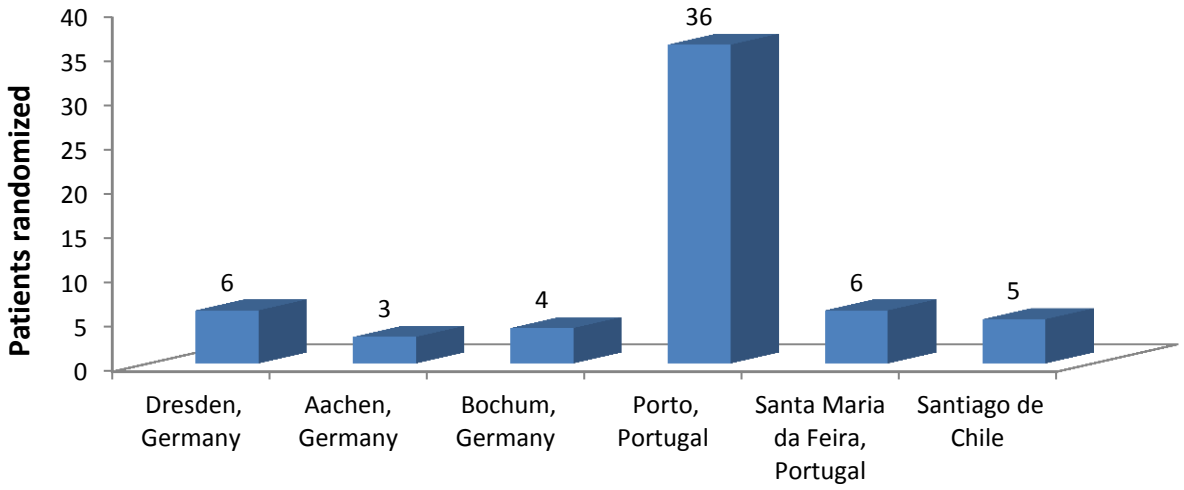
News Letter 2

Dresden, December 23, 2014

Dear National Coordinators and Local Investigators of PROBESE,
Dear Friends,

a successful year will end soon. 2014 was the year in which we launched with our PROBESE trial, kicked off at Euroanaesthesia in Stockholm in June, and randomized the first 60 patients. Congratulations for that and thank you very much so far.



PROBESE was appointed as official study of the ESA Clinical Trial Network!

We are very happy to inform you that PROBESE has been selected as an official study of the Clinical Trial Network (CTN) of the European Society of Anaesthesiology with a grant of € 30.000. We want to thank all investigators and steering committee members for their terrific work so far, which allowed us such achievement. The ESA CTN support permits us to better advertise the trial, promote investigator meetings during upcoming Euroanaesthesia meetings, and conduct

monitoring of compliance of investigation sites to the research protocol, all of which will certainly enhance the study quality.

Reporting of Adverse Events

Please follow our policy to enter all (severe) adverse events into the online database REDCap (the electronic Case Report Form). It is investigator's duty to report **AEs within one week** and **SAEs as well as all related or possibly related events within 24 hours of reception**. In case of a SUSAR (suspected unexpected serious adverse reaction) as well as death of study patients our SAE manager (Ary Serpa Neto, MD, PhD) has to be informed additionally by email (aryserpa@terra.com.br).

Follow Up

When you randomize a patient for PROBESE using REDCap you are kindly asked to **follow up the patient** until discharge or withdrawal of informed consent in any case, **independent of any protocol violation that happened**. This measure is necessary to finally analyze the data according to the intention-to-treat principle. To avoid possible mistakes, please randomize the patient directly before induction of anesthesia and after re-checking inclusion and exclusion criteria once again.

Deviation from the mechanical ventilation protocol

We do see that some patients may require higher PEEP levels, I:E ratios different from 1:2 and also higher F_iO_2 levels, especially in "extreme" cases like laparoscopic surgical approaches or steep Trendelenburg position. Just to provide with a rationale: F_iO_2 minimum of 40% was set in order to better control adverse events of low SpO_2. I:E ratio of 1:2 was set to achieve comparability of respiratory pressures between centers. As far as possible, those settings should be maintained, unless the patient safety requires deviation from the protocol (e.g. hypoxia, hypercapnia). In this case please enter a note in the eCRF (intraoperative part - protocol deviation and probably also in the intraoperative adverse events).

Please let us know where we could help you, wherever you are in the process to run this endeavor.
Yours sincerely,

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