

1 **Overview of protocol changes within the PROBESE trial as approved by the**  
2 **Internal Review Board at the coordinating center in Dresden, Germany**

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4 **Changes in Version 2.4.1 (Jun 2014) compared to Version 2.4 (Nov 2013) of the**  
5 **research protocol**

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8 Page 1: G. Mills, Sheffield Teaching Hospitals, United Kingdom, Operating Services,  
9 Critical Care and Anaesthesia (OSCCA) *added to the steering committee*

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11 Page 6: [While anesthesiologists tend to use PEEP higher than in non-obese patients]  
12 *deleted*

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14 Page 11: *Inclusion criteria* [Patient scheduled for open or laparoscopic surgery under  
15 general anesthesia] *changed to* [Patient scheduled for surgery under general  
16 anesthesia]

17  
18 Page 32: *Definition of Hepatic failure:* [Serum bilirubin level > 2 mg/dL with elevation of the  
19 transaminase and lactic dehydrogenase levels above twice normal values]  
20 *changed to* [Hepatic failure during short term follow up (5 postoperative days) is  
21 considered as follows: Ratio of total bilirubin on postoperative day 5 to  
22 postoperative day 1 > 1,7 and ratio of international normalized ratio (INR) on  
23 postoperative day 5 to postoperative day 1 >1,0; during long term follow up (until  
24 postoperative day 90) at new presence of hepatic encephalopathy and  
25 coagulopathy (INR > 1,5) within 8 weeks after initial signs of liver injury (e.g.  
26 jaundice) without evidence for chronic liver disease]

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29 **Changes in Version 2.4.2 (Oct 2014) compared to Version 2.4.1 (Jun 2013) of**  
30 **the research protocol**

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33 Page 12: *Section 6.5* [Interim Analyses: Planned interim analyses will be performed after  
34 50% of the patients required (n=374 patients) have been randomized and treated  
35 in the study. Early termination of the study may be considered if very strong  
36 differences between the two treatment groups become apparent. Very strong  
37 differences are defined as risk ratio smaller than 0.5 (e.g. event rate in higher  
38 PEEP group < 20%, event rate in lower PEEP group 40%) or greater than 2.0 (e.g.  
39 event rate in higher PEEP group > 80%, event rate in lower PEEP group 40%).  
40 The decision to terminate the study early will be made by a data and safety  
41 monitoring board (DSMB). Except in the case of early study termination, the results

42 of the interim analysis will not be disclosed to the participating study centers.] is  
43 deleted. There will be no interim analyses during the study.

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45 Page 22: *The statistical analysis section (8.2) is actualized and extended. The primary*  
46 *endpoint and its analysis plan were clearly defined.*

47

48 Page 23: *Details on how to report Adverse Events (AE) are added by using the new*  
49 *Appendix v. (page 34-35)*

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51 Page 23: [Prof. H. van Aken, University of Münster, Germany] *deleted. Since he is not a*  
52 *member, at present, the DSMB is composed of four individuals.*

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54 Page 33: *The study sheet (Appendix iv) was overall actualized. Mainly, patient visits on*  
55 *postoperative days 2 and 4 are added. These additional visits were already*  
56 *described in the text (page 19) in the former versions of the protocol (2.4 and*  
57 *2.4.1).*

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## 59 **Changes in Version 2.5 (Feb 2016) compared to Version 2.4.2 (Oct 2014) of the** 60 **research protocol**

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63 Page 12: Since the overall sample size needed to be increased, we adapted both the  
64 number of centers and the number of patients per center to be randomized. We  
65 now expect to have 90 centers (instead of 60), each randomizing at least 24  
66 (instead of 12 to 13) eligible patients.

67 Page 13: Sample size was re-calculated as newly described. The original description of the  
68 methods was kept in place and slightly modified. The following text was added:  
69 *[Accordingly, the previous Sample size was re-estimated based on*  
70 *recommendations of the DSMB after data on the first 618 patients revealed that*  
71 *the incidence of the collapsed composite outcome was considerably lower than*  
72 *expected. In the revised calculations, the control group incidence was assumed to*  
73 *be 0.20 (instead of 0.40), and sample size was calculated to have 80% power at*  
74 *the overall 0.05 significance level to detect a relative risk (as originally planned) of*  
75 *0.75. This design requires a maximum of 1912 patients, adjusting for the interim*  
76 *monitoring for efficacy and futility as described in section 8.2. Assuming a dropout*  
77 *rate of 5%, a total of 2013 patients need to be included into the study. East 6.0*  
78 *interim monitoring software (Cytel, Cambridge, MA, USA) was used.]*

79

80 Page 23: Interim analyses were planned. The following text, including one table and one  
81 figure was added: *[Interim analyses for efficacy and futility will be conducted at*  
82 *50% (N=956), 75% (N=1434) and 100% (N=1912) of the planned enrollment, as*

83 needed, using a non-binding group sequential design with gamma spending  
84 functions ( $\gamma = -4$  for each of alpha and beta). The table below shows the  
85 alpha and beta spent over the trial, z-statistic boundaries for efficacy and futility,  
86 and boundary crossing probabilities under the alternative hypothesis (H1). The  
87 corresponding P-value boundaries for efficacy (futility in parentheses) at the 1st,  
88 2nd and final looks, respectively, are  $P \leq 0.006$  ( $P > 0.82$ ),  $P \leq 0.015$  ( $P > 0.35$ ) and  $P$   
89  $\leq 0.044$  ( $P > 0.044$ ). The Figure below displays the z-statistic boundaries for  
90 efficacy/harm and futility as a function of accrued sample size.]

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92 Page 25: Prof. A. Hoeft, University Hospital of Bonn, Germany joined the Data Safety and  
93 Monitoring Board (DSMB). Now, the DSMB is composed of 5 individuals.

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95 **Changes in Version 2.6 (Oct 2016) compared to Version 2.5 (Feb 2016) of the**  
96 **research protocol**

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99 Page 20: One additional preoperative parameter is recorded, thereby extending the  
100 measurement of SpO<sub>2</sub> with the patient in beach chair position breathing room air:  
101 SpO<sub>2</sub> (10min in room air, *supine* position), %; if SpO<sub>2</sub> in beach chair position  $\geq$   
102 92%

103