# GENERATOR Trial

# Data Entry Instructions (e)CRF

# Getting started with Castor

## Blinding

In the GENERATOR trial we aim to blind the outcome assessor, therefore it is important that the investigator responsible for the randomization and the intraoperative data collection is not tasked with postoperative data collection. To ensure the blinding of the outcome assessor, all local investigators will receive two separated Castor accounts. The first account ("investigator 1") enables to collect pre- and intraoperative variables. The second account will be used to collected postoperative variables ("investigator 2"). Investigator 2's Castor account will not show to which randomization group the patient is allocated. Investigators are allowed to switch roles (investigator 1 or investigator 2) at their convenience.

## Log in on Castor and create a new record

1. Go to:Castor - Top-Rated eClinical Data Management Platform (castoredc.com)
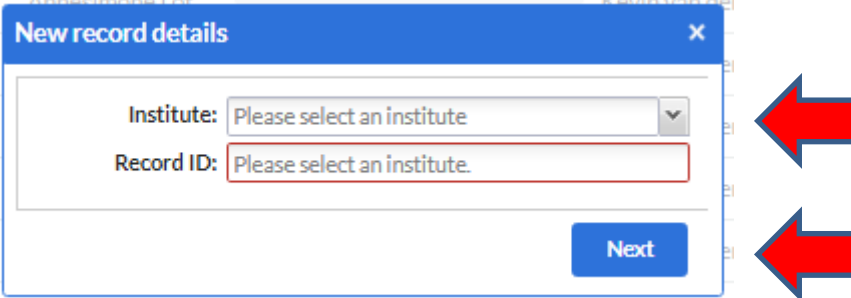2. Select        'User        login'        in        the        top        right        cor
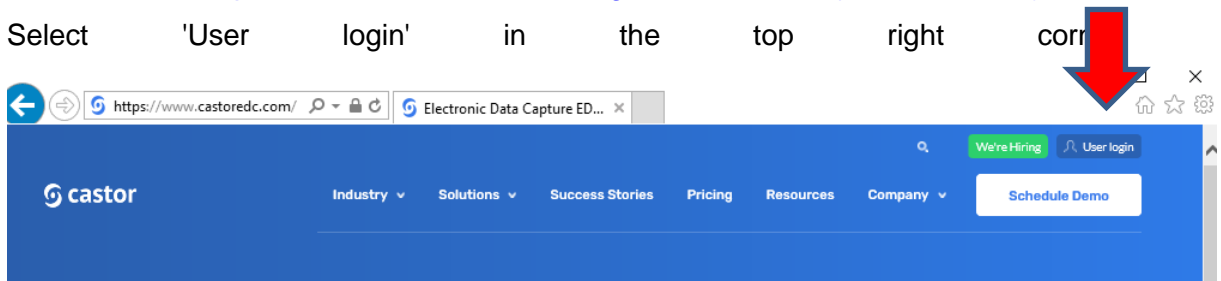


3. Log in with your email address and password, or choose 'Sign up here' if you don't have a Castor account yet.



4. Choose your institute (if applicable) and select GENERATOR
5. Choose + New to create a record

6.  Select which hospital the patient will be included in
7.  Click on Next – a new study record will be created, and a record ID will be automatically assigned



A new record is created. You can start collecting data!

If you want to edit a study record, select your patient from the list of study patients and navigate to the forms you wish to edit.

## Tips and tricks entering data in Castor

We aim to avoid 'over collection of data'. Therefore, we carefully assessed the necessity of each parameter in the current database. It is crucial to minimize 'missing data', please fill in as much variables as possible.

If a variable is unknown or not collected, please select 'user missing' in the cogwheel to the right of the variable and choose the reason (typically 'Not done' (-99)). If applicable, you can add a comment. Please do not leave the value empty, as empty values are treated as missing data and can impact the analysis.

Some variables have an '(i)' next to them; clicking on it expands the definition of the variable.
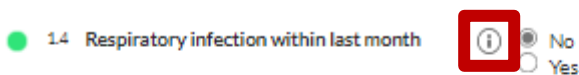


## Audit trail

An audit trail will be conducted in Castor in accordance with Good Clinical Practice (GCP) guidelines. If you save the form and reopen it later to modify variables or add incomplete data, a pop-up screen will appear. Please provide the reason for the data changes made in the form. For example: 'Data entry was incomplete.'

