

Appendix 7

Postoperative pulmonary complications in emergency abdominal surgery. Incidence, risk factors and protective ventilatory strategies.

Protocol version: PEAL + IMPROVE-EAL. Version 03.0 data: 11-february-2020

Sponsor: Department of Anesthesiology and Critical Care, Hospital Clinic de Barcelona.

Protocol registration numbers:

Clinicaltrials.gov identifier: NCT04229810

Ethics Committee number: HCB/2020/0030

Charter for the independent data monitoring and safety committee

Introduction

The Data Monitoring and Safety Committee (DMSC) will constitute its own plan of monitoring and meetings. However, this charter defines the minimum of obligations and primary responsibilities of the DMSC, its relationship with other trial components, its membership, and the purpose and timing of its meetings, as perceived by the iPROVE-EAL Steering Committee. The charter also outlines the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC are responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the trial. The DMSC will provide recommendations about stopping or continuing the trial to the Steering Committee of the iPROVE-EAL trial. The DMSC may also – if applicable - formulate recommendations related to the selection/recruitment/retention of participants, their management, adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the iPROVE-EAL Steering Committee. The Steering Committee will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically or by phone at their own discretion in order to evaluate the planned interim analyses of the iPROVE-EAL trial. The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail to discuss the safety for trial participants. The DMSC can, at any time during the trial, request information about the distribution of events, including outcome measures and serious adverse events (SAEs) according to group allocation. Further, the DMSC can request unmasking of the interventions, if deemed important (see section on 'closed sessions'). The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the iPROVE-EAL Steering Committee. As fast as possible, and no later than 48 hours, the Steering Committee has the responsibility to inform all trial sites and investigators, about the recommendation of the DMSC and the Steering Committee decision hereof.

Members of the DMSC

The IDMSC is an independent multidisciplinary group consisting of three clinicians and a biostatistician that, collectively, has experience in the conduct, monitoring and analysis of randomized clinical trials.

DMSC Clinicians

To be nominated in due time

DMSC Biostatistician

To be nominated in due time

Conflicts of interest

The members of the DMSC will fill-in and sign a conflicts of interest form. DMSC membership is restricted to individuals free of conflict of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, or individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. Furthermore, the DMSC members do not own stocks in the companies having products being evaluated by the iPROVE-EAL trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organization (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the trial. Any DMSC members who develop significant conflicts of interest during the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the trial, the Steering Committee will appoint the replacement(s).

Formal interim analysis meetings

One formal interim analysis meeting will be held to review data related to protocol adherence, treatment efficacy and participant safety. The 3 members of the DMSC will meet when 30-day follow-up data of 366 participants (50% of sample size) have been obtained.

Final analysis meeting

The 3 members of the DMSC will meet when 30-day follow-up data the full sample size (732 participants) have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure that the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data aggregated by treatment group.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the Steering Committee. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions could be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about protocol adherence and the relative efficacy and safety of interventions. To ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participants, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the Steering Committee.

Closed reports will include analysis of the primary outcome measure and rates of SAEs. These closed reports will be prepared by the study biostatistician, with assistance from the trial data manager and/or principal investigator, in a manner that allow them to remain blinded to group assignment. The closed reports should provide information that is accurate, with follow-up on the primary outcome that is complete as soon as possible and at latest within one month from the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The DMSC statistician will prepare these open reports in co-operation with the trial data manager and/or principal investigator. The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The IDMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Management Committee

The planned interim analyses will be conducted after participant no. 366 have been followed for 30 days.

After the interim analysis meetings, the DMSC will make a recommendation to the Steering Committee to continue, hold or terminate the trial.

