e-prone trial

Manual of Operations

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Version 1

Mobile/Print version

Manual of operations

For questions, please contact the Trial Coordinating Center:

Karla Ramos RN, MPP, MSc
Project Manager

eprone@gmail.com

Pontificia Universidad Católica de Chile

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INCLUSION CRITERIA

- Age ≥18 years
- Endotracheal intubation and mechanical ventilation ≤ 72 hours
- Moderate-severe ARDS:
  - Within one week of a known clinical insult or new/worsening respiratory symptoms
  - Bilateral infiltrates not fully explained by effusions, lobar/lung collapse, or nodules.
  - Respiratory failure not fully explained by cardiac failure or fluid overload.
  - PaO2/FiO2 < 150 mmHg in the supine position.

- Prone positioning has been indicated by the attending physician or initiated within the last 16 hours*.

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INCLUSION CRITERIA

- *Note: This criterion must be met in the last arterial blood gas evaluation conducted in the supine position before prone positioning, following a stabilization period on invasive mechanical ventilation with PEEP ≥ 5 cmH2O and tidal volume between 5-7 ml/kg (ideal body weight). PaO2/FiO2 evaluations obtained after prone positioning will not be considered for eligibility.

EXCLUSION CRITERIA

- Contraindications to prone positioning:
  - Intracranial pressure > 20 mmHg
  - Massive hemoptysis
  - Recent tracheal or sternotomy surgery
  - Open abdominal surgery
  - Recent facial trauma or surgery
  - Unstable spine
  - Femur or pelvic fracture
  - Anterior thoracic drain with air leak
  - ECMO before randomization

- Chronic respiratory failure requiring long-term oxygen therapy or non-invasive ventilation (NIV).
- Known pregnancy
- Transitioning to palliative care or anticipated withdrawal of life-sustaining treatment.
- Cognitive disability prior to hospitalization.

Follow-up

Physiological and respiratory variables and prone evaluations will be conducted until day 7. Data on mechanical ventilation will be collected until day 28, along with ICU and hospital stay, and vital status up to day 90.

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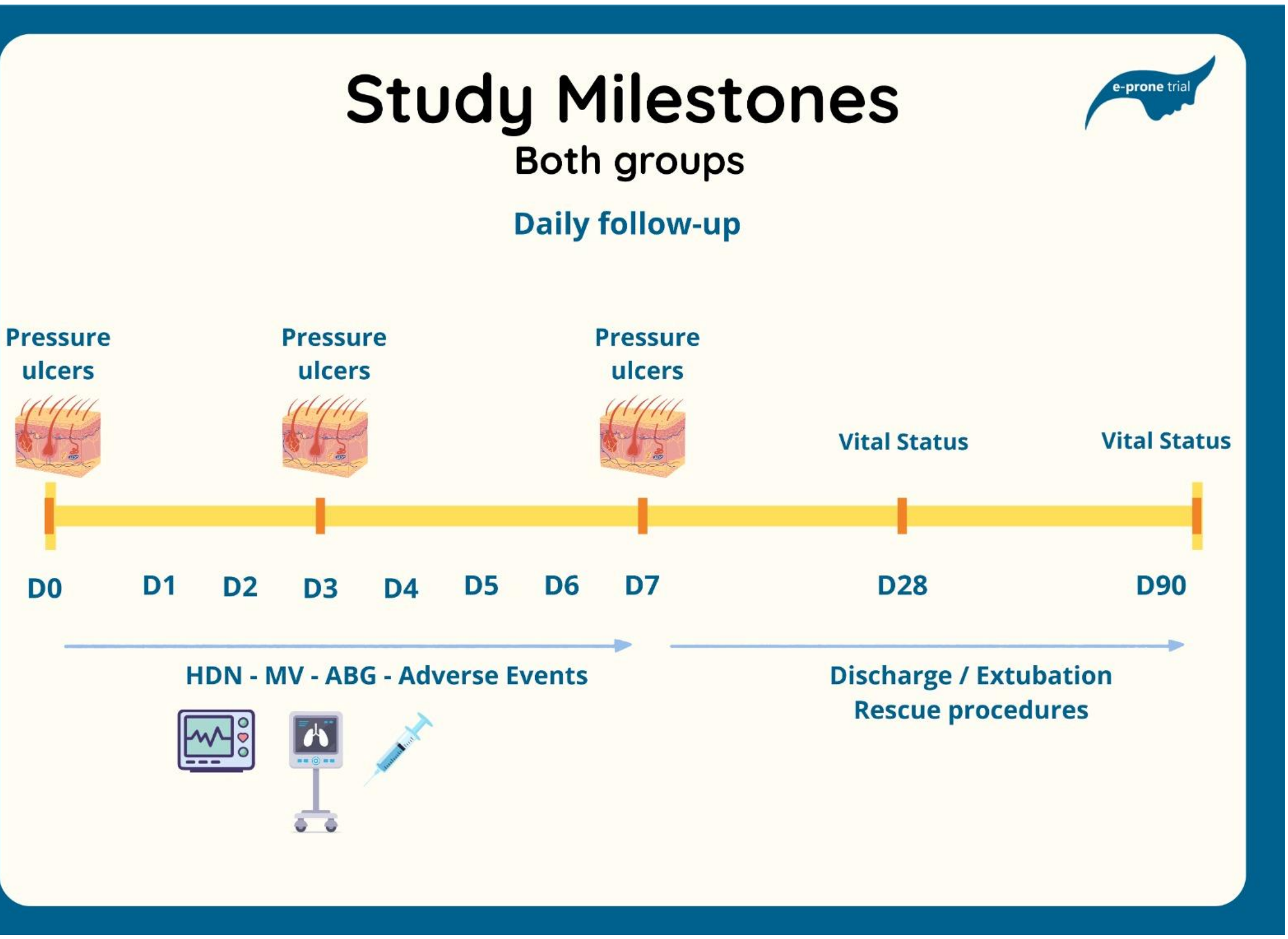
General milestones (both groups)