# Overview of the Castor setup

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8. Randomization

## Intraoperative

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12. Intraoperative variables & complications
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## Postoperative

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22. Day 5
23. Day of discharge
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# Preoperative

## 1. ARISCAT score & inclusion criteria

The ARISCAT score can also be calculated using the following link: https://www.mdcalc.com/calc/10022/ariscat-score-postoperative-pulmonary-complications

In order to be eligible to participate in GENERATOR, a patient must meet the following criteria:

1. age > 18 years;

2. scheduled for minimally invasive abdominal surgery; AND

3. increased (i.e., intermediate or high) risk of PPCs according to the ARISCAT risk score (≥ 26 points, see above); **OR**

4. the combination of age > 40 years, scheduled surgery lasting > 2 hours and planned to receive an intra–arterial catheter* for blood pressure monitoring during the surgery;

A patient must meet either point 3 or 4 above; therefore, it is possible that a patient with less than 26 ARISCAT points may still be eligible based on the specified combination in point 4.

*The intra-arterial catheter should not be placed specifically for the trial, only if deemed clinically necessary by the attending anesthesiologist (at the preoperative screening).

## 2. Exclusion criteria

2.4: Patients with a confirmed pregnancy are not eligible for this trial. A pregnancy test is not to be performed specifically for this study.

2.5: Patients with consent for another interventional study during anesthesia are excluded. However, patients with consent for intraoperative observational studies can be included. Additionally, patients with consent for interventional studies before or after (but not during) anesthesia can be included. Please check to ensure that the interventions do not interfere.

2.10: Acute Respiratory Distress Syndrome (ARDS) according to the Berlin criteria:

| Berlin criteria | |
|---|---|
| Timing | within 1 week of a known clinical insult or new or worsening respiratory symptoms |
| Chest imaging | bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules |
| Origin of edema | respiratory failure not fully explained by cardiac failure or fluid overload need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present |

| Oxygenation | *mild*: 200 mm Hg < PaO2/FiO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2O |
| | *moderate*: 100 mm Hg < PaO2/FiO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O |
| | *severe*: PaO2/FiO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O |

## 3. Patient details

3.2/3.3 If the patient does not consent to the retention of personal data for an extended period or to being contacted again after this study for a follow-up, he/she can still be included in the GENERATOR trial.

3.9 The predicted bodyweight (PBW) can be calculated manually using the formula on page 4 of the CRF paper. Alternatively, the PBW can be automatically calculated in the eCFR by filling in the patient's sex and length, triggering an automatic PBW calculation.

## 4. Preoperative vitals

If preoperative vital(s) are not measured (and it is not possible to measure them because the patient is, for example, not in the hospital), please select 'user missing' in the cogwheel to the right of the variable and choose the reason (typically 'Not done' (-99)). If applicable, you can add a comment. Do not leave the variables empty, as empty variables are considered missing data and will influence the analysis.

## 5. Thoracic imaging and blood tests

Thoracic imaging or blood tests need to be documented in the (e)CRF only if collected for clinical reasons. These variables are not required specifically for this study. If you select 'yes', more options will follow. These tests should be conducted within the last month, given that the patient's clinical condition remains unchanged. Do not enter the blood test or thoracic imaging result into Castor if these variables were obtained more than one month before surgery or if there has been a significant change in the patient's condition.

If only some blood tests are available, fill in the available variables and select 'user missing' in the cogwheel on the right for the non-available variables and specify the reason, for example, 'not done (-99)'.

## 6. Comorbidities

6.4/6.5 History of previous disease: the disease does not need to be currently active. For example: if a patient was diagnosed with ACS before but has fully recovered from it: still enter 'yes'.

6.7 If a patient has stopped smoking more than 3 months ago, select 'former'. If the patient has stopped smoking within the last 3 months, select 'current smoker'.

## 8. Randomization
For randomization instructions: see document 'GENERATOR trial randomization instructions version 1.0 dd 01-12-2023'.

