Author's response to reviews

Title: Influence of early goal-directed therapy using arterial waveform analysis on major complications after high-risk, abdominal surgery: study protocol for a multi-center, randomized controlled, superiority trial.

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Author's response to reviews: see over
Dear Editors-in-Chief,

Thank you for considering our study protocol for publication in Trials. We hereby send you the revision of the manuscript. For your convenience, we added line numbers in the revised protocol. As requested, we changed the title to meet the journal style for study protocol articles. Below, we will give a point-by-point response to the reviewers’ comments:

Response to reviewer 1:
Reviewer: Xavier Griffin
Reviewer’s report:
This protocol is acceptable for publication in its current format.
1. Will the study design adequately test the hypothesis?
YES
2. Is the planned statistical analysis appropriate?
YES
3. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?
YES
4. Is the writing acceptable?
YES
Response to reviewer 2:

Reviewer: Christoph Hofer
Reviewer’s report:

GENERAL
1. Summary: This is a very well-written, extensive manuscript about an important multi-centre, randomized controlled trial investigating the impact of early goal-directed therapy (EGDT) in elective high-risk abdominal surgery. As the authors point out, an up-to-date, well-designed large study on EGDT is lacking (outdated data, changes in the use of monitoring, many smaller studies, inclusion of minor complications etc.) and may help to better understand and to further implement EGDT.

2. Methods: 3 (+1) hospitals include elective patients undergoing a wide range of major abdominal procedures and apply perioperative standard care or standard care + EGDT after randomization 1:1 based on procedures. 1° Outcome: composite: Mortality + morbidity (cardiovascular (4), respiratory (4), renal (1), gastrointestinal (2), infection (2) 30 day period. 2° Outcome: Accordion Severity Grading system, minor complications, fluid balance, inotropic support, hemodynamics, LOS (hospital, ICU, PACU, readmission, QoL, long-term 3, 6, 12 months)

MAJOR
1. Patient population: The authors include a variety of major abdominal procedures that differ considerably regarding perioperative care, complication rate, and expected survival. These include esophagectomy, pancreatectomy, aortic repair (all patients) but also gastrectomy, colorectal and other major intraabdominal procedures (patients with higher risk ASA III or IV). A major concern is therefore the potentially limited data interpretation:
   - Is it still possible to answer if EGDT should be used and result in an improved outcome with improved QoL for instance in patients undergoing aortic repair or in patients having esophagectomy?
   - Why didn’t the authors restrict it to one procedure that is quite standardized such as colorectal surgery?

   Ad. 1:
   Thank you for this valuable comment. We agree that, especially from a methodological point of view, it would be advisable to include a restricted, more homogeneous group of patients. In practice however, the application of EGDT will not be confined to one type of procedure rather than to high-risk abdominal surgery in general. Restricting the eligibility criteria to colorectal surgery would limit the generalizability of the results to other fields of high-risk, abdominal surgery in which EGDT could be useful. An analysis of our own hospital data revealed that the procedures included in the present trial were associated with the same complications, but to a different extent. Subgroup analyses will be performed retrospectively to investigate if, and to which extent, the incidence of these complications is influenced by EGDT.

2. Sample size: In order to minimize patient numbers the authors have chosen to use a composite outcome (they nicely discuss the problems related to sample size calculation). Still, a major concern is that a larger sample size would have been advisable in order to
   - better elucidate the impact of EGDT for one procedure such as colorectal procedures or
   - minimize the need of a composite outcome.

Ad. 2:
We thank the reviewer for addressing this important topic, which has been extensively discussed in our group. Ideally, the influence of EGDT is investigated with sufficient power to draw conclusions in different types of surgery for a single outcome measure (e.g. anastomotic leak). This however requires very large sample sizes (thousands of patients). For the present study, this was not feasible. Both the number of eligible patients within the specific study period and the financial resources were limited. Moreover, from an ethical point of view, very large sample sizes may be considered
disadvantageous. If a study in 500 patients reveals a reduction in the number of complications embedded in a composite primary endpoint, it may be considered unethical to include another 4,500 patients to confirm the treatment effect in a single outcome measure, e.g. mortality. In this way, 2,250 patients would be subjected to standard care, withholding the intervention that has already been shown to reduce complications.

3. Standard treatment protocol: While the EGDT protocol is well described, the standard care leaves room to interpretation (how much fluids, types of colloids, maximum level of norepinephrine etc.). This reviewer was wondering if combined anaesthesia (general + epidural) is being used in these patients undergoing major abdominal surgery. Combined anaesthesia has been shown to improve outcome as a part of a “bundle” in the ERAS protocol.

-Do the centres, or one of the 3 centres apply combined anaesthesia (when yes, how do the anticipate the related loss of sympathetic tone after induction and during the procedure)?

-Do the centres or one of the centres apply any form of ERAS protocol (when no, do the have a standardized protocol for perioperative care for all 3 centers including for example bowel preparation, early nutrition and early mobilization)?

Ad. 3:

We agree with the reviewer that there is room for interpretations in terms of standard care. First, we decided to limit the conditions for standard care for reasons of generalizability. In case of strict definitions for standard care, the results from the study may become less applicable for institutions with a different approach to peri-operative care. Second, we would like to emphasize that EGDT is meant as an addition to standard care, not as a replacement. As a result, the difference between the standard care and intervention groups is solely expected to be the result of the consequences of EGDT in terms of continuous optimisation of cardiac output. Due to randomization, other important treatment effects such as the use of epidural analgesia, ERAS protocols, basic fluid regimes, corrections for pre-operative fasting, but also the use of robotic surgery, and safety checklists, are expected to be balanced between the groups. In addition, these treatment effects are not influenced by the application of EGDT. EGDT may however interfere with the handling of other hemodynamic variables. Therefore, we decided to define target values for a number of hemodynamic variables other than cardiac output, and transfusion criteria. In addition, we described the treatment of hypotension after induction of anesthesia, since EGDT cannot start until an arterial line has been inserted. Finally, the use of stroke volume variation requires specific settings for mechanical ventilation. These settings should be applied in the standard care group as well.

In all participating centers, combined anesthesia is applied for major abdominal surgery. The loss of sympathetic tone associated with epidural analgesia is treated using vasopressive agents and fluids, as described in the protocol (page 12, lines 245-248). Moreover, all participating centers already use ERAS protocols as standard care. As a result, the application of epidural analgesia and ERAS protocols in the participating centers is homogeneous.

We added the considerations brought up by the reviewer to the methods/design section (page 12, lines 255-256) and discussion section (page 25, lines 542-546).

4. EGDT protocol: One problem to EGDT is the fact that there is no widely accepted standardized protocol although the ESA has published some recommendations regarding DGT application. The authors of this study now further modify EDGT (different CO goals based on age): Did they test these different goals in a pilot study?

In case of hypotension in the EGDT groups when / how much norepinephrine is allowed? How often are variables assessed indicating adequate tissue oxygenation such as ScvO2, lactate or BE?

Ad. 4:

Thank you for this comment. We did not test these different goals in a pilot study. In general, cardiac index declines with age, which has been addressed by modifying the CO goal in our protocol. Besides this, the use of age-dependent target values for cardiac index was clinically driven. In clinical practice, researchers from our group noticed that they used different treatment threshold values for rather young and elderly patients. This effect is frequently observed, e.g. during cardiac surgery.
We did not define a maximum dose for the administration of norepinephrine. It is our experience that clinicians will consider the use of fluids or beta-symphaticomimetics if high doses of vasopressive agents are needed. The assessment of lactate, base excess and central venous oxygen saturations is allowed at any time, but only prescribed at certain time points, i.e. after induction of anesthesia, during surgical closure, after admittance in the ICU/PACU, and the morning after surgery (page 16, lines 343-344) as part of the secondary outcome measures. We added this to the methods/design section (page 12, line 256-258).

MINOR
1. Abstract: Page 3 Methods/Design: “early goal-directed therapy is added to standard care, consisting of continuous monitoring of cardiac output with arterial waveform analysis”: EGDT doesn’t consist of continuous CO monitoring, it is a treatment protocol based on variables assessed by advanced HD monitoring, please revise.
Ad. 1:
Thank you for this suggestion. We changed this sentence (page 3, line 53).

2. Discharge criteria: Please add references
Ad. 2:
We added the reference (“[30]”).

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I have received lecturing fees and research grants from Edwards Lifesciences in the past.
I am interested in EGDT and will implement it in the near future as part of a QIP in my hospital.

Reviewer 3:

Reviewer: Alexey Smetkin
Reviewer’s report:
Major Compulsory Revisions
1. Randomization
“A randomization procedure is used to allocate patients to standard care (control group) or standard care with EGDT (intervention) in a 1:1 ratio.” Will you keep this 1:1 ratio in all included centers or this is cumulative 1:1 ratio? In last case, it is possible that you will compare data of control group prevailing in one center and date of intervention group prevailing in another center.
Ad. 1:
Thank you for this comment. The randomization procedure is separate for each participating center. The maximum block size is 4 patients, which means that the maximum discrepancy in group size is 2 patients per center, or 8 patients in total. The change that this “maximum discrepancy” occurs, is 1:256 or 0.4%.

