PRIME-AIR Statistical Analysis Plan

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PRIME-AIR

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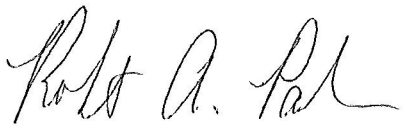

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3 Abbreviations and Definitions

CCC	Clinical Coordinating Center
cIRB	Central Institutional Review Board
C_{rs}	Respiratory system compliance
DP	Driving pressure
EMR	Electronic Medical Record
PACU	Post-Anesthesia Care Unit
PEEP	Peak End-Expiratory Pressure
POD	Post-Operative Day counting the day of surgery as POD0
PPC	Postoperative Pulmonary Complication
PRIME-AIR	Mnemonic name for the study
PROMIS	Patient-Reported Outcomes Measurements
SAP	Statistical Analysis Plan
SDCC	Statistics and Data Coordinating Center
UC	Usual Care
WBC	White Blood Cell count

4 Overview

4.1 Study Design

The PRIME-AIR trial is a prospective multicenter randomized controlled pragmatic trial with a blinded assessor. We studied 751 adult participants with moderate or high risk for PPCs undergoing elective major open abdominal surgery. Enrolled participants were randomized 1:1 to receive either the perioperative intervention (PRIME-AIR bundle) or control (usual care); randomization was stratified by site.

The overall aim for this specific analysis is to compare the number and severity of PPCs in patients receiving an individualized perioperative anesthesia-centered bundle to those receiving usual anesthetic care during open abdominal surgery as well as the secondary outcomes for the comparison between the two treatment groups.

4.2 Description of Intervention

Our intervention is an anesthesia centered individualized bundle consisting of pre-, intra-, and postoperative interventions aimed at optimizing perioperative lung expansion. The bundle consists of the following perioperative interventions:

1. preoperative education on postoperative pulmonary complications
2. individualized PEEP with recruitment maneuvers to maximize respiratory system compliance (C_{rs}) and minimize driving pressures (DP)
3. protocolized neuromuscular blockade administration and reversal based on neuromuscular monitoring
4. postoperative incentive spirometry with daily goals and adherence enhanced by supervision and
5. encouragement for ambulation with daily goals.

4.3 Description of Control Group (Usual Care)

The control group follows the usual care at each of the individual sites, without any attempt to standardize the care provided across the institutions. As all sites are academic medical centers or affiliated with academic medical centers, the usual care arm is expected to be representative of current high-quality care for the population.

4.4 Inclusion-Exclusion Criteria and General Study Population

4.4.1 Participant Inclusion Criteria

All the following inclusion criteria (copied from "Inclusion criteria" from Section III of the protocol) must be met for a participant for the study:

- Adults (≥18 years) scheduled for elective surgery with expected duration ≥2 hours
- Open abdominal surgery including: gastric, biliary, pancreatic, hepatic, major bowel, ovarian, renal tract, bladder, prostatic, radical hysterectomy, and pelvic exenteration
- Intermediate or high risk of PPCs defined by an ARISCAT risk score≥26 (Appendix 1 of this document)

Potential individuals excluded for failure to meet these inclusion criteria are not recorded in the study database.

4.4.2 Participant Exclusion Criteria

Any of the following (copied from "Exclusion criteria" from Section III of the protocol) would preclude an individual from participating in the study:

- Inability or refusal to provide consent

- Inability or significant difficulty to perform any study interventions, including incentive spirometry, ambulation and/or maintaining follow-up contact with study personnel for up to 90 days after the date of surgery
- Participation in any interventional research study within 30 days of the time of the study
- Previous surgery within 30 days prior to this study
- Pregnancy
- Emergency surgery
- Severe obesity (above Class I, BMI≥35 kg/m^2)
- Significant lung disease: any diagnosed or treated respiratory condition that (a) requires home oxygen therapy or non-invasive ventilation (except nocturnal treatment of sleep apnea without supplemental oxygen), (b) severely limits exercise tolerance to <4 METs (e.g., patients unable to do light housework, walk flat at 4 miles/h or climb one flight of stairs), (c) required previous lung surgery, or (d) includes presence of severe pulmonary emphysema or bullae
- Significant heart disease: cardiac conditions that limit exercise tolerance to <4 METs
- Renal failure: peritoneal or hemodialysis requirement or preoperative creatinine ≥2 mg/dL
- Neuromuscular disease that impairs ability to ventilate without assistance
- Severe chronic liver disease (Child-Turcotte-Pugh Score >9, Appendix 3)
- Sepsis
- Malignancy or other irreversible condition for which 6-month mortality is estimated ≥20%
- Bone marrow transplant
- Pulmonary hypertension

4.5 Outcome Measures

The protocol ("Study Outcomes" in Section V of the protocol) lists the outcomes. For convenience they are separated into efficacy and safety outcomes in the list below.