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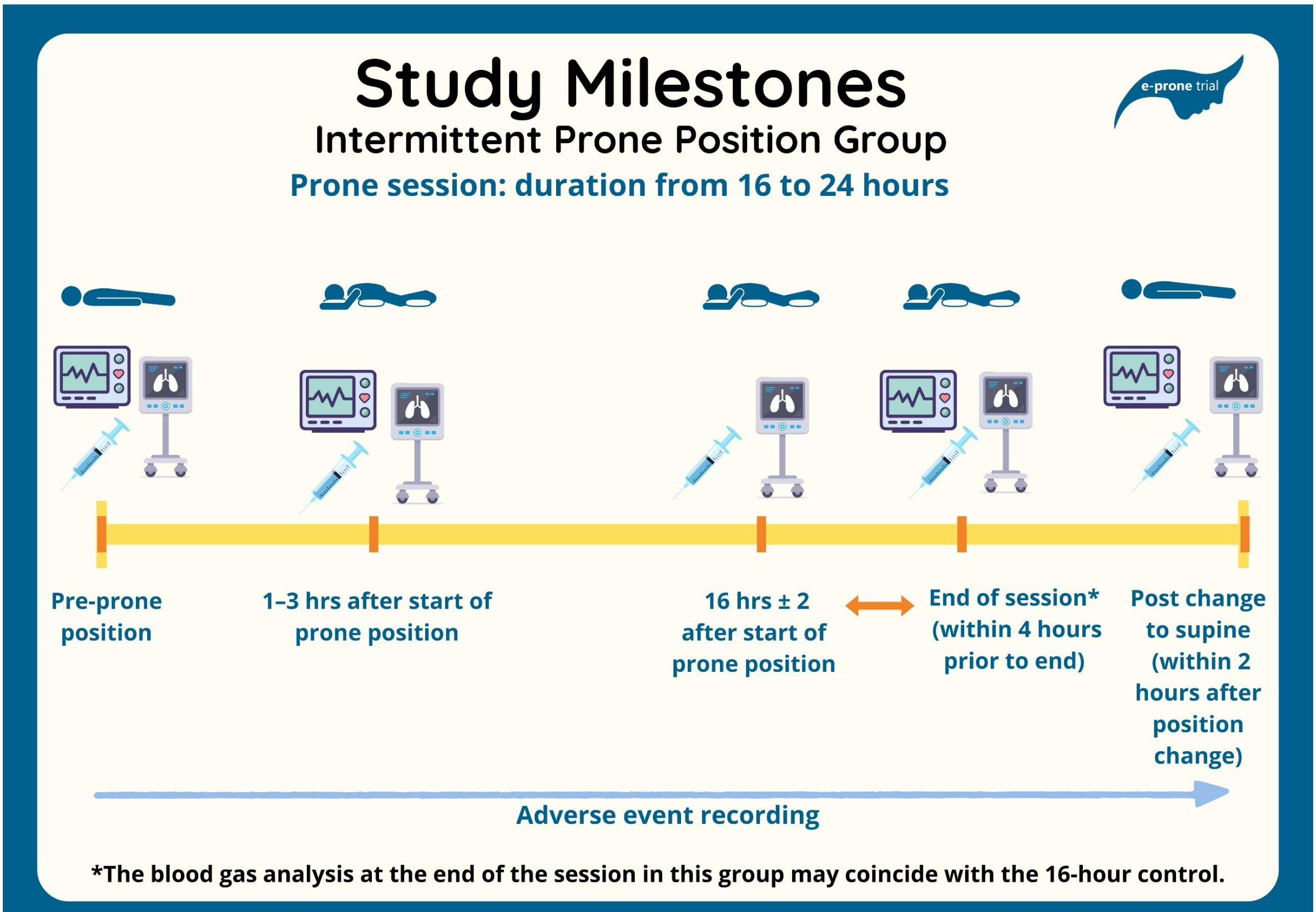
Milestones – Intermittent Prone Group



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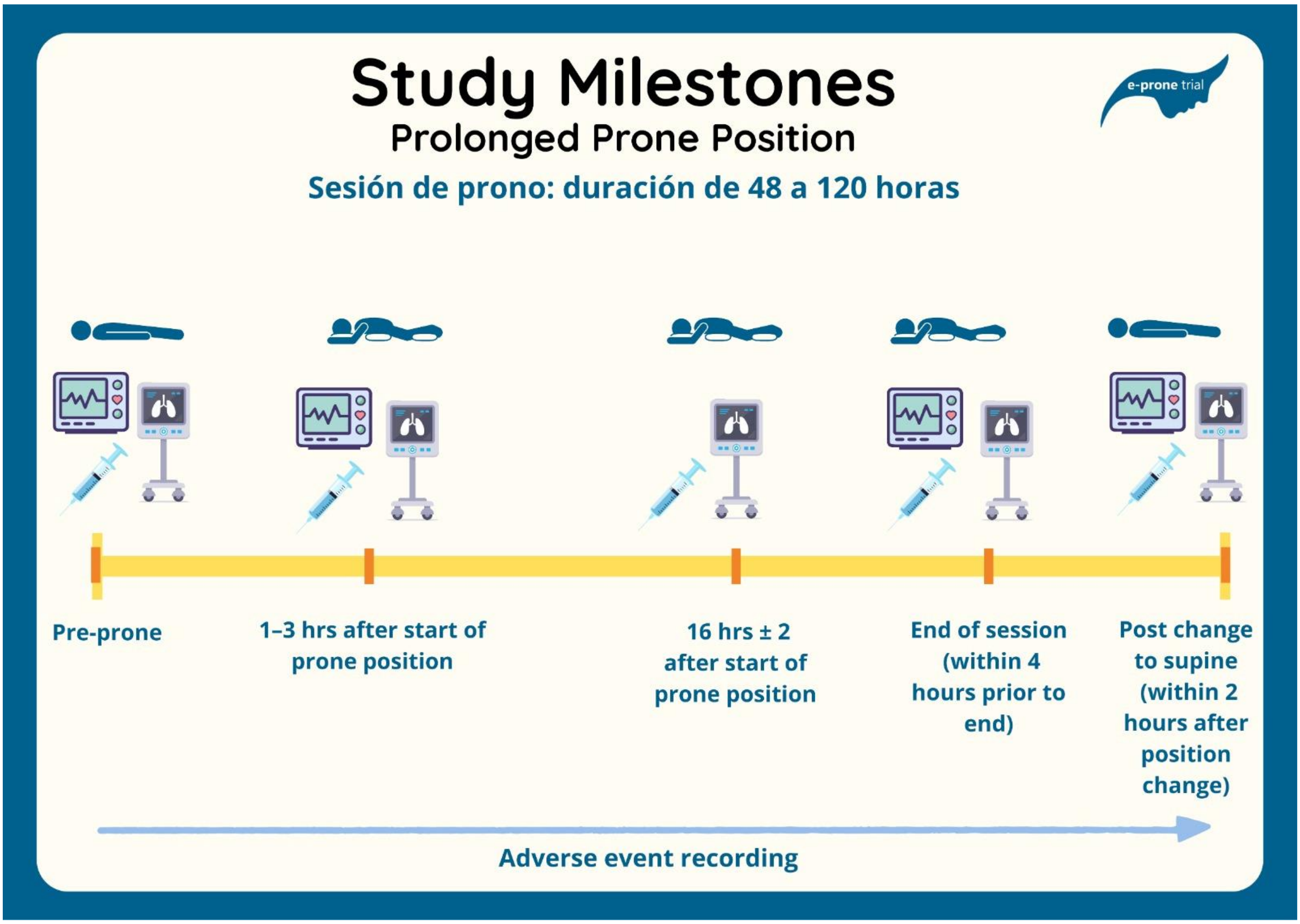
Milestones – Prolonged Prone Group



OUTCOMES

PRIMARY OUTCOME:

- 28-day mortality.

SECONDARY OUTCOMES:

- All-cause mortality at 60 and 90 days
- Ventilator-free days at 28 days
- ICU-free days at 28 days
- Hospital-free days at 28 and 90 days
- Use of rescue procedures
- Physiological and ventilatory parameters up to day 7
- Incidence of pneumothorax up to day 7
- Pressure ulcers at days 3 and 7, by grade and location
- Adverse events potentially related to prone position up to day 7 (e.g., endotracheal tube displacement, vascular catheter or gastric tube displacement, endotracheal tube obstruction, unplanned extubation, desaturation, hypotension, bradycardia, cardiac arrest)

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Intervention Group

- The session will last at least 48 hours.
- If it reaches 48 hours, the PaO2/FiO2 ratio should be ≥ 200 mmHg to return to the supine position.
- If continuous prone positioning reaches 120 hours, the patient must return to the supine position regardless of the PaO2/FiO2 ratio.
- If the PaO2/FiO2 ratio worsens and decreases to < 150 mmHg after returning the patient to supine position, prone positioning will be restarted with a new session at any time (until day 7).
- Sessions can be repeated until day 7, always following the same temporal criteria for this group.
- After day 7, the decision to continue prone positioning and its duration will depend on the clinical care team.

Suspension of intervention:

- If PaO2/FiO2 in the prone position is < 20% of PaO2/FiO2 in supine position for > 2 consecutive sessions.
- Complications: Unplanned extubation, cardiac arrest, bradycardia, etc.
- Urgent procedure
- ECMO

Control Group

- The session duration will be extended for a minimum of 16 hours and a maximum of 24 hours, regardless of the PaO2/FiO2 ratio.
- If the PaO2/FiO2 ratio worsens and decreases to < 150 mmHg after returning the patient to the supine position, prone positioning will be restarted with a new session at any time (until day 7).
- Sessions can be repeated until day 7, always following the same temporal criteria for this group.
- After day 7, the decision to continue prone positioning and its duration will depend on the clinical care team.

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Comparative Table of Groups

	Maximum time in the prone position	Minimum time in the prone position	Criteria to return to the supine position
Extended prone (intervention)	120 hours	48 hours	- If it reaches 48 hours with a PaO2/FiO2 ratio ≥ 200. - If it reaches 120 continuous hours: return to the supine position regardless of the PaO2/FiO2 ratio.
Intermittent prone (control)	24 hours	16 hours	Return to the supine position regardless of the PaO2/FiO2 ratio.

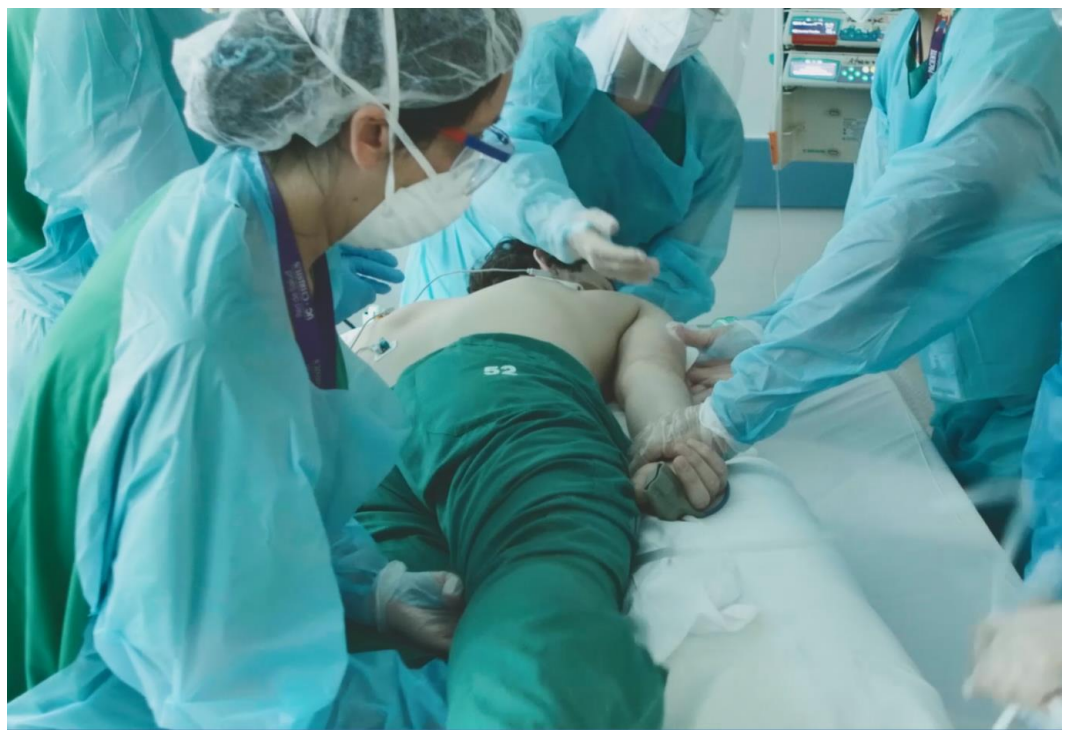
Similarities in both groups:

- **If the PaO2/FiO2 ratio worsens in the supine position to < 150 mmHg, the patient must be returned to the prone position.**
- **The time for repeating sessions indicated in E-Prone is until day 7.**

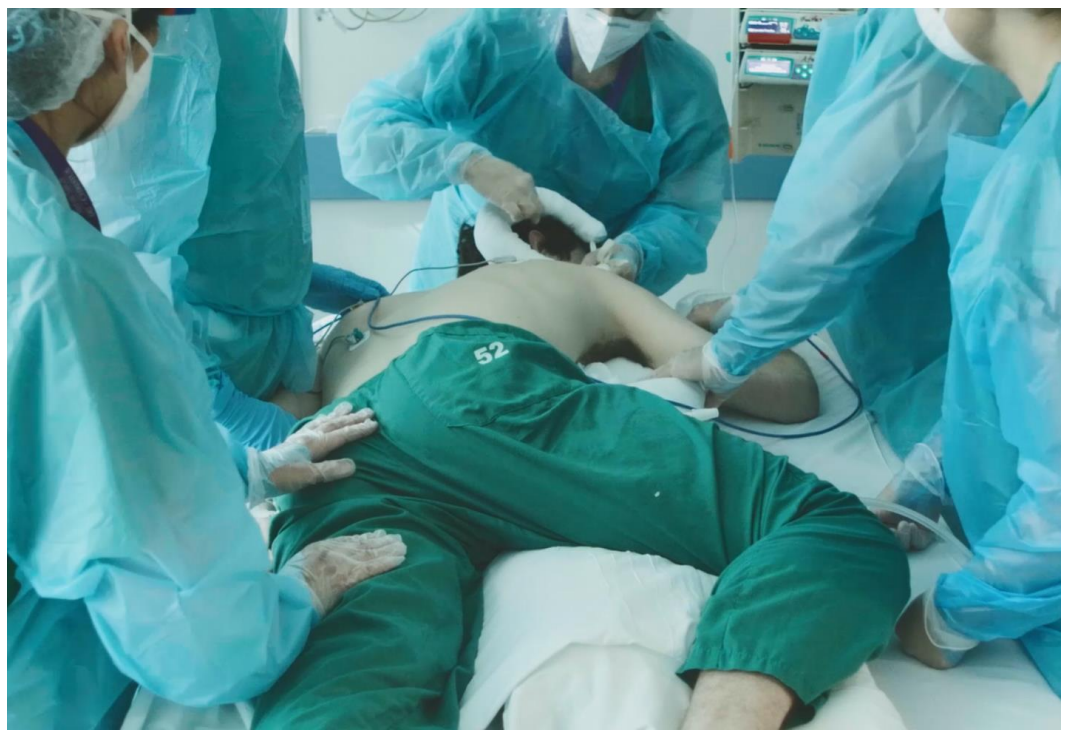
Management Recommendations

Prone Position Care

Change position every 2 hours using pillows to support the thorax and abdomen.



Elevate the hand and leg on the side where the head is turned. Use pillows to elevate the leg.



Place a C-shaped cushion under the head (page 14)

Management Recommendations

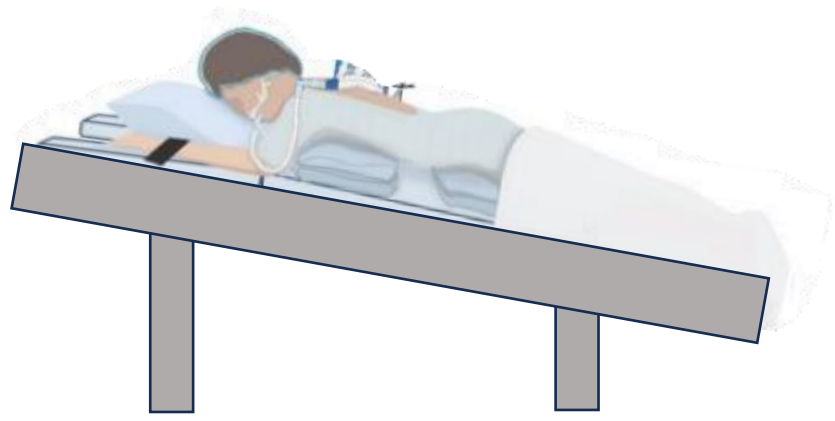
Prone Position Care

- C-shaped cushion

The open part of the "**C**" shaped cushion should be placed in the mouth area, and the curved part should surround from the chin to the forehead.

- Bed in the anti-Trendelenburg position

After positioning the patient in the prone position, adjust the bed to an inclination of approximately 10° - 15° in the reverse Trendelenburg position.