2. Standard care
What kind of anaesthesia do you use? Is it standard procedure, for instance, combined – general and regional (e.g. epidural) anaesthesia or general anaesthesia only? This may affect vascular tone and thereby cardiac output.
Ad. 2:
Thank you for this remark. We refer to the response to reviewer 2, item 3.

3. Standard care
Will all the patients be well preoperatively hydrated? What approach do you use to preoperative fasting? What is the basic perioperative fluid therapy?
Ad. 3:
Thank you for this valuable remark, which resembles the comments by reviewer 2 (item 3). We therefore refer to the response to reviewer 2, item 3. In addition to this, we would like to further clarify the methods used in the participating centers. With respect to pre-operative hydration, all patients are allowed to drink clear liquids up to 2 hours before surgery, and are encouraged to do so. This will limit pre-operative dehydration due to fasting. As a result, intra-operative corrections are not made by most attending anesthesiologists in the participating centers. Nevertheless, corrections for pre-operative fasting are allowed depending on the preference of the attending anesthesiologist. We did not define requirements for basic peri-operative fluid therapy, and expect differences to be equally balanced between the groups. We clarified this in the manuscript (page 12, lines 255-256, and page 25, lines 542-546).

4. Intervention
“The choice of AWA technique depends on the institution in which the study is performed”

Of course, this approach provides an opportunity to involve more centers in the study and make the algorithm more versatile. Nevertheless, various AWA techniques have different accuracy in measuring the cardiac output and different trending ability. In this situation, if the number of patients in the intervention group is not equal in each center, the efficiency will be shifted (for better or worse, depending on the method used in the center) toward the center with a large number of patients.

Ad. 4:
Thank you for this interesting remark. We acknowledge the difference in accuracy and trending ability between the available arterial waveform analysis cardiac output monitoring devices. The deviation between cardiac output as depicted on the arterial waveform analysis based monitor and the true underlying cardiac output is however not fixed, as indicated by the limits of agreement using Bland-Altman analysis. Therefore, arterial waveform analysis derived cardiac output differs from its true value in each single patient and procedure. The extent to which the use of different cardiac output monitors further increases this effect, is expected to be small in the relatively large group of patients. Nevertheless, it appears that all participating centers use the same method for measuring cardiac output: the FloTrac/Vigileo monitor (Edwards Lifesciences, Irvine, USA).

5. Intervention
“If the CI increases 10% or more during PLR, a 500 ml FC is given.”
How fast will be fluid load performed?

Ad. 5:
This will depend on the clinical circumstances and is not prescribed. In practice, the fluid challenge is given in a period varying between 10 and 30 minutes.

Intervention
“If both measurement of SVV and PLR testing are not possible, a small 250 ml FC is given. If the CI subsequently increase, another 250 ml is given”
At which an increase in cardiac index is considered a positive response?

Ad. 6:
If cardiac index increases to any extent after administrating 250 ml of fluid, another 250 ml is given. Usually, a small fluid challenge of 250 ml will not lead to major increases in cardiac index. Therefore, we decided not to define a specific response in terms of a percentage increase. However, the increase in cardiac index observed after volume loading should be sustained, as the cardiac index signal will vary in time.

7. Risk assessment
“EGDT involves fluid therapy and inotropic support, which are commonly used in patients undergoing high-risk surgery. Additional risk associated with its use in the treatment algorithm is therefore not likely in comparison with routine practice.”

This is provided that the cardiac output is measured properly. It is known that less invasive methods of measuring cardiac output are less accurate in comparison with thermodilution techniques.
Therefore, if the monitor underestimates cardiac output, according to the algorithm patient will receive unnecessary treatment.

Ad. 7:
Thank you for this interesting comment. In theory, it is possible indeed that patients receive “unnecessary” treatment. As discussed in the systematic review however, results from previous studies do not alert to this effect. Yet, the manuscript points to the option to stop treatment in terms of EGDT if the clinician suspects any unwanted effects of vasoactive medication or deliberate use of fluids indicated by the EGDT algorithm.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests

We would like to thank the reviewers for the thorough reading of our manuscript and their interesting comments.

On behalf of all authors, yours sincerely,

Leonard J Montenij, MD.