4.5.1 Efficacy Outcomes

- The primary outcome is the participant's PPC severity during the first 7 days after surgery. PPC severity will be classified from none to Grade 4 based on the most

serious PPC occurring during those 7 days. The protocol provides details of the specific PPCs in Table 5; this is included in Appendix 2 for reference.

- Secondary efficacy outcomes include:
    - Proportion of participants with highest grade being Grade 1 or 2 through POD 7
    - Proportion of participants with highest grade being Grade 3 or 4 through POD 7, 30, 90 (3 outcomes)
    - Proportion of participants with Hypoxemia by POD 7 (either Grade 1 or Grade 2)
    - Proportion of participants with Atelectasis by POD 7
    - Proportion of participants with Pneumonia (suspected and proved) by POD 7
    - Proportion of participants with Ventilatory dependence or failure by POD 7

4.5.2 Safety Outcomes

The co-primary safety outcomes will be: 1) the proportion of patients with any intraoperative cardiovascular events or pneumothorax; and 2) the proportion with both intraoperative hypoxemia and rescue recruitment maneuvers. Specifically:

- Proportion of participants with intraoperative cardiovascular events (hypotension, bradycardia, tachycardia, arrhythmias, new ST-segment changes, and cardiac arrest) or pneumothorax
- Proportion of participants with both intraoperative hypoxemia and rescue recruitment maneuvers

Other secondary safety outcomes include:

- Length of postoperative oxygen therapy/other respiratory support
- Length of hospital stay
- Proportion of participants with any major extrapulmonary complications (detailed definition is in Appendix I of the protocol; included in Appendix 3 of this document for reference)

4.6 Sample Size

We estimated that 40% of participants in the control group would have pulmonary complications. If the bundle decreases the proportion of participants with complications by 35.29% (i.e, 25.88% would have complications in the intervention group compared to 40% in the control group), with no change in the distribution of the severity of complications, 750 participants (375 / treatment group), will provide 93% power to

detect the treatment effect as statistically significant (Cochran-Mantel-Haenszel test, row mean score test; α=0.05, two-sided; based on simulations). The grant proposal contained a detailed discussion of the assumptions.

When the study was fully implemented the study team realized that approximately 6% of randomized participants would fail to be included in the study (revoking assent/consent on the day of surgery; no longer being a candidate for surgery; other reasons). The study team had not anticipated that this would occur. Therefore, we revised our plan to recruit approximately 795-800 participants to achieve 750 randomized participants having surgery with written consent.

4.7 Data monitoring through study

4.7.1 Routine monitoring and quality control

The study data was subject to routine checks, initially monthly but then every two weeks. Query reports were run on the data and individual query reports were sent to sites. Separate reports were prepared for the unblinded coordinator(s) (which included screening issues) and the blinded coordinator(s). Query reports addressed incomplete or missing forms, illogical or inconsistent data, range checks for values and dates, and other issues as needed. Sites were required to address all queries on the report and return them to the SDCC data manager in a timely manner and resolve issues with the SDCC data manager as necessary.

Monthly quality monitoring reports were generated through the course of the study for the CCC. This included details about the implementation of incentive spirometry, ambulation, and about doses and monitoring of neuromuscular blocking agents and their reversal in intervention participants for each site. Data monitoring activities were unblinded, but there was no systematic summary of results, and data was used only to monitor for quality issues and track data collection.

4.7.2 DSMB monitoring

The study was monitored by a DSMB convened by NIH twice a year. The DSMB recommended continuation of the study without modification of the study protocol at each review.

