger to staff). The scores −1 to −5 were assigned for patients with varying degrees of sedation based on their ability to maintain eye contact: −1 for more than 10 seconds, −2 for less than 10 seconds, and −3 for eye opening but no eye contact. If physical stimulation was required, then the patients were scored as either −4 for eye opening or movement with physical or painful stimulation or −5 for no response to physical or painful stimulation. The RASS has excellent interrater reliability and intraclass correlation coefficients of 0.95 and 0.97, respectively, and has been validated against visual analog scale and geropsychiatric diagnoses in 2 ICU studies.[37,38]

†In completing the visual ASE, the patients were shown 5 simple pictures (previously published[34]) at 3-second intervals and asked to remember them. They were then immediately shown 10 subsequent pictures and asked to nod "yes" or "no" to indicate whether they had or had not just seen each of the pictures. Since 5 pictures had been shown to them already, for which the correct response was to nod "yes," and 5 others were new, for which the correct response was to shake their heads "no," patients scored perfectly if they achieved 10 correct responses. Scoring accounted for either errors of omission (indicating "no" for a previously shown picture) or for errors of commission (indicating "yes" for a picture not previously shown). In completing the auditory ASE, patients were asked to squeeze the rater's hand whenever they heard the letter *A* during the recitation of a series of 10 letters. The rater then read 10 letters from the following list in a normal tone at a rate of 1 letter per second: *S, A, H, E, V, A, A, R, A, T*. A scoring method similar to that of the visual ASE was used for the auditory ASE testing.

Appendix 5: Telephone Survey

We would like to ask you (the PATIENT) some questions about your (the PATIENT'S) health:

- In general, how would you say your health is now?

☐ Excellent
☐ Very good
☐ Good
☐ Fair
☐ Poor

- Sometimes it is necessary to spend most of the day in bed. Is this true for you now?

☐ Yes
☐ No
☐ Don't know

- Have you fallen since discharge/since the last time our team talked with you by phone?

☐ Yes
☐ No
☐ Don't know

- If you have fallen since discharge/since the last time our team talked with you by phone, did you see a doctor or go to an emergency department to get checked out after the fall?

☐ Yes
☐ No
☐ Don't know

- Have you been admitted to a hospital since your hospital discharge/the last time our team spoke with you by phone?

☐ Yes
☐ No
☐ Don't know

- Since discharge or the last time our team spoke with you, have you spent any time living in a nursing home, group home/assisted living facility, or rehabilitation facility?

☐ Yes
☐ No
☐ Don't know

- Did (you/PATIENT) need help washing or bathing (yourself/HIMSELF/HERSELF)?

☐ Yes
☐ No
☐ Don't know

- Do you need help dressing and undressing?

☐ Yes
☐ No
☐ Don't know

- Do you need help eating, including cutting food?

☐ Yes
☐ No
☐ Don't know

- Do you need help getting in and out of the bed and a chair?

☐ Yes
☐ No
☐ Don't know

- Do you need help cleaning yourself for either bowel or bladder functions?

☐ Yes
☐ No
☐ Don't know

- Do you sometimes have an accident with your bowels either during the day or night?

☐ Yes
☐ No
☐ Don't know

- Do you sometimes wet yourself either during the day or night?

☐ Yes
☐ No
☐ Don't know

Do you do the following on your own (NO HELP), with some help, or are you unable to:

- Use the telephone, including looking up and dialing numbers, and answering the phone?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Get to places out of walking distance by using public transportation or driving your car?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Shop for groceries or clothes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Prepare, serve and provide meals for yourself?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do light housework, such as dusting or doing dishes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Take pills or medicines in the correct amounts and at the correct times?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Handle your own money, including writing checks and paying bills?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do your laundry?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Walk across the room either on your own or with a cane or walker?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

The following questions are about your living situation.

- Where do you currently live?
  - ☐ Your (the PATIENT'S) own apartment or house
  - ☐ A relative or friend's apartment or house
  - ☐ A nursing home, group home/assisted living facility, or long-term care facility
  - ☐ A homeless shelter
  - ☐ Other_____

- How many people live with you (the PATIENT)? _____

- What is your current weight? _____

- If you (the PATIENT) need extra help when you get home from the hospital, is there someone who can help you (the PATIENT)?
  - ☐ No
  - ☐ Yes

If "Yes", what is this person's relationship to you (the PATIENT)?