# Intraoperative

## 9. Anesthetic and surgical overview
9.1 Start of anesthesia is defined as time of start induction

9.2 End of anesthesia is defined as time of extubation or discharge from operation room in case patient remains on mechanical ventilation

9.4 Maintenance anesthesia does not include the anesthetic drug used for induction. For example if the patient was induced with propofol but received only sevoflurane during surgery, select 'volatile.' If the patient was induced with propofol but received both propofol and sevoflurane during surgery, select 'combined.

## 10. Decremental PEEP trial
This form only needs to be completed for patients randomized to the intervention group. Please remember to email the first 10 performed driving pressure–PEEP graphs of intervention patients to generator@amsterdamumc.nl. Additionally, make sure to save your paper intraoperative CRF in the local ISF, even after completing data entry in Castor.

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.

## 11. Repeated decremental PEEP trial
This form only needs to be completed for patients randomized to the intervention group. The decremental PEEP trial is repeated after: (i.) a radical change in patient position or (ii.) a radical change in intra–abdominal pressure (e.g. conversion to laparotomy). Accordingly, if the additional decremental PEEP trial results in a different optimal PEEP level, this PEEP will be used until the end of surgery or until another radical change in patient position or intra–abdominal pressure.

## 12. Intraoperative variables & complications
We strongly advise documenting the predicted bodyweight and tidal volume (e.g., 8 ml/kg predicted bodyweight) on the paper intraoperative CRF before the start of surgery. The formula

for calculating the predicted bodyweight is provided in the paper preoperative CRF. Alternatively, the predicted bodyweight and tidal volume can be automatically calculated in the eCRF at the 'Preoperative' visit, in the 'Patient Details' section, variables 3.9 and 3.10.

The first hour column should be entered one hour after start anesthesia i.e. intubation.

The intraoperative table with ventilator parameters is built to resemble the table of the paper CRF.

12.1 'What unit of etCO2 is used? [kpa or mm Hg]' refers to the variables etCO2 in the table

12.3 For I:E variables, enter values only for expiration (E). Regarding the FiO2 variables, please fill in the fraction of FiO2 and not percentages. For example 0.4 or 0.7.

If any of the pre-specified intraoperative complications, position changes or rescue strategies (see study protocol) occurs during surgery, you can fill this in by selecting 'yes' in the corresponding hour.

*Example 1: Patient X is randomized to the control group and intubated at 08:15h. After induction, complete the 'After Induction' column in the intraoperative table (for instance, at 8:25). If any intraoperative complications (such as hypotension, desaturation, arrhythmias, or excessive use of vasoactive drugs beyond what is needed to compensate for vasodilating effects of anesthesia) occur between intubation and the time you fill in the 'After Induction' column, please mark the corresponding 'After Induction' timeslot in the intraoperative complication section of the CRF.*

*The 'First Hour' column should be filled one hour after intubation (in this case, at 09:15h). Indicate if any intraoperative complications occurred in the preceding hour that have not yet been recorded in the CRF. Exclude the period from intubation until data collection in the first column ('After Induction') since data for this period have already been collected in the first column.*

> *"Resume: patient X experienced hypotension between 08:15h and 08:25h. From 08:25h till 09:15h, patients did not become hypotensive again. State in the CRF that the intraoperative complication hypotension occurred 'After induction''. Do not select hypotension in 'Hour 1'. '*

*Example 2: patient Y is randomized to the <u>intervention group</u> and is intubated at 08:15h. The recruitment maneuvers and decremental PEEP trial are performed between 08:50 and 08:55h.*

*Fill the 'after induction column' directly after induction, for example at 8:20. When the patient is in a surgical steady state, please fill out 'before recruitment 1' before starting the decremental PEEP trial, for example at 8:50. Data have to be collected after the second recruitment maneuver again (in this case 08:55h). The first hour column ('hr1') should be filled one hour after intubation (in this case 09:15 hour. Exclude the period from intubation until data collection in the first column ('After induction') and the period during the RM + decremental PEEP trial since you already collected data over this period in the first, second and third column (respectively 'after induction (if intervention: just before recruitment 1)', 'Before Recruitment 1' and 'After recruitment 2'.*

➔ *Resume: patient Y experienced hypotension just before the recruitment maneuvers and decremental PEEP trial (08:40 – 08:45 hour). Patient did not become hypotensive before this period (from 08:15-08:40) or after this period during the recruitment maneuvers and the rest of the first hour (08:55 – 09:15). State in the CRF that the intraoperative complication hypotension occurred 'Before recruitment 1'. Do not select hypotension in the 'After induction', 'After recruitment 2' and ''Hour 1' column.*

## 13. Pre-approved protocol deviation and violation

13.1 If changes are made to the ventilation due to pre-approved clinical reasons specified in the protocol, please select 'yes' and specify. Any other deviation is classified as a protocol violation, see below.

