OFFICIAL TITLE OF THE STUDY:

PROTECT-ICU: Impact of a Formative Training Intervention on the Implementation of an Expanded ABCDEF Care Bundle and Its Effect on PICS: a Multicenter Cluster-Randomized Pre-Post Clinical Trial with Post-ICU Follow-up NCT NUMBER: Not yet assigned

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1. INTRODUCTION

Survival following intensive care has steadily improved over the past decade, but a significant percentage of patients develop post-intensive care syndrome

(SPCI), with physical, cognitive, and psychological sequelae that substantially impact quality of life, return to activity, and use of healthcare resources. The frequency and severity of PICS vary greatly depending on the evaluation time point (1, 3, 6, or 12 months), the population type (medical/surgical, COVID/noCOVID), and the instruments used to measure each domain, with significant heterogeneity among studies and meta-analyses. In large cohorts and recent reviews, this variability is described and the need for standardized and longitudinal evaluations is emphasized to adequately interpret the evolution of PICS in clinical practice.

The ABCDEF bundle (analgesia/light sedation; spontaneous breathing trials; choice/monitoring of sedation; detection and management of delirium; mobilization; family involvement) is associated with process improvements (less deep sedation, less delirium, more mobilization, and family participation) and, potentially, better intermediate outcomes. However, adherence to the bundle is uneven between centers, and evidence of its direct relationship with PICS at 3–12 months in multicenter and routine-practice settings is limited and methodologically heterogeneous. Meanwhile, post-discharge follow-up strategies (e.g., post-ICU clinics) have shown heterogeneous results and sometimes no benefit in clinically relevant outcomes; therefore, focusing interventions within the ICU and measuring their implementation with robust methods emerges as a priority improvement approach.

Standardized training of personnel is a key factor in optimizing the implementation of complex care. Structured programs — with homogeneous materials, coverage verification, and mini-comprehension audits — have been shown to be feasible and transferable in multicenter networks (e.g., “Zero”-type initiatives), although their specific impact on PICS has not been consistently measured in Spanish-speaking settings. Similarly, there is interest in expanded components to the core ABCDEF bundle (e.g., nutrition, sleep, discharge planning, rehabilitation, psychosocial support, etc.) that could provide incremental benefit; their comparative evaluation against the classic bundle remains necessary and should be approached with an exploratory framework.

In the present study, in addition to the “classic package of measures” recommended in intensive care (ABCDEF), a series of additional interventions have been incorporated that, according to available scientific evidence, could contribute to improving the quality of life of critically ill patients and reducing the incidence of post-intensive care syndrome (SPCI), called the “expanded measures package” (G–Z). The development of these complementary measures has involved the collaboration of all Working Groups of the Spanish Society of Intensive, Critical, and Coronary Medicine (SEMICYUC), each contributing specific proposals related to the comprehensive care of the critically ill patient according to their field of expertise. This multidisciplinary approach enriches and expands the framework of the ABCDEF bundle, with the aim of providing more comprehensive, patient-centered care and targeting the reduction of medium- and long-term complications, including PICS.

In this context, PROTECT-UCI proposes to evaluate, under real clinical practice conditions and using a multicenter methodology, whether a standardized training program that reinforces the implementation of the ABCDEF bundle (with expanded components) improves ICU adherence and translates into a lower incidence of PICS measured at 3 months post-hospital discharge, maintaining follow-up at 1, 6, and 12 months.

2.- HYPOTHESES

- **(Primary)** An increase in ABCDEF bundle adherence achieved through a standardized training program is associated with a clinically significant reduction in PICS at 3 months (target: an absolute reduction of ~20 percentage points, from 50% to 30%).
- **(Process)** The training intervention significantly and sustainably increases overall and component adherence to the ABCDEF bundle in participating ICUs.
- **(Exploratory)** The expanded components of the ABCDEF bundle provide additional incremental benefit on PICS compared to the core bundle.

3.- OBJECTIVES

3.1. Primary

Evaluate the effect of a training intervention directed at ICU healthcare staff focused on adherence to the “classic” ABCDEF package of measures on the incidence of post-intensive care syndrome (SPCI) at 3 months post-hospital discharge.

3.2. Secondary

3.2.1. Process outcomes (ICU bundle):

1. Evaluate whether the training intervention modifies adherence to the classic ABCDEF package of measures and its components.
2. Evaluate whether the training intervention modifies adherence to the expanded ABCDEF package of measures and its components.
3. Determine whether implementation of the training program for the classic and expanded package of measures leads to a reduction in the incidence of delirium in ICU patients.
4. Evaluate the change in overall adherence in each center and the proportion of ICUs that experience a ≥20 point improvement in compliance after training.