Spouse	1	Neighbor or landlord	7
Other partner	2	Other friend	8
Child	3	Floor nurse	9
Parent	4	Visiting nurse	10
Brother or sister	5	Home attendant or health aide	11
Other relative	6	Some other person	12
(specify)		(specify)	

- What does this person do during the day if he/she is not helping you (the PATIENT)?
  - ☐ Work outside the home without pay
  - ☐ Work outside the home for pay
  - ☐ Work in the home without pay
  - ☐ Work in the home for pay
  - ☐ Other (specify) _____

- How old is this person?

☐ Under 18
☐ 18-49
☐ 50-64
☐ 65-74
☐ 75-84
☐ 85-89
☐ 90 or greater

Title: Noninvasive Ventilation in Patients with Respiratory Failure: A Comparison of Face mask versus Helmet interface

PROTOCOL AMENDMENT 6

Date: April 28, 2015

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Background:
Respiratory failure characterized by acute deterioration of gas exchange is often treated with endotracheal intubation and mechanical ventilation (figure 1). Similarly, the classic teaching in the treatment of patients with shock required intubation to "take away the work of breathing." Although, the institution of mechanical ventilation is considered life saving, the associated complications of tracheal stenosis,[xxii] ventilator associated pneumonia,[xxii] barotrauma[xxii], and neuromuscular weakness[xxii] are not without considerable morbidity and mortality.

Over the past years non-invasive ventilation delivered by facemask (figure 2) has become an attractive option to improve gas exchange without an artificial airway, thus preserving airway defense mechanisms, speech and swallow capabilities, and allowing interaction between patients and care providers while avoiding the complications of endotracheal intubation. This strategy of non-invasive ventilation has demonstrated significant mortality benefit in patients with hypercapnic respiratory failure from COPD,[xxii,xxii] acute cardiogenic pulmonary edema,[xxii,xxii] and hypoxemic respiratory failure in immunocompromised patients.[xxii,xxii] In addition to successfully avoiding endotracheal intubation, non-invasive ventilation has been used to successfully liberate patients from mechanical ventilation via an endotracheal tube to extubation and transition to non-invasive mechanical ventilation. As such non-invasive ventilation has been a standard therapy for certain types of respiratory failure for more than 15 years.

Despite the advantages of non-invasive ventilation, up to forty percent of patients fail facemask trials in part because of mask intolerance and severity of disease.[xxii] Some common complications contributing to mask intolerance include claustrophobia, nasal bridge skin necrosis, acneiform rash, and conjunctivitis and if present prompt premature discontinuation of non-invasive ventilation and endotracheal intubation. Further limitation to facemask non-invasive ventilation is that the seal integrity is lost when higher pressures are required. For example, non-invasive ventilation via a nasal or full face mask typically begins to demonstrate leaks when the pressures required exceed 15-20 cm H2O. Unfortunately, certain types of respiratory failure such as that due to hypoxemia or shock

may require such higher pressures. In an attempt to improve patient tolerability and deliver higher pressures, a transparent helmet has been proposed as a novel interface for non-invasive ventilation. The helmet is made of transparent latex-free PVC with a soft collar that adheres to the neck ensuring a seal when inflated (figure 3). It encloses the entire head and neck of the patient and is secured by two armpit braces. The design of the helmet confers some important advantages: 1) the transparency allows the patient to interact with the environment; 2) the lack of contact to the face lowers the risk of skin necrosis; 3) the helmet avoids problems of leaking with higher airway pressures that are seen with the face mask. Accordingly, it can be used to deliver airway pressures up to 40 cm H2O without leaking. Such higher pressures are more often needed to provide effective mechanical ventilation to patients with hypoxemic respiratory failure and/or shock; 4) it can be applied to any patient regardless of facial contour.[xxii]

The helmet interface has been compared to face mask in small case control studies for the treatment of hypoxemic respiratory failure (AHRF). While both interfaces have similar improvement of oxygenation, intubation rates, and mortality, the helmet had good tolerability that allowed for longer continuous application of noninvasive ventilation and in some cases sustained improvement of gas exchange even after discontinuation of therapy in immunocompromised patients,[xxii,xxii] non-cardiogenic acute hypoxemic respiratory failure,[xxii] and acute cardiogenic pulmonary edema[xxii]. Given this initial experience and success with helmet ventilation, larger randomized studies comparing this intervention to face mask in patients with AHRF and shock need to be done to understand the potential benefits of helmet ventilation.

