EMPRESS
A Multicenter Randomized Controlled Trial

Data and Safety Monitoring Board Charter for the EMPRESS Trial

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) of the EMPRESS trial — Early Methylene Blue for Mortality Reduction in High-Dose VasoPREssor-Dependent Septic Shock: A Multicenter Randomized Controlled Trial (ChiCTR2500112352).

The Charter defines the primary responsibilities of the DSMB, its membership, and the purpose and timing of its meetings. It also provides the statistical monitoring guidelines to be implemented by the DSMB, and an outline of the content of both open and closed sessions.

2. Trial Summary

The EMPRESS trial is an investigator-initiated, multicenter, prospective, parallel-group, open-label, blinded-endpoint randomized controlled trial (RCT), enrolling adult patients with septic shock requiring high-dose vasopressor support across more than 50 ICUs in mainland China.

Study Objective: To evaluate whether early methylene blue (MB) administration significantly reduces 28-day all-cause mortality in adult septic shock patients requiring norepinephrine equivalent doses >0.3 μg/kg/min within 24 hours of vasopressor initiation.

Experimental Intervention: MB 2 mg/kg loading dose over 20 minutes, followed by 0.25 mg/kg/h continuous infusion for up to 48 hours, or until 4 hours after discontinuation of all vasopressors, whichever comes first.

Control Intervention: Equal volume of 5% dextrose solution, administered at identical rates and durations.

Primary Outcome: 28-day all-cause mortality.

Randomization and Stratification: 1:1 allocation, stratified by baseline SOFA-1 score (>10 vs. ≤10) and study center, using a permuted block scheme (block sizes 2, 4, or 6).

Target Sample Size: 566 patients (283 per group), based on an assumed 28-day mortality of 50% in controls, an anticipated 25% relative risk reduction with MB, two-sided $\alpha = 0.05$, power = 80%, and a 10% dropout allowance.

Blinding: Due to the visible blue discoloration of mucous membranes and urine caused by MB, complete blinding of healthcare providers and patients is not feasible. However, outcome assessors will be blinded to treatment allocation and will not participate in clinical care.

Sponsor: Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China.

3. Responsibilities of the DSMB

The primary responsibilities of the DSMB are as follows:

1) To help ensure the safety of trial participants by protecting them from avoidable harm through regular review of accumulating safety and efficacy data.
2) To provide the Steering Committee (SC) with independent advice regarding the conduct of the trial and the integrity of the data, so as to protect the validity and scientific credibility of the trial. The DSMB may provide suggestions regarding participant selection, recruitment and retention, study interventions, adherence to protocol-specified regimens, and procedures for data management and quality control. The DSMB acknowledges that its role in this respect is limited, given that its detailed review of trial progress will occur only at pre-specified intervals.
3) **To evaluate interim analyses and independently judge efficacy, potential harm, and futility, using pre-specified statistical boundaries as guidelines (not rigid rules).**
4) To review serious adverse events (SAEs) related to the trial treatments and assess whether the frequency or severity of SAEs warrants modification or termination of the trial.
5) To consider relevant external evidence, including results from other ongoing or recently completed trials in related patient populations, when formulating recommendations.
6) To make recommendations to the Steering Committee regarding continuation, modification, suspension, or termination of the trial.
7) To maintain the confidentiality of all interim data, unblinded analyses, and internal deliberations.

4. DSMB Composition

The DSMB consists of three independent members with complementary expertise spanning critical care medicine, sepsis research, clinical trial methodology, and biostatistics. All members are independent of the EMPRESS investigators, Steering Committee, and Coordinating Center.