4.7.3 Safety monitoring

The DSMB was notified of all deaths (within 24 hours of the SDCC becoming aware of the event). The DSMB was notified within 7 days of the SDCC becoming aware of the event of:

- all intraoperative complications judged significant by the attending anesthesiologist;

- all other adverse events occurring on the day of the surgery or the day after surgery;
- any adverse event that is serious, unexpected and suspected of being related (probably or possibly related) to the study procedures; and
- any unanticipated problems.

As specified by the central Institutional Review Board (cIRB, Massachusetts General Brigham, Boston), the cIRB was notified of all deaths and any unanticipated problems within 7 days of the SDCC becoming aware of the event and any adverse event that was serious, unexpected and suspected of being related (probably or possibly related) to the study procedures. All other adverse events were included in the annual reports to the cIRB.

4.8 Ethical Issues

The cIRB approval was obtained by the Clinical Coordinating Center (CCC), which covered all but one site (Miami Veterans Administration) that obtained its local IRB approval. A separate IRB approval was obtained by the Statistics and Data Coordinating Center (SDCC).

5 Additional Measurements Included in Primary Paper

5.1 Baseline Characteristics

The following characteristics will be used to describe the participants in the study

- age, gender (female), race (White/Black/Asian/Other or more than one race), Hispanic, BMI
- comorbidities (active cancer; hypertension; GERD; diabetes)
- medications (statin use).
- total ARISCAT score on the day of surgery
- ASA Physical status
- hemoglobin
- preoperative O2 saturation
- primary surgical organ classified as: gastric; pancreatic; hepatobiliary [combined]; colorectal [combined]; urological (kidney, bladder combined), and other
    - more than one organ is possible
    - “other” is used for surgery addressing topography other than those specified

5.2 Adequacy of implementation of the intervention bundle

Measures of the adequacy of the implementation of the intervention bundle will be prepared including:

- pre-operative education
- receipt of a minimum number of PEEP titrations
- receipt of the planned recruitment maneuvers and PEEP titrations
- receipt of protocol defined neuromuscular blockade
- receipt of protocol defined neuromuscular blockade reversal
- used incentive spirometry consistent with the protocol
- adequate visits by the study coordinator each day (process measure)
- achievement of ambulation standards each day

5.3 Intraoperative Characteristics

A range of intraoperative characteristics will be used to describe the surgical course of the two groups, and the impact of the intervention bundle on intraoperative characteristics. These include:

- duration of surgery
- duration of mechanical ventilation
- multiple measures of the mechanical ventilation itself (e.g, tidal volume, PEEP, peak pressure, modified driving pressure (based on PEEP) and modified respiratory system compliance, etc.)
- heart rate
- mean arterial pressure
- fluids (crystalloids; colloids)
- blood loss
- vasoactive medications

6 General Analysis Considerations

6.1 Statistical Standards

6.1.1 Statistical Software

All analyses will be done in the latest version of SAS or R available at the Massachusetts General Hospital Biostatistics Center, the SDCC for the study.

6.1.2 Reporting Conventions

Given the planned sample size (375 participants per group), percent will be reported in whole numbers (no decimal places), rounded as needed.

For continuous variables, results will be reported to the same precision as the raw data. For derived variables, one decimal place will be used (two for the coefficient of variation of PEEP).

6.1.3 Summary Statistics

Summary statistics for categorical variables will be counts and percents. The percents for valid responses will be based on non-missing responses (e.g., if the variable has responses for Yes and No, the total of the two percents will be 100 even if some data is missing).

Summary statistics for continuous variables will be means and standard deviations.

6.1.4 General Analysis Approach

For the primary endpoint (the highest value on 5-Point PPC Grade, 0 to 4 through POD7), the Row Mean Score test from a Cochran-Mantel-Haenszel test stratified by site is used. Differences in the Row Mean Score and the associated 95% confidence limit are provided.

A Cochran-Mantel-Haenszel test (with site as a stratification variable) is used for binary variables. The relative risk and the associated 95% confidence limit will be provided.

A standard t-test is used for continuous variables and the difference between the groups and the associated 95% confidence will be provided. This approach provides results that are easier to understand than those using a difference estimate derived from a model adjusting for site, which would not be the same as the difference between the two observed means.

6.2 Analysis Population

We will do a modified intention-to-treat analysis including all available data for participants who are included in the study population. Participants were excluded after randomization from the study population for the following reasons:

- Withdrawal of assent/consent before surgery
- Loss of candidacy for surgery

- Failure to obtain informed consent on the day of surgery for logistical reasons
- Presence of exclusion criteria on the day of surgery (N=5, occurring early in the study before the enrollment process was modified).