Purpose:
The objective of our study is to evaluate the efficacy of helmet ventilation as compared with face mask ventilation in patients with acute hypoxemic respiratory failure and evidence of shock, specifically assessing improvement of oxygenation, need for mechanical ventilation, and rates of ICU complications.

Hypothesis:
Noninvasive positive pressure ventilation delivered by helmet will improve oxygenation and/or ventilation and avoid the need for endotracheal intubation in more patients with respiratory failure than noninvasive ventilation via face mask. This may result in improved outcomes with decreased rates of ICU related complications.

Methods:
Study Design
We propose a single center randomized controlled trial studying the efficacy of noninvasive ventilation delivered via helmet in patients with respiratory failure (hypoxemic, ventilatory, or failure due to shock). All patients admitted to the adult medical intensive care unit at the University of Chicago will be screened for eligibility.

Subject Inclusion

Patients aged ≥18 years of age who require noninvasive mechanical ventilation via facemask for ≥ 8 hours for the management of respiratory failure including:

4. hypoxemic failure due to cardiac pulmonary edema and non-cardiogenic acute hypoxemic respiratory failure (AHRF) and/or
5. shock and/or
6. Ventilatory failure due to Chronic obstructive Pulmonary disease (COPD)/Asthma,

will be eligible for enrollment. Additional inclusion criteria include:

- Intact airway protective gag reflex
- Able to follow instructions (e.g. squeeze hand on command, eye contact with care provider, stick out tongue on command)

Acute hypoxemic respiratory failure will be defined as moderate to severe dyspnea, pulmonary infiltrates, and PaO2/FIO2 ratio less than 300.

Shock will be defined as mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite administration of intravenous fluids (at least 1000 ml of crystalloids or 500 ml of colloids, unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter)[xxii].

Subject exclusion
The criteria for exclusion include:

- Cardiopulmonary arrest
- Glascow coma scale <8
- Absence of airway protective gag reflex
- Elevated intracranial pressure
- Tracheostomy
- Upper airway obstruction
- Pregnancy.
- Patients who refuse to undergo endotracheal intubation, whatever the initial therapeutic approach

Helmet group
Patients randomized to the intervention group will switch from noninvasive ventilation delivered via facemask to a latex-free helmet connected to the ventilator by conventional tubing. The helmet contains the head and the neck of the patient, has a rigid ring and is secured by two armpit braces; a soft collar adheres to the neck and ensures a sealed connection once the helmet is inflated. The rigid ring has an opening for the passage of nasogastric tube (if needed).

Patients randomized to helmet ventilation will have the helmet applied and connected to a ventilator. The ventilator delivers pressure through the helmet inlet tubing and exhaled breaths are released though the helmet outlet tubing. The positive end-expiratory pressure (PEEP) will be increased in increments of 2-3 cmH_20 to improve peripheral oxygen saturation of at least 90% at an inspired oxygen requirement (FiO2) of ≤ 60%. Pressure support will be increased in increments of 2-3cmH_20 to obtain respiratory rate <25 breaths/min and disappearance of accessory muscle activity. After application of the helmet, arterial blood gas sampling will be utilized to follow gas-exchange; this is a part of usual care for the management of patients with acute hypoxemic respiratory failure and/or shock. Noninvasive support will be reduced progressively in accordance to clinical improvement and will be discontinued if patient maintains respiratory rate <30breaths/min and PaO2 >75mm Hg with FiO2 0.5 without ventilatory support. If endotracheal intubation is required, the helmet will be removed and the patient will be intubated without delay.

Control Group
Patients assigned to the control group will continue to wear face mask for delivery of noninvasive ventilation. The expiratory positive airway pressure will be titrated in 2-3cm H20 increments to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). The inspiratory positive airway pressure will be titrated as well to decrease tachypnea (<25 breaths/min) and improve work of breathing. Blood gas analysis will be obtained to determine appropriate gas exchange.

Predetermined criteria for intubation for both groups will include:

- Inability to achieve an arterial oxygen saturation by pulse oximetry or arterial blood gas ≥ 88%
- Respiratory rate > 36 breaths/min
- Loss of ability to maintain ventilation to keep arterial blood pH ≥ 7.20
- Loss of protective airway gag reflex (seizure disorder, severe encephalopathy, Glascow Coma Scale <8)
- Respiratory or cardiac arrest
- Intolerance of the helmet or face mask
- Development of airway bleeding, persistent vomiting, and development of copious tracheal secretions.