13.2 Any change in ventilation that does not fit a pre-approved protocol deviation, please select 'yes' at protocol violation and specify.

## 14. Vasoactive drugs, fluids, transfusion & total out

If vasoactive drugs are administered to the patient during anesthesia, select 'yes' for the relevant drug name and enter the cumulative dose. If the administered drug is not listed, choose 'other vasoactive drug' and specify the name and cumulative dose of the administered drug.

If the patient received any crystalloids, colloids, or albumin, please select 'yes' and enter the appropriate dose.

If the patient received any packed red blood cells, fresh frozen plasma, platelets or omniplasma started during surgery, please select yes accordingly and fill in dose. If a transfusion has been started before the surgery and is still ongoing during surgery, please fill in the details in form 7 'Surgical procedure & preoperative transfusions' in the Preoperative visit).

If you filled in all the above fluids, the automatic TOTAL IN will be calculated. Oral or intravenous medication <u>do not</u> contribute to the TOTAL IN and fluid balance calculation.

If measured, please fill in the quantity of urine production, blood loss, ascites and other fluid loss (for example emesis). TOTAL out and the fluid balance will be calculated automatically.

### 15. Arterial blood gas

These variables should only be filled in if the ABG has been done for clinical care. An arterial blood gas (ABG) does not need to be specifically performed for the study.

# Postoperative (e)CRF

### 16. EQ-5D-5L

Follow the following steps to schedule the questionnaire so that it is automatically sent to the patient via email for completion:

Step 1: click on the EQ-5D-5L button

Step 2: in the send on date/schedule section, click on  click on 'on a specific date or schedule

Step  3: fill out the date of 90 days after surgery

Step 4: click  on create: the survey is now scheduled!

It is also allowed to go through the questionnaire with the patient over the phone during the day 90 visit. You will still have to create the survey invitations for the participant (patient) in Castor EDC by clicking on the EQ-5D-5L button. Since an email is required to do this, you can enter your own email address. Just select 'decide later' when asked to set the time of sending so you do not actually receive the email invitation. To fill out the survey, follow the following steps:
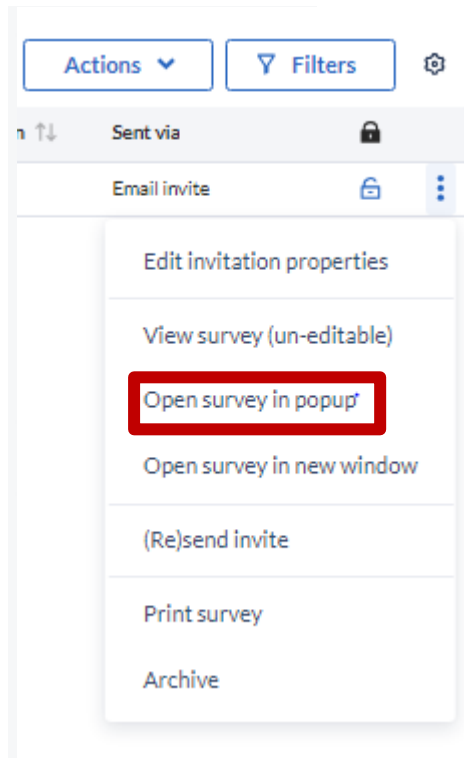
Step 1: log in with your postoperative user account (Investigator 2') and access the survey in the participant's overview on the left under the 'Surveys' section.
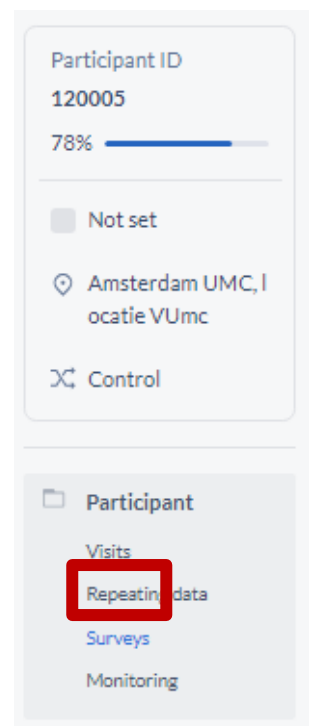
Step 2: click on the 3 dots on the right
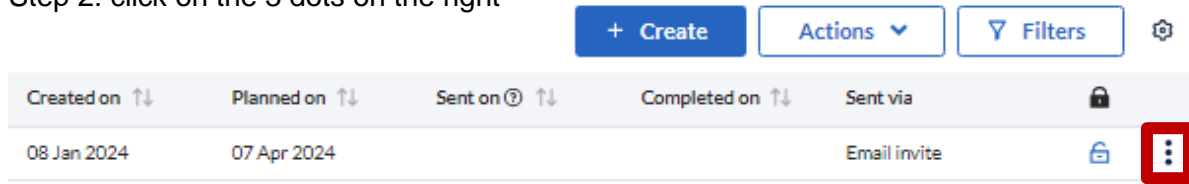


Step 3: choose 'Open survey in popup' and you can fill in the survey



## 17-22. Postoperative day 0-5

Time frames:

1. Postoperative day 0 and 1: postoperative day 0 is defined as the day of surgery. On postoperative day 0, data collection starts at the end of surgery and ends at 23:59 that same day. Postoperative day 1 represents the first day after surgery. For example: patient X undergoes surgery on 01-01-2024 from 08:00 till 13:00. Postoperative day 0 = 01-01-2024 from 13:00 untill 23:59. Postoperative day 1 = 02-01-2024 from 00:00 untill 23:59 p.m.

2. Postoperative day 2: two days after surgery. For patient X: 03-01-2024 (00:00 till 23:59)

3. Postoperative day 3: three days after surgery. For patient X: 04-01-2024 (00:00 till 23:59)

4. Postoperative day 4: four days after surgery. For patient X: 05-01-2024 (00:00 till 23:59)

5. Postoperative day 5: five days after surgery. For patient X: 06-01-2024 (00:00 till 23:59)

The first question on the postoperative form (day 1 – day 5) addresses whether the patient is still admitted to the hospital on the current day. If the patient is admitted to the hospital for the entire day, select 'yes' and complete the visit details. If the patient is not hospitalized for the entire day (for example, due to discharge or decease), select 'no' and provide the specific reason.

**Example: If patient X is discharged home on postoperative day 3, complete the postoperative day 2 form. Select 'No' for 'Was the patient still admitted to the hospital this day?' on the postoperative day 3, 4, and 5 forms and specify the reason. Please do not leave a visit empty.**

## Postoperative day 0-5 forms practical tips

Urine output: if the urine output is not adequately measured: select ''not measured'. Only select 'Yes' if the quantity of urine output is known. Please fill in the urine production over the entire day (from 00:00 to 23:59).

*Example. Patient X undergoes surgery on 01-01-2024. He produces 1800 mL urine on 04-01-2024 between 00:00 and 23:59. Open the postoperative day 3 form, select 'Yes' for urine output and enter 1800 ml in the quantity variable (which will pop up after selecting 'Yes' for urine output).*

Vitals: if a vital variable is not measured, please select 'user missing' in the cogwheel to the right of the variable and choose the reason (typically 'Not done' (-99). If more than one measurement is measured during the day, please choose the value closest to 06:00 AM.

Blood tests do not need to be performed specifically for the GENERATOR trial. However, if blood tests (such as hemoglobin, creatinine, or white blood cell count) are available for clinical reasons, please record them in the (e)CRF. If you answer 'Yes' to the question 'Were (one of) the following bloodtests obtained? Hemoglobine, creatinine, white blood cell count?' additional variables will appear

*Example: on postoperative day 3 for patient X, hemoglobin is measured, but creatinine and white blood cell count are not. Enter the hemoglobin level in the postoperative day 3 form and select 'user missing' for creatinine and white blood cell count in the cogwheel, and specify the reason.*

**Postoperative Pulmonary complications (PPCs)**

A PPC is always considered as an Adverse Event (AE) or a SAE (Serious Adverse Event). Therefore, if a patient develops a PPC, please don't forget to also complete a (S)AE form (see below).