The number excluded after randomization for each reason will be indicated in the CONSORT diagram for the primary publication.

One (1) participant withdrew consent and (as allowed by state law) withdrew all data from the study. This participant will be noted by a footnote for the CONSORT diagram.

6.3 Covariates and Subgroups

The primary outcome measure (highest grade of PPC through POD 7) will be summarized for the following subgroups:

- gender (male; female)
- age (under 50; 50-80, over 80)
- BMI (under 18.5; 18.5-24.9; 25.0-29.9;30-34.9)
- race (white / non-white)
- ethnicity (Hispanic / not Hispanic)
- duration of surgery (under 4 hours, 4-6 hours; > 6 hours)
- ASA physical status (I and II vs. III and IV)
- ARISCAT score (intermediate [26-44] vs high [45 or higher])
- Neuraxial intraoperative analgesia (Y/N)
- Neuromuscular blockade monitoring (quantitative vs qualitative/missing)
- Neuromuscular blockade reversal agent (Sugamadex vs Neostigmine)

6.4 Missing Data Imputation

As under 1% of participants withdrew EMR consent during the study, missing data imputation is not being done.

6.5 Interim Analyses

Two formal interim analyses were done using a Haybittle-Peto boundary (P<0.001) stopping for efficacy. The second interim analysis also included the possibility of stopping for futility. The adjusted significance level allowing for the interim monitoring is P=0.0499023 (two-sided; Z-score = 1.96080) for the primary endpoint.

6.6 Multiplicity Considerations

There is one primary efficacy outcome, so multiplicity adjustment will not be made for it (i.e., $P < 0.05$ will be considered statistically significant, using the adjusted P-value specified in Section 6.5 for the primary endpoint). No formal adjustment for multiplicity will be made for secondary or exploratory measurements, but if the primary endpoint is not statistically significant, then these P-values will be considered another summary measure and not indicative of statistical significance between the treatment groups. Confidence limits are not adjusted for multiple comparisons and should not be used for hypothesis testing.

6.7 Calculation of Adjusted Variables

Some variables are calculated on an adjusted basis (e.g., per kg, per hour, etc.). If any element of the calculation (numerator or denominator) is missing, the value will be considered missing for the participant.

7 Summary of Study Data

7.1 Participant Disposition

Participant disposition will be summarized for a CONSORT diagram for the study.

7.2 Protocol Deviations

A list of protocol deviations is included in each report to the DSMB and will not be included in the final report for the study.

7.3 Summary of Baseline Characteristics

Baseline characteristics (specified in Section 5.1) will be summarized for the entire analysis population overall and separately by treatment group. Statistical tests **will not** be used for comparison of the treatment groups, consistent with CONSORT reporting principles.

7.4 Summary of Implementation Measures

Many implementation measures are collected only in the intervention group (e.g., number receiving pre-operative education). For implementation measures collected in both intervention and usual care groups, statistical tests will be done.

7.5 Summary of Intraoperative Characteristics

Intraoperative characteristics will be summarized for the entire analysis population overall and separately by treatment group. Statistical tests will be used for comparison of the treatment groups, as all intraoperative characteristics may be affected by the intervention.

8 Analysis of Outcomes

8.1 Efficacy Outcomes

8.1.1. Primary Outcome: Highest Grade of PPC in the First 7 Days

This is analyzed using the Row-Mean-Score from a Cochran-Mantel-Haenszel test, stratified by site. As stated in Section 6.5 (Interim Analyses) a P-value of 0.0499023 (two-sided) will be used to determine statistical significance for a nominal alpha-level of 0.05.

8.1.2 Other Efficacy Outcomes

Other efficacy outcomes are binary variables (presence/absence of a specific PPC or grade of PPC on a specific day) so will be summarized as counts (percents) and differences between groups assessed using a Cochran-Mantel-Haenszel test stratified by site.

8.2 Safety Outcomes

Safety outcomes will be analyzed as discussed in Section 6.1.4 (General Analysis Approach).