The independent DMSC will recommend pausing or stopping the trial if group-differences in the primary outcome measure or suspected unexpected serious adverse reactions (SUSARs) are observed at the interim analysis with statistical significance levels. If the recommendation is to stop the trial, the DMSC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all participants included at the time (including participants randomized after this interim analysis) or whether a moratorium shall take place (setting the trial at hold) in the further inclusion of participants during these extra analyses. If further analyses of the participants included after the interim analysis is recommended, the rules for finally recommending stopping of the trial should obey the stopping boundary. The DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility will not be an option as an intervention effects less than those estimated in the power calculation for the primary outcome may be clinically relevant as well.

All recommendation will be based on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol. The Steering Committee is jointly responsible with the DMSC for safeguarding the interests of participants and for the conduct of the trial. Recommendations to amend the protocol or change the conduct of the trial made by the DMSC will be considered and accepted or rejected by the Steering Committee. The Steering Committee will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

After completion of the interim analysis, the recommendations from the DMSC and the conclusion reached by the Steering Committee will be submitted to the Ethics Committee.

After completion of the full analysis of primary outcome at day 7 (i.e. PPCs), and secondary outcomes at 30 days, the DMSC will make a recommendation to the Steering Committee to submit a primary report on 7-day and 30-day outcomes.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analysis plan in the iPROVE-EAL trial protocol. For the two intervention groups, the DMSC will evaluate data on:

- Patients free of PPCs at postoperative day 7th

- Patients free of PPCs at postoperative day 30th

The DMSC will be provided a masked data set (as group 0 and 1) from the coordinating centre. The data set will include data on stratification variables and outcome measures according to the outcomes above in the two groups. Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating center and when to perform the next analysis of the data.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Disclosure of Potential Conflicts of Interest and Confidentiality Statement

This form is to be used by DMSC members to declare any conflict of interest with the study to be reviewed.

Members of the Data Monitoring and Safety Committee (DMSC) are selected to reflect the disciplines and medical specialties necessary to interpret data from the study named: iPROVE-EAL

All members of the DMSC are required to be independent of the study being reviewed and all members are required to sign a DMSC Conflict of Interest and Confidentiality statement.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsors of the trial or with sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. Conflict of interest can include personal, professional (in the sense of the trial outcome benefiting the individual professionally), financial or regulatory in nature. The DMSC members will be responsible for advising fellow members of any changes that occur during the course of the trial. Disclosure will serve to protect the integrity of the DMSC and its role in monitoring and oversight of the study and will also help protect the DMSC member from allegations of inappropriate behavior. The DMSC will be responsible for deciding whether those consulting agreements or financial interests materially impact their objectivity. The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

Confidentiality and Non-Disclosure of Materials and Proceedings

Materials and information made available to the DMSC that are not in the public domain, as well as the discussions that take place during the meetings, are strictly confidential and must not be disclosed to or discussed with anyone who is not a member of the DSMB. Furthermore, confidential information obtained as a DMSC member may not be used by the member for personal benefit or for the benefit of the member's family, associates, or of organizations with which the individual is associated or has a financial involvement.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the MC will appoint the replacement(s).

DMSC Members Signature Page

Printed name:

Institution:

- I agree to be a part of the Data Monitoring and Safety Committee (DSMC) Board for the iPROVE-EAL study.

- I understand and agree to all the terms and conditions outlined in the DMSC charter for the above named study. I confirm that I am not a part-time or full-time, paid or unpaid employee of any organizations that are involved in the iPROVE-EAL trial. I fully understand the confidential nature of the DMSC process and agree not to disclose or discuss the materials associated with the review or substance of any confidential discussions about the study with any individual not a member of the DMSC or to use the information for my personal benefit or the benefit of others.

- I have no conflicts of interests to disclose that make me ineligible to sit on this committee. I agree that in the event that the above may change during my tenure as a member of the DMSC I will disclose and discuss the risk with the Sponsor/Principal Investigators upon discovery of a risk and sign a new Conflict of Interest and Disclosure Statement form, and will include a description of the conflict. This includes the discovery that an organization with which I am affiliated meets the criteria for a conflict of interest.

Signature:

Date: