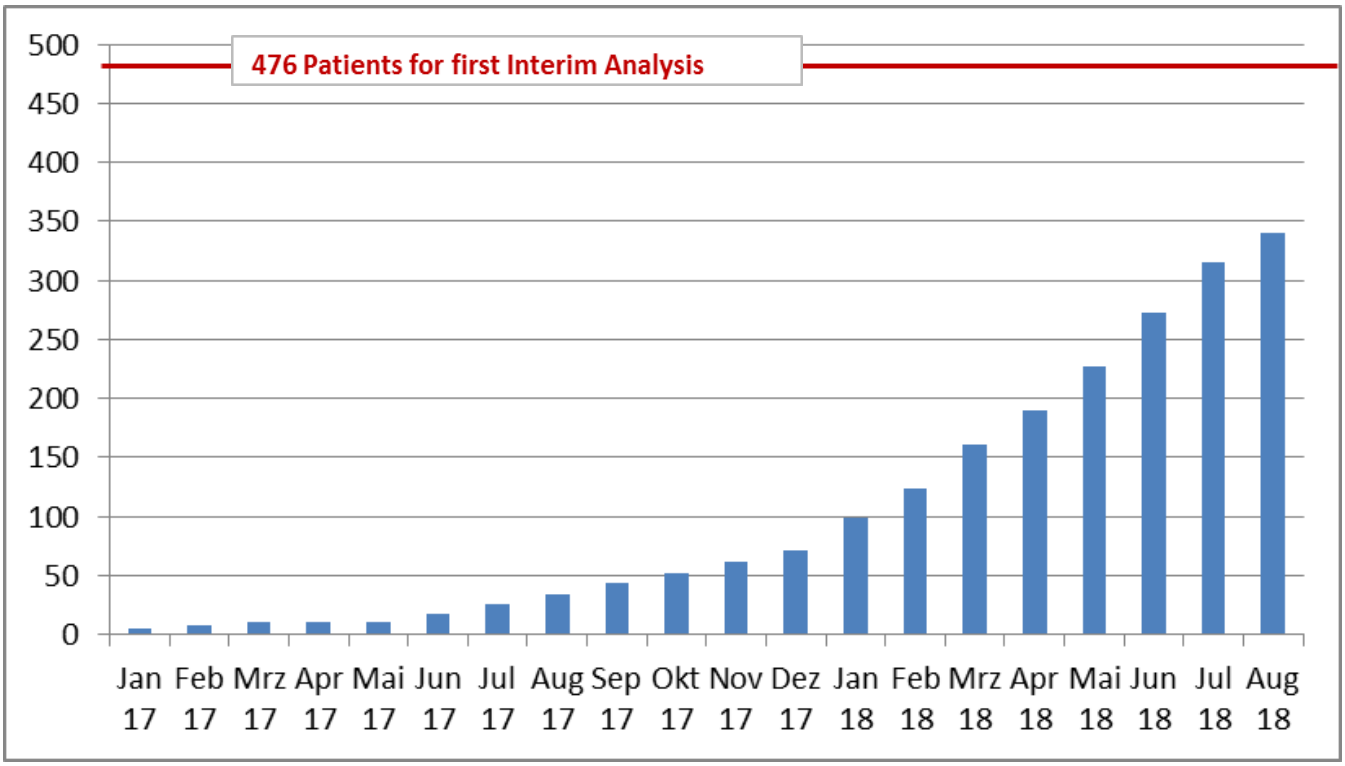
PROTHOR Newsletter 3/2018

Dresden, September 7, 2018

Dear National Coordinators and Local Investigators of PROTHOR,

Four months have elapsed since the last Newsletter. I want to give you a short overview on the general progress. We have 32 registered centers working on the study (and the number of centers is still increasing), we have 345 randomized patients in the study (effective 28.08.2018). We need 131 more patients to reach the point for the first interim analysis. When this point is reached, we have gained 20% of the total patient count for the study (2378 patients are needed for the study to finish).

Overview of randomized patients over time



Overview of the randomized patients per center

001	Istanbul	25
002	Dresden	20
003	Magdeburg	0
004	Coswig	44
005	Münster	0
006	Cornell	5
007	LMU München	19
008	Valencia	2
009	Freiburg	14
010	Gran Canaria	7
011	Amsterdam	7
012	Aachen	2
013	Vigo,Spain	23
014	Zagreb	19
015	Sotiria,Greece	42
016	Bucharest	0
017	Belgrade	24
018	La Ribera	24
019	Genova, Italy	6
020	Prague	1

021	Barcelona	16
022	Central Military Emergency University Hospital Bucharest	0
023	Nijmegen, The Netherlands	14
024	Athens, Greece	9
025	Ljubljana, Slovenia	0
026	Foggia, Italy	10
027	HOSPITAL MARIE LANNELONGUE, France	0
028	Merheim Hospital Cologne Germany	0
029	Heraklion	3
030	Fudan, Shanghai, China	9
031	Ferrara, Italy	0
032	Nis, Serbia	0

Completeness of datasets

In the last weeks, we have started checking the datasets of all centers. We have introduced new automatic validity checks, which will warn you during data entry, if the entered values are out of a predefined range. We have noticed that several datasets are not complete although the time for follow up (90 days after randomization) has already passed. Please complete all datasets during the upcoming weeks, this will help us with database monitoring and improve data quality. All entered data has to be complete for the first interim analysis.

Changes to the database

We have introduced validity checks which will give warning messages during data entry if the entered values are out of the expected range. The following three figures should demonstrate the validity check for entry of the tidal volume as an example.

Figure 1. Tidal volumes for two-lung-ventilation (7ml/kg) and one-lung-ventilation (5ml/kg) are automatically calculated from the patient height and be found in the “intraoperative visit” section

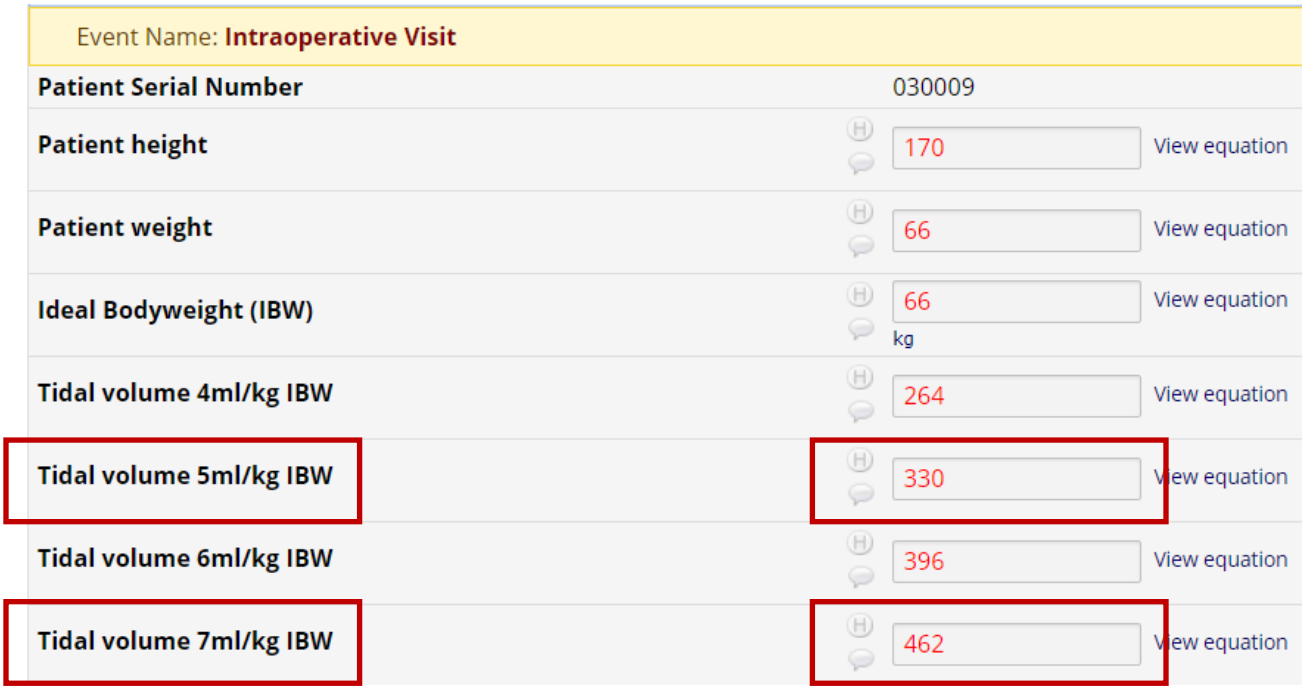


Figure 2. When entering tidal volume values out of the expected range, a warning message is displayed in red.

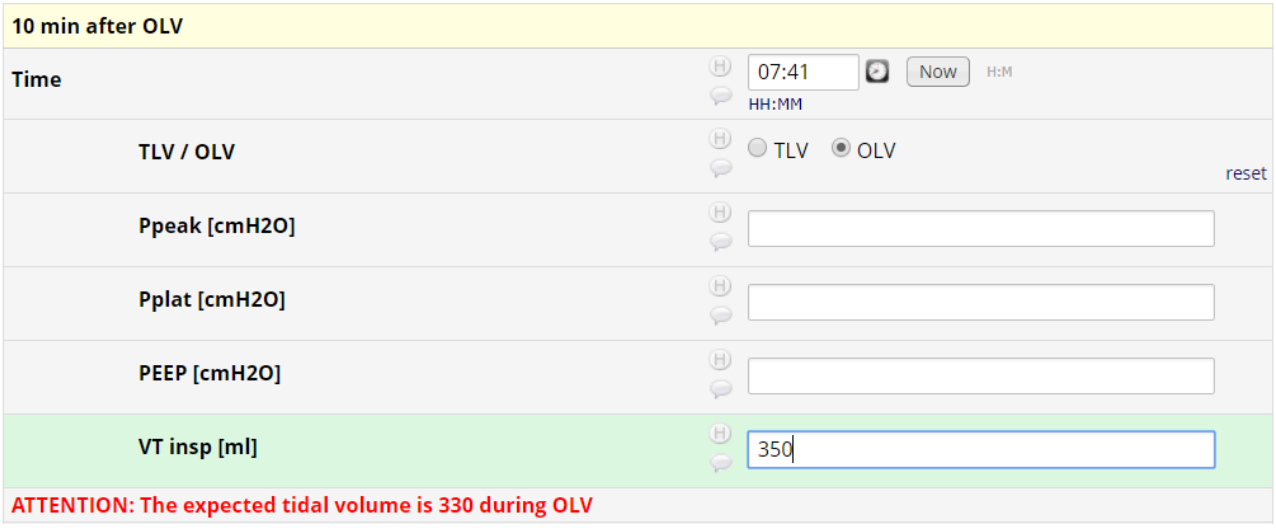
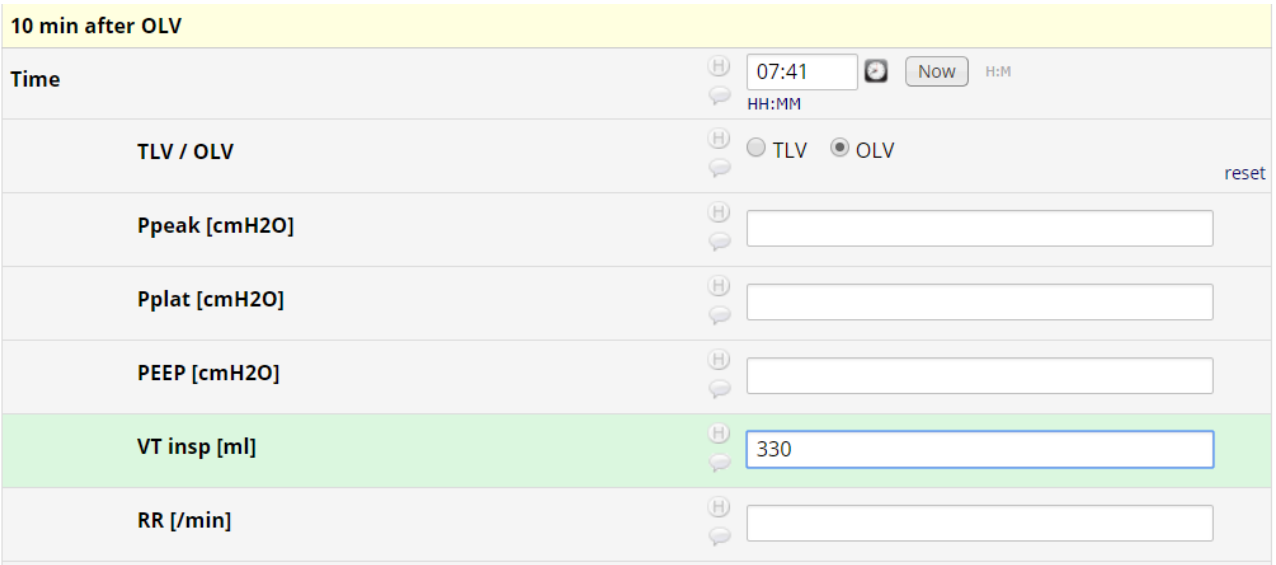


Figure 3. When entering tidal volume values within the expected range, the warning message is not displayed.



Data safety and monitoring board

The PROTHOR DSMB met May 18th via video for nearly 1.5 hours. Members present were Daniel Sessler, Arthur Slutsky, Andreas Hoeft, and Jennifer Hunter. Jean-Louis Vincent was unable to participate.

There have been only 2 serious adverse events reported, and only 1 is potentially related to the study. The Board was unsurprised by the number of SAEs (Serious Adverse Event). As expected in such a sick population, there were also many adverse events. Some severe adverse events were not reported to the SAE manager. This must necessarily be changed and reports sent, as required by law. The SAE manager proposed an Adverse Event (AE) reporting algorithm, which can be found at the end of the newsletter.

The Board recommended enrolling several pilot patients before starting formal randomization for new sites. The board also recommended considering alternatives to a simple collapsed composite for the primary outcome. The PROTHOR steering committee was asked to comment on the proposals of the DSMB. The majority agreed with the proposal to give new sites access to a training database, where they are allowed to enter virtual patient data. After database training, the input to the real database is possible. After including two patients to the real database, remote database monitoring will be performed and direct feedback to the investigators will be given. In this way, even the first patients are stored in the real database, but, data entry and protocol adherence is closely monitored, and data quality is kept on a specific level. The majority of the steering committee agreed to leave the primary endpoint as it is.

The Board plans to have the next DSMB meeting after 20% of the patients have been enrolled and their data analyzed (first designated interim analysis). At that time, it will ask to see results and complications on a Group A/B basis.

Adverse event reporting

An adverse event (AE) is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding) syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

A Serious Adverse Event is defined as any experience that suggests a significant hazard or any unwanted medical occurrence that:

- results in death or is life-threatening (risk of death at the time of the event)
- results in prolongation of hospital stay
- requires patient hospitalization after hospital discharge (during 90 day follow up period)
- results in persistent or significant disability/incapacity
- requires intervention to prevent permanent impairment or damage

Investigators should report all Adverse Events which are related to study procedures within 24 hours to the SAE manager.

Also, all serious adverse events regardless of their relationship to the study intervention should be reported to the SAE manager within 24 hours. The SAE manager will then notify the DSMB. The SAE manager is Ary Serpa Neto (ary.neto2@einstein.br).

The SAE manager will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study procedure. The SAE manager will also determine if the event is unexpected. An adverse is considered “unexpected” if it is not expected as a consequence of the study procedure.

The SAE manager will report all unexpected and study related deaths, and SAEs to the DSMB seven days after receipt of the report from a center. A written report will be sent to the DSMB within 15 calendar days. The DSMB will also review all adverse events and clinical outcomes during scheduled interim analyses. If the DSMB determines that the overall rate of adverse events is

higher in the study group than the control group the centers will be notified 15 days of this

Determining relationship of adverse events to study drug or procedures

Investigators will be asked to grade the strength of the relationship of an adverse event to study procedures as follows:

- **Related**: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedure.
- **Probably Related**: The event should be assessed following the same criteria for "Definitely Related". If in the investigator's opinion at least one or more of the criteria are present, then "probably"" associated should be selected.
- **Possibly Related**: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
- **Unrelated**: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- **Not assessable/uncertain Relationship**: The event does not meet any of the criteria previously outlined.

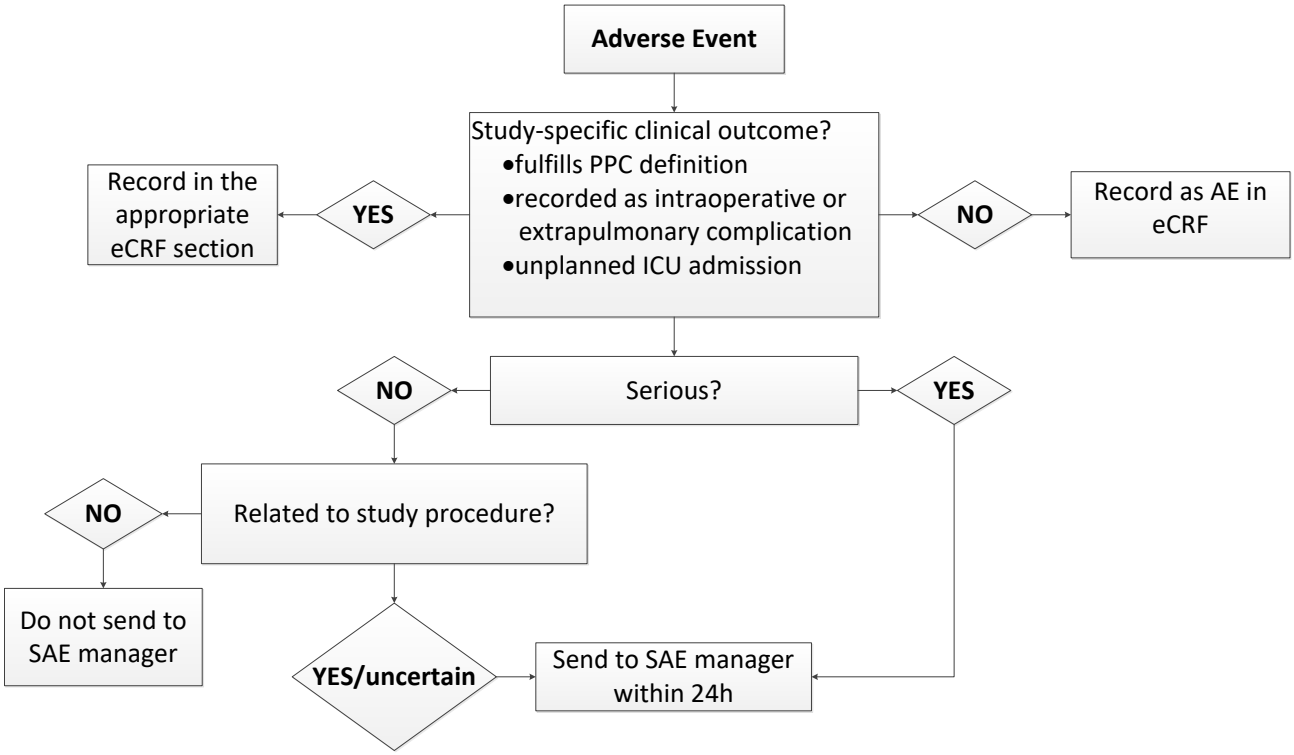
Clinical outcomes that may be exempt from adverse event reporting

Study-specific clinical outcomes are exempt from adverse event reporting and will be recorded in the specific eCRF section. The following are examples of events that will be considered study specific clinical outcomes:

- All events fulfilling the definition of postoperative pulmonary complications (PPC) according to the study protocol, e.g. ARDS, pneumonia, pleural effusion and others.
- All events that are recorded separately in the eCRF during surgery, e.g. intraoperative events like hypoxemia, bradycardia, hypercarbia or hypotension.

- All events that are entitled “extrapulmonary complications” recorded separately in the eCRF like acute kidney injury, gastrointestinal failure or others.
- Unplanned ICU admission, which is also recorded separately in the eCRF.

Decision tree for AE reporting



AE:adverse event; PPC: postoperative pulmonary complication; eCRF: electronic case report form; SAE: Serious Adverse Event

If you have any questions, please contact thomas.kiss@uniklinikum-dresden.de.

Best regards,

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