Appendix 1. ARISCAT Sore Calculation

Table 1. ARISCAT risk score for PPCs[4]	
Variable	**Score**
Age (yr)	
≤ 50	0
51 – 80	3
> 80	16
Preoperative S_pO_2, %	
≥ 96	0
91 – 95	8
≤ 90	24
Respiratory infection in the last month	17
Preoperative anemia (≤ 10 g/dL)	11
Surgical incision	
Peripheral	0
Upper abdominal	15
Intrathoracic	24
Duration of surgery, h ≤ 2	0
> 2 to 3	16
> 3	23

Appendix 2. Definition and List of PPCs from Protocol

Table 5. Operational Definitions of PPCs

Grade 1
Mild hypoxemia: SpO_2 =90-92% on room air or the equivalent imputed PaO_2/FiO_2 ratio when oxygen therapy is provided
Mild respiratory findings: abnormal lung symptoms/signs (e.g., cough, dyspnea) and temperature >37.5°C without other documented cause; chest radiograph normal/unavailable
Grade 2
Cough: productive, no other cause
Bronchospasm: new or pre-existent wheezing resulting in therapy change
Hypoxemia: PaO_2<60 mmHg or SpO_2< 90% on room air or the equivalent imputed PaO_2/FiO_2 ratio when oxygen therapy is provided
Respiratory Infection: use of antibiotic for suspected respiratory infection and at least one of the following: new or changed sputum, fever>37.5°C, WBC>12,000/mm^3
Atelectasis*: radiological confirmation + either temperature >37.5°C or abnormal lung symptoms/signs (e.g., cough, dyspnea)
Hypercarbia: transient, requiring treatment
Grade 3
Pleural effusion: resulting in thoracentesis
Pneumonia**, suspected: radiological evidence without bacteriological confirmation
Pneumonia**, proved: radiological evidence and documentation of pathological organism
Pneumothorax: resulting in intervention.
Ventilatory dependence: (non-invasive or invasive ventilation) < 48h
Grade 4
Ventilatory failure: postoperative non-invasive or invasive ventilation dependence ≥48h

*** Atelectasis:** lung opacification with shift of the mediastinum, hilum or hemidiaphragm towards affected area and compensatory overinflation. ** **Pneumonia:** new and/or progressive pulmonary infiltrates on chest X-ray and two or more of: fever ≥38°C or hypothermia (<36°C); white blood cell count (WBC)/mm^3>12000 or <4000; purulent sputum and/or onset or worsening cough or dyspnea.

Appendix 3. Details of Targeted Adverse Events

- Rate of major extrapulmonary complications, defined based on existing diagnosis in the medical chart following usual accepted definitions[61] unless otherwise specified:

  - Cardiovascular:
    - myocardial ischemia or infarction: Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria[65]:
      - Symptoms of myocardial ischemia;
      - New ischemic ECG changes;
      - Development of pathological Q waves;
      - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
      - Identification of a coronary thrombus by angiography or autopsy.
    - cardiogenic pulmonary edema: Cardiogenic pulmonary edema is defined as evidence of fluid accumulation in the alveoli due to poor cardiac function.
    - arrhythmia: electrocardiograph (ECG) evidence of cardiac rhythm disturbance.
    - cardiac arrest: The International Liaison Committee on Resuscitation defines cardiac arrest as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation[68].
    - stroke: defined as an embolic, thrombotic or hemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

  - Gastrointestinal:
    - bleeding: Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or hemorrhage) is that originating proximal to the ligament of Treitz, in practice from the esophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel or colon.
    - anastomotic breakdown: Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicemia, metabolic disturbance and/or multiple organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localized area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak[69].
    - paralytic ileus; Failure to tolerate solid food or defecate for three or more days after surgery[70].

- Liver Disease:
  Liver failure: serum bilirubin level>34 µmol/L with elevation of the transaminase and lactic dehydrogenase levels above twice normal values.

- Acute renal failure: Stage 1 or higher Kidney Disease Improving Global Outcomes (KDIGO) guidelines[71] (Table A1).