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Management Recommendations

Monitoring during supine-prone position changes

Recommended parameters prior to the maneuver

- Heart rate: > 50 and < 140 bpm
- Mean arterial pressure: > 60 mmHg with norepinephrine < 0.01 mcg/kg/min

Minimum monitoring during the maneuver:

- pulse oximeter (SpO2).

Management Recommendations

Mechanical ventilation (MV) settings

Suggestions for MV settings :

Tidal volume **should always** be adjusted according to the predicted body weight, regardless of the cause of ARDS. The goal is to achieve a tidal volume between 6 to 8 mL/kg of predicted body weight, and it is recommended to use the following formulas or tables.

Male:

Predicted weight (kg) = 50 +2.3 {[height(cm) x 0.394] – 60}

Female:

Predicted weight(kg) = 45.5 +2.3 {[height (cm) x 0.394] – 60}

Management Recommendations

Predicted Weight and Tidal Volume Table for Male

Height (cm)	Predicted weight (kg)	4 ml/kg	5 ml/kg	6 ml/kg	7 ml/kg	8 ml/kg
144	42	170	212	**255**	297	340
146	44	177	222	**266**	310	354
148	46	184	231	**277**	323	369
150	48	192	240	**288**	336	383
152	50	199	249	**298**	348	398
154	52	206	258	**309**	361	412
156	53	213	267	**320**	374	427
158	55	221	276	**331**	386	441
160	57	228	285	**342**	399	456
162	59	235	294	**353**	412	470
164	61	242	303	**364**	424	485
166	62	250	312	**375**	437	499
168	64	257	321	**385**	450	514
170	66	264	330	**396**	462	528
172	68	271	339	**407**	475	543
174	70	279	348	**418**	488	557
176	71	286	357	**429**	500	572
178	73	293	367	**440**	513	586
180	75	300	376	**451**	526	601
182	77	308	385	**462**	538	615
184	79	315	394	**472**	551	630
186	81	322	403	**483**	564	644
188	82	329	412	**494**	577	659
190	84	337	421	**505**	589	673
192	86	344	430	**516**	602	688
194	88	351	439	**527**	615	702
196	90	358	448	**538**	627	717
198	91	366	457	**549**	640	731
200	93	373	466	**559**	653	746

Management Recommendations

Predicted weight and tidal volume Table for Female

Height (cm)	Predicted weight (kg)	4 ml/kg	5 ml/kg	6 ml/kg	7 ml/kg	8 ml/kg
134	29	116	145	**174**	203	231
136	31	123	154	**184**	215	246
138	33	130	163	**195**	228	260
140	34	137	172	**206**	241	275
142	36	145	181	**217**	253	289
144	38	152	190	**228**	266	304
146	40	159	199	**239**	279	318
148	42	166	208	**250**	291	333
150	43	174	217	**261**	304	347
152	45	181	226	**271**	317	362
154	47	188	235	**282**	329	376
156	49	195	244	**293**	342	391
158	51	203	253	**304**	355	405
160	52	210	262	**315**	367	420
162	54	217	272	**326**	380	434
164	56	224	281	**337**	393	449
166	58	232	290	**348**	406	463
168	60	239	299	**358**	418	478
170	62	246	308	**369**	431	492
172	63	253	317	**380**	444	507
174	65	261	326	**391**	456	521
176	67	268	335	**402**	469	536
178	69	275	344	**413**	482	550
180	71	282	353	**424**	494	565
182	72	290	362	**435**	507	579
184	74	297	371	**445**	520	594
186	76	304	380	**456**	532	608
188	78	311	389	**467**	545	623
190	80	319	398	**478**	558	637

Management Recommendations

Lung Recruitment Maneuvers

According to the recommendations of American and European guidelines for the management of patients with ARDS, we do not suggest the routine use of lung recruitment maneuvers.

Intensive Care Med. 2023 Jul;49(7):727-759.
Am J Respir Crit Care Med. 2024 Jan 1;209(1):24-36.

However, if a lung recruitment maneuver (LRM) is exceptionally used upon the indication of the treating team, we suggest performing it as follows:

In pressure-controlled ventilation mode with a minimum respiratory rate of 10 breaths per minute, do not exceed inspiratory pressures of 40 cmH2O. In case of hemodynamic deterioration, suspend the LRM.

Management Recommendations

PEEP and FiO2 Settings

We suggest following the protocols established by each center regarding the use of low or high PEEP/FiO2 tables or the selection of PEEP based on respiratory mechanics, as there is no clear consensus on these recommendations according to international guidelines.

Intensive Care Med. 2023 Jul;49(7):727-759.
Am J Respir Crit Care Med. 2024 Jan 1;209(1):24-36.

On the following pages, you can find the methods for PEEP selection:

- PEEP/FiO2 tables
- PEEP selection based on static compliance

Management Recommendations

PEEP and FiO2 Settings

- PEEP/FiO2 Tables

Low PEEP/FiO2 Table

FiO2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	10	14	14	14	16	18	18	20	22	24

