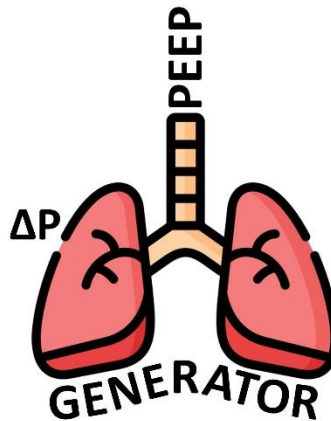


GENERATOR logistic recommendations for local Investigators

In this document, we provide advice on how the logistics of GENERATOR can be implemented in your hospital. Feel free to draw inspiration from these and assess what might work in your situation. Keep in mind that it is a dynamic process, so do not hesitate to reach out if you encounter any challenges. We are more than willing to assist you and address any questions regarding the trial logistics. You can always contact the GENERATOR coordinators at generator@amsterdamumc.nl

Tom Vermeulen en Galina Dorland

GENERATOR coordinators



Research team

From experience with the ongoing DESIGNATION trial, we see that it works well when you can distribute the work among a small team (2 to 3 individuals). Suitable examples for this role include staff members, residents, nurse anesthetists, research nurses, and (medical) students. Anyone making a significant contribution can become a co-author. Ultimately, the local principal investigators of the participating centers determine which members of their team qualify for a place on the authorship list.

Investigator site file and study administration

An Investigator Site File (ISF) contains essential documents which shows that the clinical trial site and Investigator are following the regulatory requirements set out by the ICH GCP guidelines. Maintaining an organized and up-to-date ISF is crucial for the successful conduct of a clinical trial. It enables efficient trial management, ensures data integrity, and supports the overall quality and compliance of the study. The documents may be stored electronically or in hard copy. It is important that documents with wet ink signatures, such as a signed consent form, be retained in hard copy. Electronic files should be stored in a secure folder accessible only to involved investigators. Hard copy files should be kept in a folder within a lockable cabinet accessible only to the involved researchers. We provide you with a table of contents that can be used for the (digital) ISF folder. For each required document, you can indicate whether it is stored electronically or on paper, along with its location.

Screening

The screening for eligible patients for GENERATOR can be done through the outpatient clinic or via the OR program. In Amsterdam UMC, we use EPIC, where we manually screen every Thursday based on the upcoming week's OR program.

We provide a template for the screening and enrollment log, where all patients who meet the inclusion criteria can be tracked. Subsequently, the study ID or the reason for non-participation can be recorded. This list may be stored digitally in the ISF, no personally identifiable information should be included in this file.

Informed consent procedure

Include:

- Informing the patient about the GENERATOR trial.
- Opportunity for the patient to ask questions.
- Signing forms by both the patient and the investigator (note that the date of signing for the patient and investigator must be the same)
- The consent forms must officially be signed in duplicate, One signed form for the research records (paper ISF) and one for the patient. Given that it can be challenging to have one form with the patient (for example, when you sign the paper in the preoperative holding), you may also choose to make a scan and email a copy it to the patient.
- The patient must personally note their name, signature and date. This should not be done by the investigator. If the patient is unable to provide their name, signature, and/or date due to physical limitations, the investigator must make a note with initials and date.
- The patient should have a minimum reflection time of 24 hours before the surgery.

If the patient is admitted the day before surgery:

In Amsterdam UMC, patients are often admitted the day before surgery. After screening, we call eligible potential study patients to gauge their interest in participation. During the pre-admission, we conduct the informed consent discussion, allowing sufficient reflection time for consideration and the form can be signed.

If the patient is admitted on the day of surgery:

This is the case in many peripheral hospitals. There are several strategies to ensure the informed consent process complies with the rules.

- 1) Perform the informed consent procedure directly during the preoperative screening visit.
- 2) During the physical outpatient visit or during phone contact, inform the patient about the trial and email the patient information form. Call the patient (a few days) before the surgery to inquire if they wish to participate. If so, you can sign the informed consent form upon admission as described below.