Patients who require endotracheal intubation will have initial ventilator settings of assist-control mode with delivery of tidal volumes of 6-8mL/kg of ideal body weight, and titration of PEEP to achieve oxygen saturation of 90% at lowest possible FiO2 (goal FiO_2 0.6 or less). Daily interruption of sedation, awakening and breathing trials will be performed per primary team.

If an enrolled patient is randomized to helmet noninvasive ventilation after intubation, they will undergo interruption of sedation and extubation with immediate placement of the helmet and initiation on noninvasive ventilation. Early initiation of noninvasive ventilation in patients who do not meet start criteria for extubation to facilitate early extubation has

been associated with decreased mortality, ventilator associated pneumonia, and ventilator days.[xxii]

Data Collection:
All study patients during hospitalization will have:

3. General Data collection:
    - Demographic information, including medical history number, age, race, gender
    - Details of current illness, including diagnosis, interventions, radiology imaging, laboratory results. Severity of illness scoring will occur (APACHE II – see Appendix 1) as well as daily serial organ function assessments (see Appendix 2).
    - Baseline medical/surgical/functional status history
    - Dates of mechanical ventilation, ICU and hospital length of stay
    - Discharge Location

6. Daily Data Collection
    - Daily mental status evaluations, including the Richmond-Agitation-Sedation Scale (Appendix 3) and the Confusion Assessment Method (Appendix 4)
    - Muscular strength testing by physical therapists on ICU admission, ICU discharge and hospital discharge

7. All patients after discharge
    - Telephone interviews at 1, 3, 6, and 12 months after discharge (Appendix 7)
        - Lasting approximately 5 minutes in duration
        - Assessing self-reported performance of ADL's
        - Reviewing need for medical care, including re-hospitalization, rehabilitation, physician outpatient visits
        - Current weight and nutritional status

Endpoints:
Primary
- Percentage of patients requiring endotracheal intubation
- Duration of mechanical ventilation
    - Noninvasive ventilation via face mask or helmet
    - Invasive mechanical ventilation via endotracheal tube
- ICU length of stay
- Hospital Mortality
- Improvement of oxygenation (defined as $PaO_2/FiO_2 \geq 200$ or increase from baseline by 100)

Secondary
- ICU complications

    - Ventilator associated pneumonia
    - Barotrauma
    - Gastrointestinal hemorrhage
    - Pulmonary embolism
    - Sacral Decubitus ulcer
    - Delirium
    - ICU acquired weakness
- Hospital length of stay
- Readmission to intensive care unit
- Discharge location (home, skilled nursing facility, nursing home, rehabilitation

Risks and Benefits

The risks of this study are limited beyond those experienced during routine critical care of an intubated, mechanically ventilated patient.

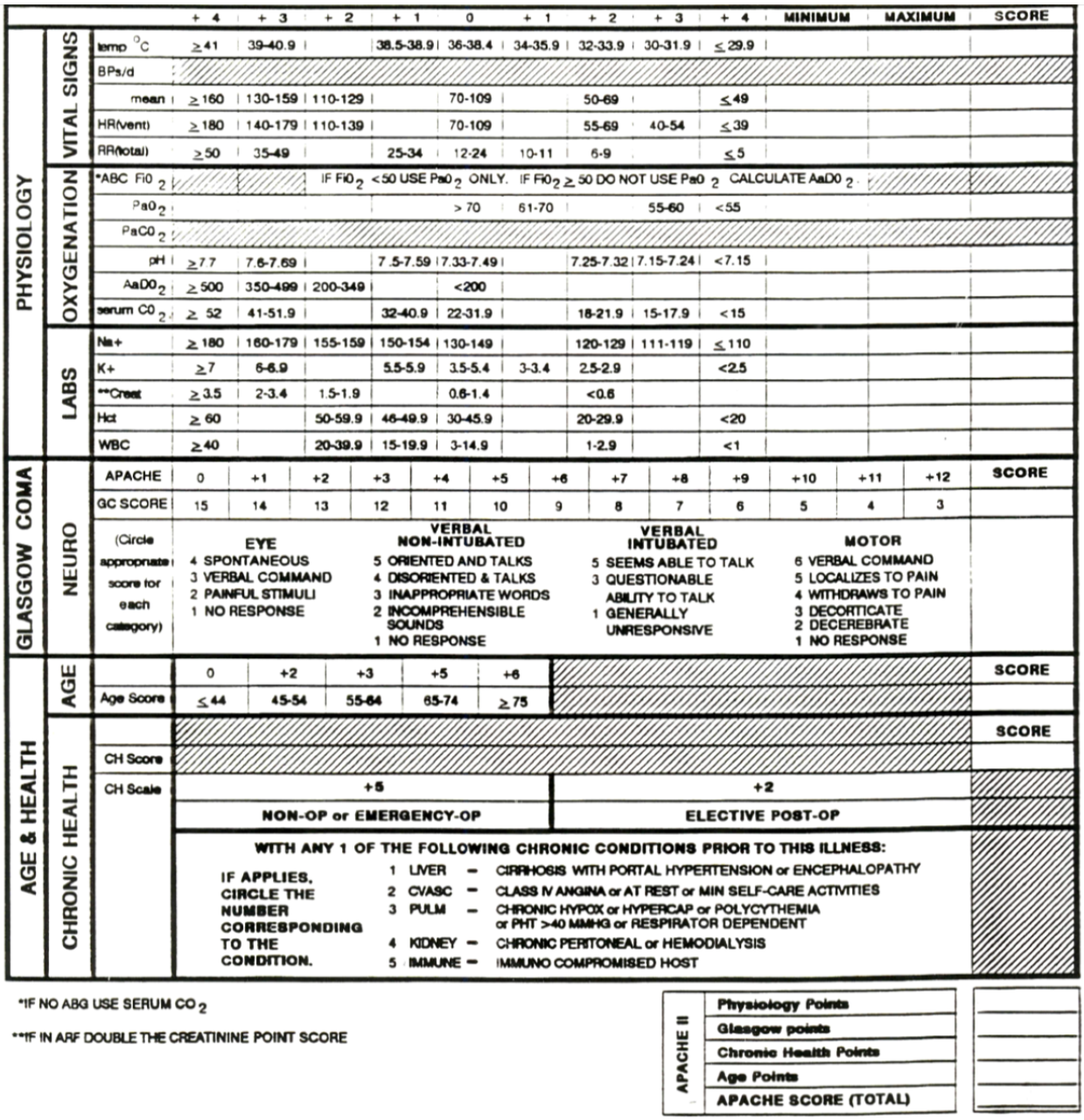
- Non-invasive mechanical ventilation may be associated with failure to stabilize respiratory gas exchange. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with failure to stabilize circulatory shock. In this case, patients will be intubated and mechanically ventilated via the endotracheal tube.
- Non-invasive mechanical ventilation may be associated with aspiration. Accordingly, only patients with an intact airway protective gag reflex will be eligible for enrollment. Aspiration is also known to occur in patients who have an endotracheal tube. Care will be taken to monitor all patients in this study for this occurrence.

Figure 1: Endotracheal Tube

Figure 2: Facemask

Figure 3: Helmet

Appendix 1: ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORING SYSTEM[xxii]



			+4	+3	+2	+1	0	+1	+2	+3	+4	MINIMUM	MAXIMUM	SCORE
PHYSIOLOGY	VITAL SIGNS	temp °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9			
		BPs/d												
		mean	≥160	130-159	110-129		70-109		50-69		≤49			
		HR(vent)	≥180	140-179	110-139		70-109		55-69	40-54	≤39			
		RR(total)	≥50	35-49		25-34	12-24	10-11	6-9		≤5			
	OXYGENATION	*ABC FiO_2	IF FiO_2 <50 USE PaO_2 ONLY. IF FiO_2 ≥50 DO NOT USE PaO_2 CALCULATE $AaDO_2$											
		PaO_2					>70	61-70		55-60	<55			
		$PaCO_2$												
		pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15			
		$AaDO_2$	≥500	350-499	200-349		<200							
		serum CO_2	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15			
	LABS	Na+	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110			
		K+	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5			
		**Creat	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6					
		Hct	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20			
		WBC	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1			

		APACHE	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	SCORE
GLASGOW COMA	NEURO	GC SCORE	15	14	13	12	11	10	9	8	7	6	5	4	3	