N Engl J Med 2000;342:1301-1308

High PEEP/FiO2 Table

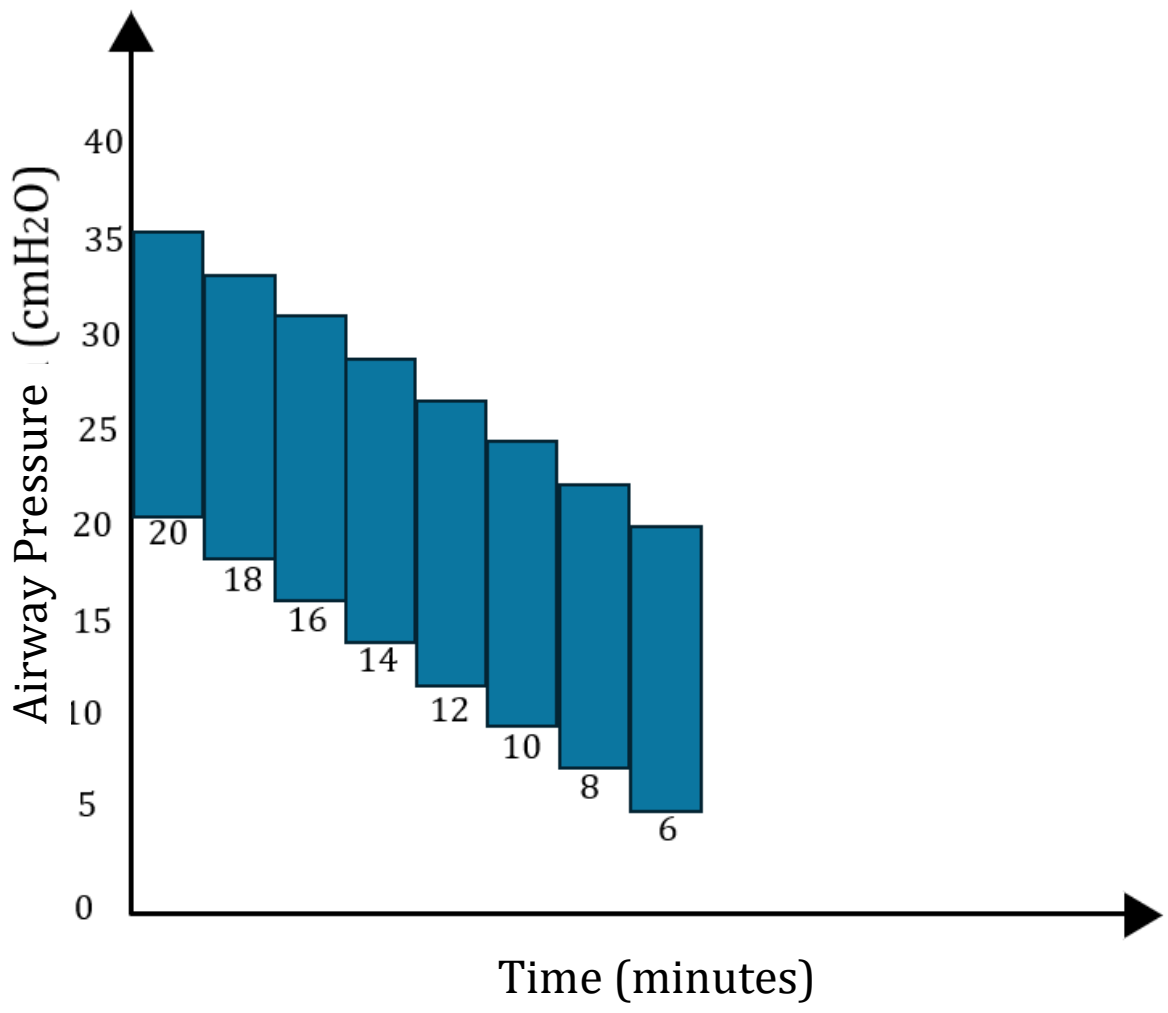
FiO2	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.7	0.8	0.9	1.0	1.0
PEEP	5	8	10	10	12	14	16	18	18	20	20	20	22	22	22	24

JAMA. 2008;299(6):637-645

Management Recommendations

PEEP and FiO2 Settings

- PEEP Selection Based on Static Compliance



- Set a volume-controlled mode with a tidal volume of 6 mL/kg of ideal body weight.

- Decrease the PEEP level by 2 cmH2O every 20 seconds (maximum time by step) and measure static compliance at each PEEP level.

- After identifying the PEEP level with the highest compliance, continue ventilation with that PEEP level.

Management Recommendations

Systemic Corticosteroids

According to American guidelines, we suggest the use of corticosteroids for patients with ARDS. However, the optimal dosage and duration remain unclear and should be determined by the treating team based on the ARDS etiology and the patient's clinical context.

Am J Respir Crit Care Med. 2024 Jan 1;209(1):24-36.