DSMB Chair

Prof. Ignacio Martin-Loeches

- Professor of Intensive Care Medicine, Trinity College Dublin (TCD), Dublin, Ireland
- Consultant in Intensive Care Medicine, St James's Hospital, Dublin, Ireland
- Research Director, Multidisciplinary Intensive Care Research Organization (MICRO)

DSMB Members

Dr. Su Longxiang

- Associate Professor and Associate Chief Physician, Department of Critical Care Medicine, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, Beijing, China
- Master's Supervisor; Assistant Director, Department of Critical Care Medicine, PUMCH
- Secretary, National Critical Care Medicine Quality Control Center, China

Dr. Yang Xiaobo

- Associate Chief Physician, Department of Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan Union Hospital), Wuhan, China

Independent Statistician

An independent unblinded statistician designated by the DSMB Chair, in consultation with the Coordinating Center, will be responsible for preparing the unblinded interim analysis reports for the DSMB's closed sessions. This individual will not serve as a voting DSMB member and will not disclose any unblinded data to the Steering Committee or trial investigators.

EMPRESS investigators, Steering Committee members, and members of the Coordinating Center are excluded from DSMB membership.

A quorum will be achieved when all three DSMB members are present. In the event that a DSMB member is unable to attend a meeting, they will receive a copy of the closed-session report and may provide written comments to the DSMB Chair for consideration at the meeting.

5. Conflict of Interest

1) DSMB members will disclose to the DSMB Chair any present conflicts of interest they consider relevant, and any new conflicts that arise as the study proceeds. The DSMB Chair will disclose his own conflicts, and any that arise, to the Chair of the Steering Committee, who will judge whether those conflicts are of concern.
2) The Steering Committee Chair and DSMB Chair have reviewed conflicts of interest and determined that current conflicts will not compromise DSMB members from executing their roles disinterestedly.
3) All members must disclose any actual or potential conflicts of interest at the time of appointment and on an ongoing basis throughout the trial.
4) Members with a significant conflict of interest in relation to a specific agenda item may be asked to recuse themselves from deliberations on that item.

6. Meetings

1) Frequency of Meetings

The DSMB will meet at least three times: once before the first interim analysis (to review and finalize this Charter), and subsequently for each scheduled interim analysis. Ad hoc meetings may be convened at any time upon request by DSMB members, the Principal Investigator, the Steering Committee Chair, or the local Institutional Review Board/Ethics Committee (IRB/EC), particularly when safety concerns arise. Decisions to hold ad hoc meetings will be made jointly by the DSMB Chair and the Principal Investigator.

Meetings will be conducted by teleconference or videoconference. In-person meetings may be organized if logistically feasible and mutually agreed upon.

2) Meeting Structure

(a) Initial Meeting

The initial meeting will be open to the Steering Committee and will serve to review, finalize, and ratify this DSMB Charter prior to any interim data review.

(b) Interim Analysis Review Meetings

Meetings to review interim analyses will follow a structured format:

i. Open Session: DSMB members, the Principal Investigator, a limited number of Steering Committee members, and members of the Coordinating Center (all of whom remain blinded to treatment-specific data) will participate. Topics discussed will include: participant accrual rates and screening performance, data timeliness and quality, completeness of follow-up, center-specific performance and concerns, protocol compliance and deviations, any proposed protocol amendments, and new external evidence from relevant ongoing or recently completed trials. No unblinded data or treatment-specific information will be disclosed during this session.

ii. Closed Session: Attended by DSMB members and the independent unblinded statistician only. The discussions are strictly confidential. The statistician will present unblinded efficacy and safety data by treatment group (which may initially be presented as Group A vs. Group B to allow the DSMB to request full unmasking if deemed necessary). Data reviewed will include primary and secondary outcomes, subgroup results, adverse events, serious adverse events, adherence and dropout rates, and the status of pre-specified statistical monitoring boundaries. The DSMB will deliberate and formulate its recommendations.

iii. Optional Executive Session: An optional session with only DSMB members present may be held to allow the committee to reach final consensus on recommendations before communicating with the Steering Committee.

iv. Follow-up Open Session: Following the closed session, the DSMB Chair may organize a follow-up open session between the DSMB and the blinded PI and Steering Committee to communicate the DSMB's formal written recommendations, once these have been finalized.

