Author's response to reviews

Title: A randomized controlled double-blinded trial comparing the effect of on demand vs deep neuromuscular relaxation on rating of surgical and anaesthesiologic conditions in patients undergoing thoracolaparoscopic esophagectomy- study protocol (DEPTH-Study).

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Author's response to reviews: see over
Amendement for Trials (1495391701156270):

The effect of on demand vs deep neuromuscular relaxation on rating of surgical and anaesthesiologic conditions in patients undergoing thoracolaparoscopic esophagectomy (DEPTH trial): study protocol for a randomized controlled trial.

Dear editor,

Below are the changes made in the manuscript. Changes in the text are marked **bold**. The changes in the protocol are minor and include only the dealing with patients with a very deep neuromuscular block. Discussion and limitation section is therefore also changed to explain the changes necessary. Hopefully the manuscript is acceptable for publication in your journal. Please let me know if there is anything else that should be changed.

Best wishes,

Denise Veelo

1) We changed the title according to the journals standards.

2) I added one co-author (B.F. Geerts) as shown on the title page.

3) We added the possibility to antagonize very deep neuromuscular block with a higher dose of Sugammadex (16 mg/kg). If the patient needs to be ventilated post-operatively for clinical reasons, a PTC of > 1 should be waited for and a dose of 4 mg/kg can then be infused if ready for extubation.

Page 7: “very deep NMB (post-tetanic count, o twitches”, Page 8: The Sugammadex dose needed in case of a very deep block (16 mg/kg) was added to the protocol after ten patients.

4. Because the amendement was made after the first ten patients, we will exclude these patients for the initial cost analysis regarding Sugammadex. In a sensitivity analysis all patients will be included for the cost analysis.

Page 13: Because of the amendement in Sugammadex dose, the first ten patients will be excluded for the cost analysis only. A sensitivity analysis will be performed, including the first ten patients.

5. Discussion and limitation section (page 14&15):

   a. However, as yet, no data on the use of Sugammadex after 8-9 hours of deep (continuous) neuromuscular relaxation and the incidence of recurarization exist. Therefore we will register time until TOF > 90%, and the incidence of recurarization.
Furthermore, lack of adequate neuromuscular monitoring (e.g. TOF), in the prone position but especially in the supine position where both hands are tucked in alongside the body, is challenging to the anaesthesiologist. Hand movements are often inhibited and TOF-counts are unreliable. In view of that, anaesthesiologists and surgeons often disagree about the operating conditions and the ability of the surgeons to judge whether the patient is adequately relaxed or not. We therefore let the surgeons (and anaesthesiologist) “estimate” at the end of the operation to which group the patient was randomized.

b. During these procedures TOF-count is not reliable in prone positioning and supine positioning because of the movement confinement of the body. Although this is part of the normal situation anaesthesiologists face during these procedures, we cannot absolutely be sure whether the patients randomized to receive deep neuromuscular relaxation are insufficiently relaxed or too deeply relaxed. Indeed, for adequate neuromuscular relaxation of the diaphragm a PTC between 0 and 1 or less is probably necessary, which is on itself very hard to accomplish in normal practice. We will use the standard dosing for continuous use that is advised in the product specifics (SPC text) of Rocuronium and Sugammadex. However because of the lack of data on continuous administration for more than 5 hours, there may be variability in neuromuscular block seen, and some patients may have a very deep block at the end of the procedure. We therefore amended the protocol after ten patients, describing more clearly management of patients with a very deep block at the end of the operation. In addition, we use the peroneal nerve to measure TOF because we expect less movement inhibition. However, it is possible that due to positional problems we cannot get a reliable TOF for every patient. Consequently we do not adjust the infused Rocuronium dose based on these measurements.