- 3) If the patient has already been to the outpatient clinic or has been contacted by phone for preoperative screening. Call the patient a few days before the surgery to inform them about the study. Arrange to send the informed consent form to the patient for review (most convenient by email). Upon admission for surgery, you can then sign the informed consent form.

Subject identification log

The subject identification log is a document used to track and manage the identification of participants or subjects. It is an essential part of the ISF and can be stored digitally. This is the only file where the study ID is linked to identifiable patient data (name, surgery date). This log should be stored in a secure (digital) file, accessible only to the involved researchers. A template will be provided.

Filling out the preoperative case report form

It is recommended to complete the preoperative visit in Castor after the informed consent forms. If the signing takes place just before the surgery (for example in the preoperative holding), it can be done earlier, for instance, the day before the surgery. Although this task takes a maximum of 10 minutes, it is not advisable to fill it out just before the surgery.

Randomization

Randomization is done in Castor, we will provide you with the randomization instructions. Randomize the patient only when you are certain that the surgery is proceeding. This is to prevent study dropouts that could impact the reliability of the trial. If a patient is randomized but does not undergo surgery, a randomization slot is wasted and we consider the patient as a drop-out. We have a limited number of drop-outs that we can account for.

If you have a drop-out, please email the study ID to the trial coordinators at generator@amsterdamumc.nl

At Amsterdam UMC, we randomize the patient when they are in the preoperative holding or enter the operating room. Never randomize a patient before the informed consent form is signed, a signed informed consent form is a strict requirement.

Control group

In the provided paper Case Report Form (CRF), all steps to be followed during surgery are explained. The control group is ventilated in volume-controlled mode and receives a PEEP of 5 throughout the surgery without lung recruitment maneuvers. The tidal volume is fixed at 8 ml/kg predicted body weight. The applicable tidal volume is automatically calculated during the preoperative visit in Castor. The hourly data collection can, for example, be effectively done by the nurse anesthetist. This information can also be easily retrieved retrospectively from the electronic patient record in most systems.

Intervention group

In the provided paper CRF, all steps to be followed during surgery are explained. In the intervention group, ventilation is also conducted in volume-controlled mode with a pre-calculated tidal volume based on the predicted body weight. After intubation, the PEEP is set at 10 and the decremental PEEP trial will be performed in a surgical steady state. Consider who in your team can perform the intervention for the study patients. The hourly data collection can be outsourced or retrieved retrospectively from the electronic patient record.

The first variable ('after induction') should be collected as soon as possible after induction. This will usually still be in a neutral position; the patient does not need to be in the surgical starting position and the abdomen does not need to be insufflated. The variable 'before RM1' should be collected in the surgical starting position after abdominal insufflation.

Tip: Fill out Castor immediately after the surgery based on the paper intraoperative CRF.

Postoperative follow-up

EQ-5D questionnaire

The questionnaire can be scheduled in Castor to be automatically emailed to the patient 90 days after the surgery, allowing the patient to fill it out themselves. Only proceed with this if the patient has given consent to fill out the questionnaire. If the patient does not have an email, the questionnaire can be discussed over the phone

during the day 90 visit. Refer to the Castor data entry instructions for guidance on scheduling or completing the questionnaire.

First 5 postoperative days and day of discharge

All necessary information can be extracted from the electronic patient record. In case of need, a physical check can be conducted.

Day 90

These variables can be retrieved from the electronic patient record if available. If not, the patient should be called (briefly), the randomization group can be disclosed to the patient during this phone call.

Tip Some researchers prefer to accumulate the postoperative days of 1 patient and then enter them all at once in Castor. This is allowed, provided that you regularly check whether the patient develops any serious adverse events (SAEs). SAEs must be reported to the trial coordinators (generator@amsterdamumc.nl) as soon as possible after discovery (within a maximum of 24 hours). Our advice is not to postpone the data entry for too long. This prevents having to enter data for dozens of patients all at once for a safety analysis.

Tip Use the provided Excel file 'Subject identification log' template to get a convenient overview of the dates of the day 90 visit.

Tip The patient doesn't have to be called exactly on day 90, as long as it happens around the respective date.