7. Minutes and Reports

1) The DSMB Chair, or a person delegated by the Chair, will take minutes at closed sessions. The PI, or a person delegated by the PI, will take minutes at open sessions. Closed-session minutes are strictly confidential and will be available only to DSMB members until the end of the trial.
2) After each meeting, the DSMB Chair will prepare a formal written summary report identifying topics discussed, the overall safety assessment, and the committee's recommendations. The rationale for recommendations will be included where appropriate. The summary report will not contain treatment-specific unblinded data. The DSMB Chair is responsible for circulating the draft to DSMB members for review and concurrence prior to dispatch. Upon approval, the final report will be forwarded to the PI, who is responsible for distributing it to all co-investigators and for transmitting a copy to each local IRB/EC.
3) In the event of findings of a serious and immediate nature, or a recommendation to

discontinue all or part of the trial, the DSMB Chair will immediately notify the PI via a confidential immediate action report. This report may contain unmasked supporting data and the committee's rationale. The PI will immediately inform the Steering Committee.

8. Decisions about Stopping the Trial

Based on interim analyses and, potentially, on external evidence, the DSMB shall decide whether there is evidence beyond a reasonable doubt that the experimental treatment (methylene blue) is deleterious in comparison to the control treatment (5% dextrose), whether the trial is futile, or whether the experimental treatment is overwhelmingly superior. The DSMB may recommend stopping the trial for harm, futility, or efficacy accordingly.

In the event that the DSMB recommends stopping the trial, the DSMB Chair will immediately notify the Principal Investigator. The DSMB will explain the basis of its recommendation to the Steering Committee and discuss the results together. If the Steering Committee and DSMB agree on the course of action, plans will be implemented for the orderly conclusion of the trial, notification of study participants, and dissemination of results.

In the unlikely event that the DSMB and Steering Committee disagree about the proper course of action, both parties will make every effort to reach a consensus through discussions. If significant differences of opinion persist despite best efforts, additional input from mutually agreed external individuals will be sought. Every attempt will be made to reach a consensus through this process.

The DSMB recognizes that statistical boundaries are guidelines and not mandatory rules. Any recommendation to stop or modify the trial should be based on the totality of evidence, including the pattern across all outcomes (efficacy and safety), the consistency of effects across key subgroups, external evidence, and clinical judgment.

9. Interim Analyses

1) Role of the Independent Statistician

The independent unblinded statistician will be responsible for conducting all interim analyses and presenting the results to the DSMB. The Coordinating Center will provide all necessary data to the independent statistician without undue delay, in order to safeguard participant safety. Results of interim analyses must not be shared with anyone outside the DSMB, except in the event that the DSMB decides to recommend trial termination.

2) Schedule of Interim Analyses

Two formal pre-planned interim analyses will be conducted:

- First Interim Analysis: When 28-day follow-up data are available for approximately 283 patients (50% of the total planned sample size). The DSMB will assess the criteria for stopping for safety, futility, and efficacy.
- Second Interim Analysis: When 28-day follow-up data are available for approximately 424 patients (75% of the total planned sample size). The DSMB will again assess the criteria for

stopping for safety, futility, and efficacy.

The exact timing of each interim analysis will be confirmed by the DSMB Chair in consultation with the PI and the independent statistician, with data lock occurring at least 10 days prior to the scheduled DSMB meeting.

3) Stopping Boundaries

The DSMB will utilize the statistical monitoring boundaries described below as guidelines, not mandatory rules. Any DSMB recommendation should be based on the totality of evidence, including all efficacy and safety outcomes within the trial and external evidence.

Stopping for Safety

If any interim analysis demonstrates that the experimental treatment (methylene blue) compared to the control (5% dextrose) is associated with an excess in 28-day all-cause mortality with a two-sided P-value <0.01, this will trigger DSMB discussions about stopping the trial for harm. A less stringent threshold is used for safety compared to efficacy, in order to protect participant safety.