3.2.2. Patient outcomes (post-ICU follow-up clinics):

5.- Evaluate the effect of a training intervention directed at ICU healthcare staff focused on adherence to the expanded ABCDEF package of measures on the incidence of post-intensive care syndrome (SPCI) at 3 months post-hospital discharge.

6.- Determine whether implementation of the classic and expanded ABCDEF package of measures, overall and by components, reduces the incidence of PICS at 1 month, 6 months, and 1 year post-hospital discharge in ICU patients.

7.- Determine whether implementation of the standard and expanded ABCDEF care bundles, overall and by individual components, improves health-related quality of life measured by SF-12 and EQ-5D at 1,3, 6, and 12 months after hospital discharge in ICU patients.

4. MÉTHODS

4.1 Design and setting of the study

Type: Cluster-randomized clinical trial, multicenter, pre-post with two sequential time points (PRE vs POST) and longitudinal follow-up at 1, 3, 6, and 12 months post-hospital discharge.
Intervention: Standardized training program for ICU professionals.
Process measurement: Compliance with the CLASSIC and EXPANDED ABCDEF bundle with daily data collection (case report form) for 21 days or until ICU discharge/death if it occurs earlier.

4.2. Population and selection criteria

4.2.1. Population

- **Setting:** Adult ICUs in Spain and participating Spanish-speaking countries.
- **Primary analysis population:** Patients discharged alive from the hospital, scheduled for post-ICU follow-up, from both the PRE and POST periods.

4.2.2. Criteria (classic and expanded ABCDEF bundle)

- **Inclusion:**
    - Patients ≥ 18 years old. ○ ICU stay ≥ 48 hours.
    - Informed consent: obtained from the patient (if decision-making capacity remains) or, if not, from their legal/family representative, to participate in the study, in accordance with current regulations.

- **Exclusion:**
    - Limitation of life support treatment, defined as the clinical and ethical decision, agreed by the medical team and, when possible, with the patient or their representatives, not to initiate, escalate, or withdraw certain advanced life support measures (e.g., invasive mechanical ventilation, prolonged noninvasive ventilation, vasopressor/inotropic drugs, renal replacement therapies, CPR, ECMO, or other extracorporeal support).
    - Imminent discharge < 24 hours from the cut-off point.
    - Inability for in-person follow-up (e.g., not reachable, language barrier, transfer to/from another hospital, inability to attend consultation).
    - Life expectancy < 3 months.
    - Severe cognitive impairment or serious pre-existing mental illness.
    - Severe traumatic brain injury or severe neurological, degenerative, or traumatic diseases that impede functional and cognitive assessment.

4.2.3. Criteria for post-ICU follow-up clinic

- **Inclusion:** Patients meeting criteria in section 4.2.2 and without exclusion criteria, discharged alive from ICU.
- **Exclusion:** Same as in section 4.2.2.

4.3. Study groups

Once the ICUs that will participate in the study have been recruited and the baseline phase of data collection on the degree of implementation of the expanded measures package (A–Z) is completed, two groups of ICUs will be formed by stratified randomization by geographic area (Spain and Latin America) and size (ICUs with <16 beds vs. ≥16 beds). Two ICU groups will be

formed: A and B. Group A will implement the classic bundle, and group B will implement the classic and expanded bundles.

- **Group A ("classic bundle"):** measures A through F.
- **Group B ("expanded bundle"):** measures A through Z.

4.4. Development and validation of the CRF by Delphi method

After the initial proposal of items prepared by the expert group of SEMICYUC Scientific Committees, based on scientific evidence, recommendations, and consensus guidelines, a Delphi method will be used to refine and reach agreement on the contents of the CRF for the classic and expanded ABCDEF bundle (A–Z). The aim will be to reach expert consensus on the relevance, clarity, and feasibility of each CRF item, and to estimate its content validity.

A multidisciplinary panel (15–20 participants) will be formed, with diversity in professional background: intensivist physicians (7–8), ICU nursing (4–5), physiotherapy/rehabilitation (2–3), hospital pharmacy (1–2), psychology/social work/ethics (1–2), and post-ICU patients/families (2). **Criteria:** ≥5 years of experience or participation in ABCDEF/Zero/post-ICU; geographic diversity (different regions of Spain and Latin America); role balance (no one group >1/3); commitment to 2–3 rounds. Study coordinators will not be part of the panel (to avoid bias); they will act as a scientific committee (design, analysis, and writing).

Delphi procedure: Rounds: 2 (with the possibility of a third if consensus is not reached). Rating scale (Likert 1–9) for each item in three domains: clinical relevance, clarity/writing, and feasibility of daily collection. **Consensus criterion (a priori):** Include if median 7–9 and ≥70% of scores are 7–9; Review if median 4–6; Exclude if median 1–3 or ≥70% of scores 1–3. Structured and anonymized feedback between rounds will be provided (aggregated statistics + qualitative comments).

Delphi results: The results will consist of the assessment of the validity of each CRF item and of the entire set, as well as agreement among experts, recording response rates and changes made to each item. This will yield the final version of the CRF v1.0 with mandatory and optional fields, clear definitions, and completion rules, together with a user manual including the variable dictionary to be used in the PRE and POST phases of the study. An approximate duration of 3 to 4 weeks is estimated, including one week for recruitment, one week for the first round, 3–5 days for analysis, one week for the second round, and, if necessary, a third round of one week. Responses will be collected via online questionnaires on a secure platform, anonymously, with encrypted storage and supervised by the principal investigator in accordance with current data protection regulations.

5. STATISTICAL ANALYSIS

5.1 Sample size calculation

5.1.1 Hypotheses and comparison objectives: The primary objective is to evaluate if a training intervention reduces the incidence of PICS at 3 months. Three groups are proposed:

- Baseline (pre-intervention): expected prevalence = 50%.
- Intervention A: reduction to 30%.
- Intervention B: reduction to 20%.
  Two primary comparisons will be made (Baseline vs A and Baseline vs B). To control the overall type I error, a Bonferroni correction will be applied, setting the significance level at $\alpha = 0.025$ (two-sided) for each comparison.

5.1.2 Power and initial calculation: With 90% power and using a two-sided test for comparison of proportions for the most demanding contrast (50% vs 30%), the required sample size without multicenter adjustment is 147 evaluable subjects per group.

5.1.3 Adjustment for design effect (multicenter): As a multicenter study, an inflation factor is applied to account for correlation between patients within the same hospital. The design effect (DE) is calculated as:

$DE = 1 + (m - 1) \times ICC$

- Intracluster correlation coefficient (ICC): 0.02.
- Average cluster size (m): evaluables per group divided by number of centers in that group.

Since center randomization is 1:1 after the baseline phase, the number of centers per group is: Baseline: 57 centers (all); A: 28 centers; B: 29 centers. Calculation per group (n_0 = 147; ICC = 0.02):

- Baseline (C = 57): n ≈ 151.9 → 152 evaluable.
- A (C = 28): n ≈ 161.0 → 161 evaluable.
- B (C = 29): n ≈ 160.3 → 160 evaluable.

To ensure both comparisons (Baseline vs A and Baseline vs B) have the required power, we take the worst case (largest n). The worst case is group A with 28 centers, so 161 evaluable subjects per group is adopted.

5.1.4 Adjustment for losses: A 47% loss rate is expected (mortality and nonattendance to follow-up). This means only 53% of scheduled patients will be evaluable. To guarantee 161 evaluable per group, approximately 304 patients per group need to be enrolled.

5.1.5 Final sample size: The final sample size will be 304 patients per group, i.e., 912 in total (304 Baseline, 304 A, 304 B).

5.1.6 Distribution by hospital: With 57 hospitals and 1:1 center randomization after the baseline phase (28 in A and 29 in B):

- Baseline (57 hospitals): 304/57 ≈ 5–6 patients per hospital.
- A (28 hospitals): 304/28 ≈ 10–11 patients per hospital.

- B (29 hospitals): 304/29 ≈ 10–11 patients per hospital.

In total, each hospital will contribute around 16 patients (5–6 in the baseline phase and 10–11 in the assigned group).

5.1.7 Sensitivity analysis: Alternative scenarios were considered:

- If ICC = 0.01 (lower), ~154 evaluable (289 scheduled) needed.
- With ICC = 0.02 (reference), 161 evaluable (304 scheduled) needed.
- With ICC = 0.03 (higher), ~169 evaluable (320 scheduled) needed. Varying the number of centers yields a range of 152–164 evaluable, so 304 scheduled per group provides sufficient statistical assurance.

5.1.8 Contingency for center dropout: If the number of active hospitals differs from planned (either before study start or due to dropout after the PRE phase), the planned sample per group will be recalculated automatically using an adaptive rule based on the actual number of active hospitals per group (H), maintaining assumptions (power 90%, α = 0.025, ICC = 0.02, losses 47%). Quotas will be redistributed proportionally among the active ICUs in the same group until the new target is reached.

5.2 Analysis of variables

Quantitative variables will be expressed as mean ± standard deviation or median (interquartile range), and categorical as absolute and relative frequencies. Comparison between categorical variables will be performed using Pearson's Chi-squared test, linear trend Chi-squared, or Fisher's exact test. Comparison between quantitative variables and a binary categorical variable will be performed using Student's t-test or the Mann–Whitney U test. To analyze independent predictive variables of PICS development, a multivariate binary logistic regression with stepwise forward method (PIN<0.10; POUT<0.05) will be used. Clinically relevant variables and those with p<0.20 in the univariate analysis will be included. Odds ratios (OR) with 95% confidence intervals will be calculated.

5.3 Propensity score analysis

A propensity score matching will be performed (nearest neighbor 1:1, no replacement). Each patient in the pre group will be matched with one in the post group based on the variables: hospital, age, sex, SAPS III, SOFA on admission, Charlson index, ARDS, septic shock, delirium, need for MV/VMI/NIV >48h, deep sedation, and ICU length of stay. Balance will be checked using standardized mean differences (<0.1 indicates adequate balance). Comparisons of the matched groups will be done using McNemar and Wilcoxon tests. The adjusted difference in 3-month PICS incidence, the number needed to treat (NNT), and the adjusted OR with 95% confidence interval will be calculated.

5.4 Subgroup analysis

The effect of the intervention will be explored in subgroups defined by: gender, age (<65 vs ≥65 years), need for mechanical ventilation ≥48h, presence of ARDS, delirium, septic shock or cardiac arrest, and ICU stay ≥5 days.

5.5 Additional sensitivity analyses

Sensitivity analyses will be performed excluding patients from units with bundle item completion <70% and by geographic regions.

5.6 Interim analysis

An interim analysis will be conducted when half of the patients have completed the 3-month post-ICU consultation.

5.7 General considerations

All tests will be two-sided and p≤0.05 will be considered statistically significant. Analyses will be performed with SPSS version 27 (IBM, Armonk, NY) and R version 4.5.1 (R Foundation for Statistical Computing).

6.- ETHICAL CONSIDERATIONS

- **Ethical approval:** The protocol will be reviewed and approved by the Drug Research Ethics Committee (CEI) of Hospital Universitario Vega Baja, and subsequently by the CEI of each participating center before study initiation.
- **Informed consent:** Written informed consent will be obtained from each patient or, if not possible, from their legal representative before inclusion in the study and for the post-ICU follow-up (Phase 4). Participants can withdraw their consent at any time without affecting the quality of care received.
- **Risks and benefits:** The study is an interventional observational study (training and standardized care bundle), without additional invasive procedures beyond standard clinical practice. No significant added risks beyond usual ICU care are anticipated. The potential benefit is the improvement of care and reduction in the incidence of post-intensive care syndrome.
- **Data protection:** All data will be anonymized using a numeric code irreversibly dissociated from personal identity. The correspondence file will be securely held by the Principal Investigator. Data processing will comply with the EU General Data Protection Regulation (GDPR 2016/679) and the Spanish Data Protection Law (LOPDGDD 3/2018).
- **Confidentiality:** Only authorized investigators will have access to the data. Results will be reported in aggregate form without the possibility of identifying participants.
- **Nature of the study:** This study is part of quality improvement and training projects and does not involve procedures outside standard care practices.

7.- MONITORING AND QUALITY CONTROL PLAN

An internal monitoring plan will be carried out with periodic review of the Case

Report Forms (CRFs), data consistency checks, and random data audits. The Principal Investigator and the Coordinating Committee will supervise the quality and completeness of the recorded information, ensuring the reliability and validity of the obtained results.

8.- DISSEMINATION PLAN

The study results will be disseminated at national and international scientific conferences and published in indexed peer-reviewed journals. International reporting guidelines will be followed (e.g., CONSORT for clinical trials and STROBE for observational studies). Patient confidentiality will be maintained at all times, and results will be presented only in aggregate form.