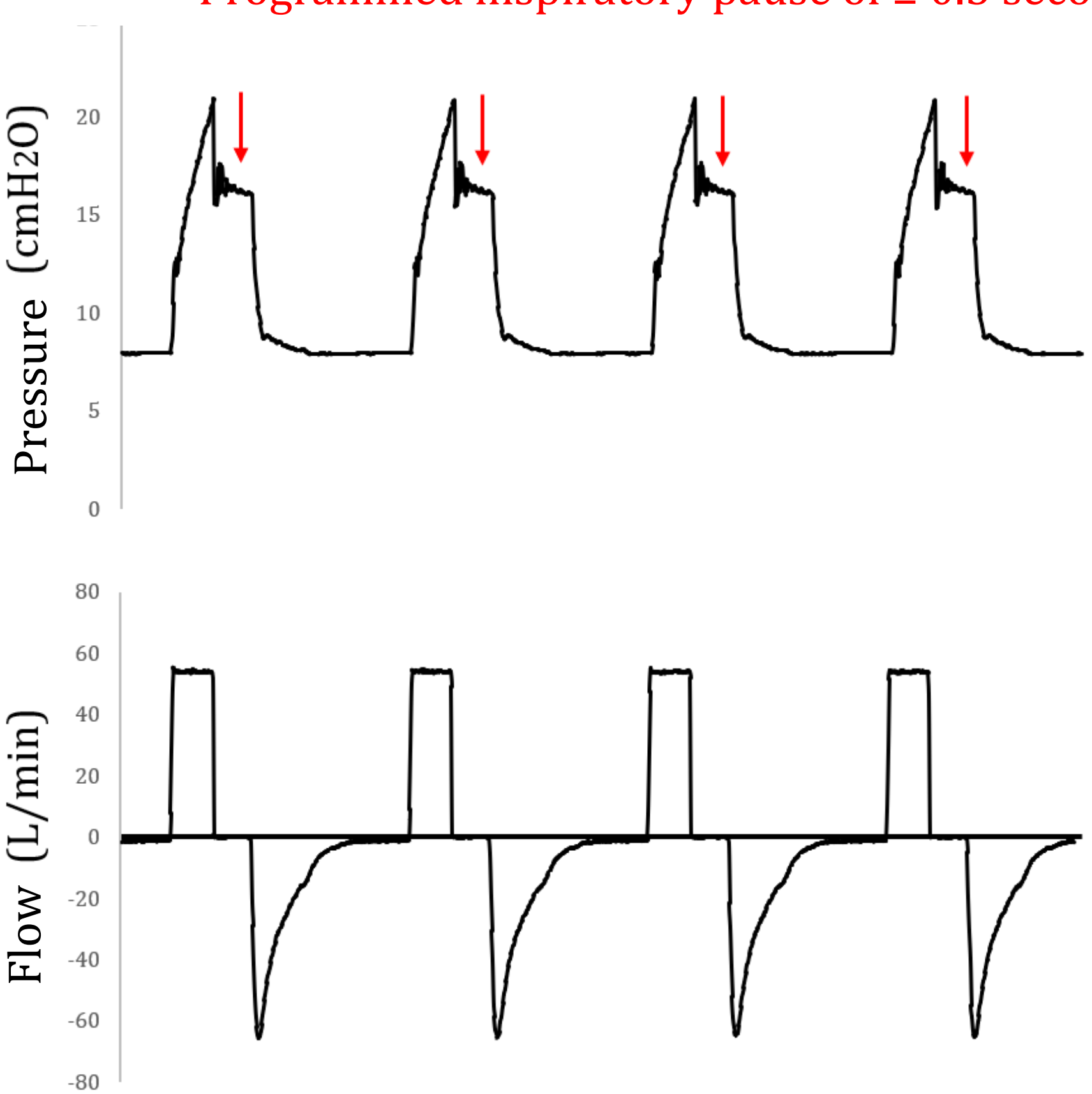
Management Recommendations

Respiratory Mechanics Measurements

- **Plateau pressure**

If a programmed pause ≤ 0.5 seconds is set, use that value. If ventilation has no programmed pause, perform a manual pause for ≤ 0.5 seconds.

Programmed inspiratory pause of ≤ 0.5 seconds



Henderson WR, et al. Am J Respir Crit Care Med. 2017 Oct 1;196(7):822-833.

Management Recommendations

Sedation

It is recommended to continue with local sedation protocols. However, it is important to use the Sedation-Agitation Scale (SAS) to quantify the level of sedation, which should be recorded on the E-prone trial platform.

Sedation-Agitation Scale (SAS)

Score	Category	Description
1	Unable to rouse	Minimal or no response to noxious stimuli, does not communicate or follow commands
2	Very sedated	Arouses to physical stimuli, but does not communicate or follow commands, may move spontaneously
3	Sedated	Difficult to arouse; awakens to verbal stimuli or gentle shaking, but drifts off again; follows simple commands
4	Calm and cooperative	Calm, awakens easily, follows commands
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting endotracheal tube
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side

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Management Recommendations

Neuromuscular Blockade (NMB)

- **We suggest the use of neuromuscular blockade (NMB) in patients with moderate to severe ARDS during the first 48 hours, particularly while the patient is in the prone position.**

- **If the patient remains in the prone position beyond this period (48 hours), the use of NMB is optional and should be determined by the local protocols of each center.**

J Respir Crit Care Med. 2024 Jan 1;209(1):24-36.

Management Recommendations

Weaning from Mechanical Ventilation

When to Perform a Spontaneous Breathing Trial (SBT):

General Considerations:

- Resolution of the underlying cause for mechanical ventilation
- Continuous sedatives discontinued

Respiratory Stability:

- Oxygenation: PaO_2/FiO_2 ratio ≥ 150 mmHg
- PEEP ≤ 8 cmH_2O
- Pressure support ≤ 10 cmH_2O
- SpO_2 ≥ 90% with FiO_2 ≤ 0.4
- Respiratory rate ≤ 35 breaths per minute
- pH ≥ 7.25

Cardiovascular Stability:

- Heart rate < 140 bpm
- Systolic blood pressure > 90 and < 160 mmHg
- Vasopressors discontinued or at low doses (≤ 0.1 mcg/kg/min of norepinephrine or equivalent)

Neurological Stability:

- Patient alert and cooperative

Management Recommendations

Spontaneous Breathing Trial (SBT)

How to Perform an SBT:

- Regardless of the patient's risk level, it is recommended to conduct an SBT without PEEP and with pressure support (PS) between 6 and 8 cmH2O for 30 minutes.

Criteria for SBT Failure

- **Clinical Evaluation**
  - Excessive agitation or anxiety
  - Low level of consciousness
  - Diaphoresis
  - Cyanosis
  - Nasal flaring
  - Use of accessory respiratory muscles (suprasternal and/or intercostal retractions)
  - Paradoxical chest/abdomen movements

Management Recommendations

Spontaneous Breathing Trial (SBT)

Criteria for SBT Failure

- **Respiratory Instability**
  - SpO_2 <90%
  - Respiratory rate > 35 breaths per minute
  - pH < 7.25 and/or $PaCO_2$ > 50 mmHg
- **Cardiovascular Instability**
  - Heart rate > 140 bpm
  - Systolic blood pressure < 90 or > 160 mmHg
  - Onset of arrhythmias (e.g., frequent ventricular ectopic beats, atrial fibrillation, etc.)

- **If there are signs of SBT failure, it is recommended to immediately discontinue the trial and revert to previous mechanical ventilation parameters for 24 hours before attempting another SBT.**
- **It is recommended to identify and treat the factors that caused the failure of the trial (e.g., anxiety, delirium, bronchospasm, abdominal distension, fluid overload, residual effects of sedatives, etc.).**

Management Recommendations

Post-extubation Respiratory Support

Patients who successfully pass the spontaneous breathing trial may be extubated.