Table A1 Kidney Disease Improving Global Outcomes Guidelines (KIDGO)

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline value within 7 days or ≥27mmol/L (≥0.3 mg/dL) increase within 48 h	≤0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline value within 7 days	≤0.5 mL/kg/h for 12 h
3	3.0 times baseline value within 7 days or Increase in serum creatinine to ≥354 mmol/L (≥4.0 mg/dL with an acute rise of >44 mmol/L (0.5 mg/dL) or Initiation of renal replacement therapy	≤0.3 mL/kg/h for 24 h or Anuria for 12 h

- Systemic inflammatory response syndrome (SIRS): Defined by the presence of two or more of the following[60]
  - Temperature >38°C or <36°C
  - Heart rate >90/min
  - Respiratory rate >20/min or $PaCO_2$ <32 mmHg (4.3 kPa)
  - White blood cell count >12 000/mm^3 or <4000/mm^3

- Infections
  - Source uncertain: The CDC defines infection, source uncertain as one where there is strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, meeting two or more of the following criteria[72] core temperature <36°C or >38°C; white cell count >12 x 10^9/L or <4 x 10^9/L; respiratory rate >20 breaths/minute or PaCO2 <4.7 kPa (35mmHg); pulse rate >90 beats/minute
  - Bacteremia (bloodstream infection): The CDC defines laboratory confirmed bloodstream infection as one which meets at least one of the following criteria[72] which should not be related to infection at another site:
    1) Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.
    2) Patient has at least one of the following signs or symptoms: fever > 38°C, chills or hypotension, and at least one of the following:

a. Common skin contaminant cultured from two or more blood cultures drawn on separate occasions
b. Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy
c. Positive blood antigen test.

- Sepsis: defined following the Sepsis-3 criteria[60]. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction. The SOFA score is included in the table below

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

- Surgical site infection: defined as one which meets the following criteria[72].
  1) Infection occurs within 30 days after surgery and
  2) Involves skin and subcutaneous tissue of the incision, or deep soft tissues (e.g. fascial and muscle layers) of the incision, or the infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia or muscle layers opened or manipulated during the operative procedure.
  3) The patient has at least one of the following:
     a. purulent drainage from the superficial/deep incision or from a drain that is placed through a stab wound into the organ/space
     b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
     c. at least one of the following symptoms or signs of infection:
        i. pain or tenderness, localized swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not

cultured. A culture negative finding does not meet this criterion.

ii. a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following symptoms or signs: fever (> 38°C), or localized pain or tenderness. A culture-negative finding does not meet this criterion.

iii. an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathological or radiological examination.

iv. an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathological or radiological examination.

d. diagnosis of a surgical site infection by a surgeon or attending physician.

- Urinary tract infection: A simplified version of the CDC recommendations defines a urinary tract infection as follows: a positive urine culture of $\geq 10^5$ colony forming units per mL with no more than two species of micro-organisms, and with at least one of the following symptoms or signs: fever (> 38°C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognized cause[72].

- Coagulation
  - Disseminated Intravascular Coagulation (DIC): defined following the 2001 definition by the International Society on Thrombosis and Hemostasis (ISTH): “DIC is an acquired syndrome characterized by the intravascular activation of coagulation without a specific localization and arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction”[74]. It will be diagnosed following the modified algorithm currently used and described[75]:

Acute DIC Algorithm Proposed by the International Society on Thrombosis and Haemostasis[a]

Algorithm
1. Presence of an underlying disorder known to be associated with DIC? If yes: proceed. If no: do not use this algorithm
2. Global coagulation results:
a. Platelet count (>100,000/μL = 0, <100,000/μL = 1, <50,000/μL = 2)
b. Fibrin degradation products such as D-dimer (no increase = 0, moderate increase = 2, strong increase = 3)
c. Prolonged prothrombin time (<3 seconds = 0, >3 seconds = 1, >6 seconds = 2)
d. Fibrinogen level (>1.0 g/L = 0; <1.0 g/L = 1)

DIC, disseminated intravascular coagulation.
[a]Interpretation of algorithm: A score of 5 or higher is compatible with acute DIC. The algorithm can be repeated on occasion if acute DIC remains a consideration and the laboratory values change. Modified from Taylor et al.[6]

- Postoperative hemorrhage: defined as blood loss within 72 h after the start of surgery which would normally result in transfusion of blood.
- Thromboembolism: A new blood clot or thrombus or embolus reducing blood circulation within the venous or arterial systems with the exception of the pulmonary venous system.
- Pulmonary embolism: A new blood clot or thrombus or embolus reducing blood circulation within the venous pulmonary system.

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