If a patient had pre-existing pulmonary abnormalities on thoracic imaging before the surgery, the question 'Was thoracic imaging performed on this day, and if yes, did the observed preoperative pulmonary condition(s) on thoracic imaging worsen?' appears in the postoperative forms. This refers to worsening in comparison to the observed preoperative abnormalities.

## Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. <u>Only pulmonary adverse events (possibly) related to the intervention reported spontaneously by the subject or observed by the investigator or his staff, will be recorded and documented in the (e)CRF</u>. The primary endpoint of the GENERATOR trial, postoperative pulmonary complications (PPCs), are also considered as adverse events. Thereby postoperative pulmonary complications has to be reported two times: in the postoperative data collection forms and via the (S)AE form. Castor will remind you if you select a PPC to also create an AE form.

Follow the following steps to register an adverse event:

Step 1: select 'yes' for the PPC/adverse event that has occurred, for example, cardiopulmonary edema'. The message 'Please register this (S)AE by using the respective buttons after answering 'yes' below in the AE or SAE question' will appear. Determine whether it is an adverse event or a serious adverse event (see section serious adverse event below).

Step 2: select 'yes' for 'Did an adverse event (AE) occur? Look in the helptext for the definition'.

Step 3: click on the button 'Register adverse event' and fill out the form. Describe the adverse event, start and stop date and outcome.

## Serious Adverse Event form

A serious adverse event is any untoward medical occurrence or effect that results in death, is life threatening (at the time of the event), requires hospitalization or prolongation of existing inpatient's hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been

based upon appropriate judgement of the investigator. An elective hospital admission will not be considered as SAE.

**All SAEs have to be reported to the trial coordinators immediately (within 24 hours of discovery)!**

Contact: Galina Dorland and/or Tom Vermeulen, email: generator@amsterdamumc.nl. All SAEs, which according to the principal investigator are related to a study procedure will be directly reported to the METC whereas SAEs which are deemed to be unrelated to a study procedure by the principal investigator will be recorded and reported to the METC in a line-listing.

To register a serious adverse event, follow these steps:

Step 1: select 'yes' for the PPC/serious adverse event that has occurred, for example, sepsis. The message 'Please register this (S)AE by using the respective buttons after answering 'yes' below in the AE or SAE question' will appear. Determine whether it is an adverse event or a serious adverse event;

Step 2: select 'yes' for 'Did an serious adverse event (SAE) occur? Look in the helptext for the definition'.

Step 3: click on the button 'Register serious adverse event' and fill out the form. Describe the adverse event, start date and if already available stop date and outcome.

Step 4: notify the trial coordinators (generator@amsterdamumc.nl), include the study ID and a brief summary of the event. Also, indicate the time elapsed since the surgery when the serious adverse event occurred.

Step 5: the relationship with the intervention will be provided by the trial coordinators after consultation with the principal investigators.

## Follow up (S)AE

Actively monitor the course of the (S)AE and update the form. To reopen the (S)AE form, select 'Repeating data' on the left side of the participant menu, choose the relevant (S)AE and complete the form.

## 23. Day of discharge

This form only has to be completed if patients remain hospitalized for **more** than 5 postoperative days. If any postoperative pulmonary complication occurred between postoperative day 5 and day of discharge, please enter them in this form.

The maximum follow up period for GENERATOR patients is 90 days. If a patient remains hospitalized for more than 90 days, please complete the 'Day of discharge' form on day 90.

## 24. Day 90

If the patient, for example, has visited the attending specialist around day 90, these variables may be directly extracted from the medical record.

On day 90 the length of hospital stay is automatically calculated.

Total length of ICU stay or total length of invasive ventilation from initial admission: if patients stayed on the ICU for ≥ 12 hours or is invasively ventilated for ≥ 12 hours, it counts as one day.