- **Patients with Low Risk of Failure**

Consider using high-flow nasal cannula (HFNC) or standard oxygen therapy immediately after extubation.

- **Patients with High Risk of Failure**
  - High-Risk Criteria:
    - Chronic lung disease
    - Heart failure
    - ≥ 65 years

Consider using non-invasive mechanical ventilation (NIV) exclusively or NIV combined with HFNC immediately post-extubation. Maintain non-invasive respiratory support for at least 48 hours.

Frequently Asked Questions

- **Can I position my patient in supine for an emergency or a procedure? Example: catheter change, endotracheal tube change, drainage placement, etc.**

Yes, it is possible to place the patient in the supine position. However, the following guidelines should be considered to avoid violations and deviations from protocols.

Intervention group (extended prone)

<u>If the patient has been in prone position for < 48 hours:</u>

- **If the period in supine position is > 4 hours:** The first prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).
- **If the period in supine position is < 4 hours:** Resume the prone position, considering that it is still the first prone session (no need to re-evaluate GSA).

<u>If the patient has been in prone position for > 48 hours:</u>

- Regardless of the time required to be in supine for the procedure or emergency, the first prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).

Frequently Asked Questions

Control group (intermittent prone)

If the patient has been in prone position for < 16 hours:

- **If the period in supine position is > 4 hours:** The prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).
- **If the period in supine position is < 4 hours:** Resume the prone position, considering it as part of the previous prone session (no need to reevaluate GSA).

If the patient has been in prone position for > 16 hours:

- Regardless of the time needed in supine for the procedure or emergency, the prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).

Frequently Asked Questions

What happens if the patient needs to undergo a computed tomography (CT) scan while in the prone position?

If your center has experience performing such exams with patients in the prone position, you may proceed with this approach. However, if your center is not familiar with this practice and typically conducts exams with the patient in the supine position, you may follow the established local protocol. In this latter case, it is suggested to consider the following guidelines to avoid protocol violations and deviations.

Intervention group (extended prone)

If the patient has been in prone position for < 48 hours:

- **If the period in supine position is > 4 hours:** The first prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).
- **If the period in supine position is < 4 hours:** Resume the prone position, considering that it is still the first prone session (no need to re-evaluate GSA).

Frequently Asked Questions

Intervention group (extended prone)

If the patient has been in prone position for > 48 hours:

- Regardless of the time required to be in supine for the procedure or emergency, the first prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).

Control group (intermittent prone)

If the patient has been in prone position for < 16 hours:

- **If the period in supine position is > 4 hours:** The prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).
- **If the period in supine position is < 4 hours:** Resume the prone position, considering it as part of the previous prone session (no need to reevaluate GSA).

If the patient has been in prone position for > 16 hours:

- Regardless of the time needed in supine for the procedure or emergency, the prone session is considered concluded. GSA should be evaluated to verify if the criteria for a new prone session are met (PaO2/FiO2 < 150mmHg).

Frequently Asked Questions

- **Can I use BIS or other anesthetic depth monitors?**

Yes, any sedation level monitoring system available for the patients can still be used. However, the sedation level must still be recorded using the SAS scale on the E-prone trial platform.

- **What happens if the patient reaches the maximum prone position time during the early morning (e.g., at 3 AM)? Can I wait until the following morning?**

It can be postponed for a maximum of 4 hours. However, the total prone cycle time must be recorded on the E-prone trial platform.

In the **intervention group (extended),** if 120 hours are reached during the early morning, it is acceptable to wait until the following morning to change to the supine position.

In the **control group (intermittent),** the session can be advanced to a minimum of 16 hours, but it should not be extended by more than 4 hours beyond the maximum time (24 hours).

Frequently Asked Questions

- **What happens if a decision is made to perform a life support adjustment/limitation during the protocol?**

It should be recorded as the reason for discontinuing the protocol. However, follow-up continues until 90 days.

- **In my center, we use esophageal pressure monitoring for the selection of optimal PEEP. Can I continue using it, or does it interfere with the protocol?**

Yes, esophageal pressure monitoring can be used. It is only necessary to complete the conventional respiratory mechanics data in the records.

- **In my center, we use electrical impedance tomography (EIT) to monitor mechanical ventilation and select PEEP. Can I continue using it, or does it interfere with the protocol?**

Yes, EIT can be used to monitor ventilation and for mechanical ventilation settings. It is only necessary to complete the conventional respiratory mechanics data in the records.

Frequently Asked Questions

- **If the treating team checks the ABG before returning to the supine position (out of protocol), and the PaO2/FiO2 ratio is below 200 mmHg, and the patient is near the end of the prone session due to time criteria, can the patient remain in the prone position beyond 24 hours (intermittent group) or 120 hours (extended group)?**

No, as these are the maximum time limits for both groups. In this case, the patient must be turned to the supine position, the arterial blood gas should be checked again, and if the criteria are met again (PaO2/FiO2 < 200mmHg), a new prone cycle may begin in the group to which the patient was randomized.

Frequently Asked Questions

- **If the patient has arterial blood gases (ABG) check before the minimum time for each group (16 hours in control and 48 in intervention) and the PaO2/FiO2 is more than 200, can I supine them?**

No. In this case, the patient must remain in position for the minimum time of each group (16 or 48 hours as appropriate), after which they may be supined. Remember that ABG should be rechecked within the following 4 hours to determine whether to keep the patient in supine position or start a new prone cycle.

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Frequently Asked Questions

- **What should I do if arterial blood gases (ABG) were not taken within the time suggested by the study?**

The most recent ABGs can be used, as long as the test was performed in the position corresponding to the record. Additionally, it is important to register the actual time of the tests in the E-prone trial platform.

- **Who can I contact in case of protocol questions?**

You can contact our Project Manager, Karla Ramos, via the following email: **eprone@gmail.com.**

Manual of operations

LATIN AMERICAN INTENSIVE CARE NETWORK