(Circle appropriate score for each category)

EYE	VERBAL NON-INTUBATED	VERBAL INTUBATED	MOTOR
4 SPONTANEOUS	5 ORIENTED AND TALKS	5 SEEMS ABLE TO TALK	6 VERBAL COMMAND
3 VERBAL COMMAND	4 DISORIENTED & TALKS	3 QUESTIONABLE ABILITY TO TALK	5 LOCALIZES TO PAIN
2 PAINFUL STIMULI	3 INAPPROPRIATE WORDS	1 GENERALLY UNRESPONSIVE	4 WITHDRAWS TO PAIN
1 NO RESPONSE	2 INCOMPREHENSIBLE SOUNDS		3 DECORTICATE
	1 NO RESPONSE		2 DECEREBRATE
			1 NO RESPONSE

			0	+2	+3	+5	+6	SCORE
AGE & HEALTH	AGE	Age Score	≤44	45-54	55-64	65-74	≥75	

			+5	+2	SCORE
AGE & HEALTH	CHRONIC HEALTH	CH Score			
		CH Scale	NON-OP or EMERGENCY-OP	ELECTIVE POST-OP	

WITH ANY 1 OF THE FOLLOWING CHRONIC CONDITIONS PRIOR TO THIS ILLNESS:

IF APPLIES, CIRCLE THE NUMBER CORRESPONDING TO THE CONDITION.

1 LIVER – CIRRHOSIS WITH PORTAL HYPERTENSION or ENCEPHALOPATHY
2 CVASC – CLASS IV ANGINA or AT REST or MIN SELF-CARE ACTIVITIES
3 PULM – CHRONIC HYPOX or HYPERCAP or POLYCYTHEMIA or PHT >40 MMHG or RESPIRATOR DEPENDENT
4 KIDNEY – CHRONIC PERITONEAL or HEMODIALYSIS
5 IMMUNE – IMMUNO COMPROMISED HOST

*IF NO ABG USE SERUM CO_2

**IF IN ARF DOUBLE THE CREATININE POINT SCORE

APACHE II	
Physiology Points	
Glasgow points	
Chronic Health Points	
Age Points	
APACHE SCORE (TOTAL)	

Appendix 2: Serial Organ Function Assessment[18][xxii]

SOFA score	1	2	3	4
			Respiration with respiratory support	
Respiration with respiratory support PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
Coagulation Platelets $x10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dl	1.2-1.9	2-5.9	6-11.9	> 12
Cardiovascular Hypotension >15 or (doses in ug/kg·min) cathecolamines> 0,1	MAP < 70mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine > 5 or cathecolamines ≤ 0.1	Dopamine
Neurologic Glasgow Coma Score	13-14	10-12	6-9	< 6
Renal Creatinine mg/dl or Urine output ml/zi	1.2-1.9	2-3.4	3.5-4.9 (200-500)	> 5 (< 200)

Appendix 3. Richmond agitation–sedation scale[xxii]

TABLE 1. RICHMOND AGITATION–SEDATION SCALE

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under DESCRIPTION)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1).
   Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2).
   Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score −4).
   Patient has no response to voice or physical stimulation (score −5).

APPENDIX 4: Confusion Assessment Method (CAM-ICU)[xxii]

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course*		
A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?		
II. Inattention†		
Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?		
III. Disorganized thinking		
Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up this many fingers. (Examiner holds 2 fingers in front of the patient.) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)		
IV. Altered level of consciousness		
Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environment and interacts appropriately Vigilant: hyperalert Lethargic: drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4): Yes___ No___		

*The scores included in the 10-point RASS range from a high of 4 (combative) to a low of −5 (deeply comatose and unresponsive). Under the RASS system, patients who were spontaneously alert, calm, and not agitated were scored at 0 (neutral zone). Anxious or agitated patients received a range of scores depending on their level of anxiety: 1 for anxious, 2 for agitated (fighting ventilator), 3 for very agitated (pulling on or removing catheters), or 4 for combative (violent and a danger to staff). The scores −1 to −5 were assigned for patients with varying degrees of sedation based on their ability to maintain eye contact: −1 for more than 10 seconds, −2 for less than 10 seconds, and −3 for eye opening but no eye contact. If physical stimulation was required, then the patients were scored as either −4 for eye opening or movement with physical or painful stimulation or −5 for no response to physical or painful stimulation. The RASS has excellent interrater reliability and intraclass correlation coefficients of 0.95 and 0.97, respectively, and has been validated against visual analog scale and geropsychiatric diagnoses in 2 ICU studies.[37,38]

†In completing the visual ASE, the patients were shown 5 simple pictures (previously published[34]) at 3-second intervals and asked to remember them. They were then immediately shown 10 subsequent pictures and asked to nod "yes" or "no" to indicate whether they had or had not just seen each of the pictures. Since 5 pictures had been shown to them already, for which the correct response was to nod "yes," and 5 others were new, for which the correct response was to shake their heads "no," patients scored perfectly if they achieved 10 correct responses. Scoring accounted for either errors of omission (indicating "no" for a previously shown picture) or for errors of commission (indicating "yes" for a picture not previously shown). In completing the auditory ASE, patients were asked to squeeze the rater's hand whenever they heard the letter *A* during the recitation of a series of 10 letters. The rater then read 10 letters from the following list in a normal tone at a rate of 1 letter per second: *S, A, H, E, V, A, A, R, A, T*. A scoring method similar to that of the visual ASE was used for the auditory ASE testing.

Appendix 5: Telephone Survey

We would like to ask you (the PATIENT) some questions about your (the PATIENT'S) health:

- In general, how would you say your health is now?

☐ Excellent
☐ Very good
☐ Good
☐ Fair
☐ Poor

- Sometimes it is necessary to spend most of the day in bed. Is this true for you now?

☐ Yes
☐ No
☐ Don't know

- Have you fallen since discharge/since the last time our team talked with you by phone?

☐ Yes
☐ No
☐ Don't know

- If you have fallen since discharge/since the last time our team talked with you by phone, did you see a doctor or go to an emergency department to get checked out after the fall?

☐ Yes
☐ No
☐ Don't know

- Have you been admitted to a hospital since your hospital discharge/the last time our team spoke with you by phone?

☐ Yes
☐ No
☐ Don't know

- Since discharge or the last time our team spoke with you, have you spent any time living in a nursing home, group home/assisted living facility, or rehabilitation facility?

☐ Yes
☐ No
☐ Don't know

- Did (you/PATIENT) need help washing or bathing (yourself/HIMSELF/HERSELF)?

☐ Yes
☐ No
☐ Don't know

- Do you need help dressing and undressing?

☐ Yes
☐ No
☐ Don't know

- Do you need help eating, including cutting food?

☐ Yes
☐ No
☐ Don't know

- Do you need help getting in and out of the bed and a chair?

☐ Yes
☐ No
☐ Don't know

- Do you need help cleaning yourself for either bowel or bladder functions?

☐ Yes
☐ No
☐ Don't know

- Do you sometimes have an accident with your bowels either during the day or night?

☐ Yes
☐ No
☐ Don't know

- Do you sometimes wet yourself either during the day or night?

☐ Yes
☐ No
☐ Don't know

Do you do the following on your own (NO HELP), with some help, or are you unable to:

- Use the telephone, including looking up and dialing numbers, and answering the phone?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Get to places out of walking distance by using public transportation or driving your car?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Shop for groceries or clothes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Prepare, serve and provide meals for yourself?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do light housework, such as dusting or doing dishes?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Take pills or medicines in the correct amounts and at the correct times?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Handle your own money, including writing checks and paying bills?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Do your laundry?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

- Walk across the room either on your own or with a cane or walker?

☐ On own/no help
☐ Some help
☐ Unable to do this
☐ Don't know

The following questions are about your living situation.

- Where do you currently live?
  - ☐ Your (the PATIENT'S) own apartment or house
  - ☐ A relative or friend's apartment or house
  - ☐ A nursing home, group home/assisted living facility, or long-term care facility
  - ☐ A homeless shelter
  - ☐ Other_____

- How many people live with you (the PATIENT)? _____

- What is your current weight? _____

- If you (the PATIENT) need extra help when you get home from the hospital, is there someone who can help you (the PATIENT)?
  - ☐ No
  - ☐ Yes

If “Yes”, what is this person’s relationship to you (the PATIENT)?