Stopping for Futility

The DSMB may recommend stopping the trial for futility if the conditional power for the primary outcome falls below the following pre-specified thresholds, calculated under the assumption of the originally hypothesized treatment effect:

- Lower than 15% at the first interim analysis (at 50% of the sample size)
- Lower than 20% at the second interim analysis (at 75% of the sample size)

Stopping for Efficacy

The DSMB will adopt strict criteria for stopping for efficacy, in recognition that: (1) early discontinuation of trials due to efficacy tends to produce biased (overestimated) effect estimates that may lead to erroneous clinical guidelines; (2) according to the ethical principle of non-maleficence, a new treatment should not be adopted until clear and objective evidence of benefit is available; and (3) clinical practice typically does not change unless convincing, robust evidence exists.

In accordance with the EMPRESS protocol, the stopping criterion for efficacy is based on the **Haybittle-Peto principle**: a difference of at least **3 standard errors** (corresponding to a two-sided P-value of approximately 0.003, $Z \geq 3.00$) in the primary outcome (28-day all-cause mortality) between the methylene blue and control groups at either interim analysis will justify DSMB deliberation about recommending early termination for efficacy. Given the minimal impact of this approach on the overall type I error rate, no adjustment is made to the final significance level of $\alpha = 0.05$.

The DSMB may also request a confirmatory interim analysis after an additional 50–100 patients complete follow-up, in order to allow regression of the test statistic and effect estimate toward the mean, prior to making a final recommendation to stop for efficacy.

10. Serious Adverse Events

Serious adverse events (SAEs) that are considered study-related by site investigators must be urgently reported to the Coordinating Center within 24 hours of onset. A SAE is considered directly related to the study if it meets both of the following criteria:

1) Any fatal or life-threatening event (immediate risk of death), any event causing permanent sequelae or disability, or any event extending hospitalization; AND
2) The primary treating physician believes that the event is related to the patient's participation in the EMPRESS study; specifically, that the event was probably caused by the study intervention and follows a plausible temporal sequence following its administration.

SAEs reported to the Coordinating Center will be immediately forwarded to all DSMB members. Data on the occurrence of study-related SAEs will be presented to the DSMB by the independent statistician during the closed session at each scheduled meeting. Although no specific statistical stopping rule is defined for SAE frequency per se, SAE data must be considered by the DSMB alongside the primary outcome and could trigger discussions about modifying or stopping the trial.

Given that methylene blue is associated with known potential adverse effects — including methemoglobinemia, hemolysis, and oxygenation deterioration — the DSMB will specifically review these safety endpoints at each interim analysis in addition to the primary outcome.

11. Publication Policy

1) The Principal Investigator will provide the DSMB with a copy of the intended main trial results publication 14 days prior to the intended submission, in order to allow the DSMB to review the manuscript and provide input.
2) The DSMB may recommend changes to the manuscript that it reasonably believes are necessary for scientific accuracy or integrity. The Principal Investigator and Coordinating Center agree to thoroughly consider the implementation of all such recommended changes. Notwithstanding the above, the final decision regarding the content of any publication shall rest with the Steering Committee.
3) The Steering Committee will invite a meeting with the DSMB to present the trial results before the main publication is submitted.
4) The DSMB will be acknowledged in all publications arising from the EMPRESS trial.

12. Confidentiality

All proceedings, deliberations, unblinded data, and materials reviewed by the DSMB are strictly confidential. DSMB members may not share any information outside the DSMB except through official channels as specified in this Charter. This obligation extends beyond the conclusion of the trial unless the information enters the public domain through official publication.

The Closed Session Report prepared by the independent statistician is considered confidential and will not be disclosed to any member of the clinical trial team (other than the designated independent statistician) or to the Steering Committee.

13. Amendments to the Charter

This Charter may be amended during the initial DSMB meeting with the agreement of all DSMB members and the Steering Committee Chair. Thereafter, amendments may only be made before the unblinding of any interim data, must be agreed upon by all DSMB members and the Steering Committee Chair, and must be documented and dated.

14. Signatures and Ratification

This Charter is agreed upon and ratified by the DSMB members and the Principal Investigator.