Spouse	1	Neighbor or landlord	7
Other partner	2	Other friend	8
Child	3	Floor nurse	9
Parent	4	Visiting nurse	10
Brother or sister	5	Home attendant or health aide	11
Other relative	6	Some other person	12
(specify)		(specify)	

- What does this person do during the day if he/she is not helping you (the PATIENT)?
  - □ Work outside the home without pay
  - □ Work outside the home for pay
  - □ Work in the home without pay
  - □ Work in the home for pay
  - □ Other (specify) _____

- How old is this person?

□ Under 18
□ 18-49
□ 50-64
□ 65-74
□ 75-84
□ 85-89
□ 90 or greater

Statistical Considerations

Randomization

Patients are randomized 1:1 to the two arms (mask ventilation or helmet ventilation) by prepared sealed envelopes.

Primary Endpoint

The primary outcome measure is the proportion of patients requiring and undergoing endotracheal intubation (timeframe). In our experience in the medical ICU, approximately 50% of all patients who require non-invasive ventilation via facemask ultimately require invasive endotracheal intubation. This trial will target an absolute reduction of this failure rate of 20% (and equivalent to a relative reduction of 40%), resulting in 30% of patients on helmet noninvasive ventilation requiring endotracheal intubation.

Power and Sample Size

We specify two-sided (type I error) $\alpha = 0.05$ and seek power of 80% for the effect size control group rate and effect size above, leading to a sample size requirement of 103 patients in each group (206 total patients). As the sample size for this endpoint depends in part on the control (facemask) group intubation rate, and depending on this rate, different improvements might be considered a clinically material gain, sample size is shown for a range of control group rates and relative reductions (the first column represents a 40% reduction in the rate of the rate as planned in this study).

Control Group Intubation Rate	N per group (rate) for 40% relative reduction	N per group (rate) for 50% relative reduction
0.40	145 (0.24)	91 (0.20)
0.45	122 (0.27)	77 (0.225)
0.50	103 (0.30)	66 (0.250)
0.55	88 (0.33)	57 (0.275)

It can be seen that approximately 105 patients/arm will be adequate for detecting reductions in intubation rate of 40% or larger, when control group intubation rates in the range of 47.5%-50%. During the trial, the control group rate will be reassessed in order to determine if sample size adjustment (based on the control group rate only, not the effect size) is warranted.

Analytic Methods

The primary analysis will involve testing for a difference of proportions between the two randomized groups, if there are imbalances in patient characteristics between groups, analysis

using logistic regression to will be used to provide a test adjusted for differences in these factors. Stratified table analysis may also be employed.

Interim Monitoring

Safety and study conduct will be monitored continuously by the investigators and reviewed periodically by an independent Data and Safety Monitoring Board (DSMB). The assumed control group intubation rate as stated above is 50%, Since the statistical power at a given sample size depends on this parameter, it will be inspected at the time of interim analysis to determine if there is a strong deviation from this anticipated rate. If the rate differs by more than 10%, then sample size adjustment may be considered. Note that this re-assessment is independent of the specified effect size, and thus does not alter the operating characteristics of the trial with respect to alpha level and power.

Statistical monitoring for the primary endpoint will be conducted to determine if early trial stopping warrants consideration (at the pre-specified alternative hypothesis of a 40% relative reduction in intubation rate), The study will primarily monitored for futility, or early determination that the two groups are unlikely to differ with respect to the primary endpoint (intubation rate). A futility boundary will be established via conditional power, defined as Pr (reject H_0 at end of trial current data and assumed H_1 effect), If this probability is sufficiently small, then stopping at a given point prior to the planned trial end may be justified. Here, we will consider conditional power approaching 20% as warranting consideration of early stopping.

Early stopping for efficacy in this trial would only be considered under extraordinary evidence of benefit, and thus an extreme significance level will be specified for early rejection of the null hypothesis and declaration that the helmet strategy is superior. This specification has the advantage of having no material effect on significance level for the definitive hypothesis test at study end.

The following table provides the criteria for the primary endpoint monitoring plan.

Analysis after assessment of	Fraction of total information	Efficacy Stopping:		Futility Stopping: Consider stop if:	
		Z >	P <	Z <	P >
35 patients per group	0.333	3.08	0.001	-0.966	0.833
70 patients per group	0.667	3.08	0.001	0.678	0.249
Final Test (105/group)	1.00	1.96	0.025	---	---

It is noted that these boundaries serve as guidelines for the investigators and DSMB, and decisions should be made in conjunction with other information from the trial.