PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)
AUTHORS	Nickel, Felix; Studier-Fischer, Alexander; Haussmann, David; Klotz, Rosa; Vogel-Adigozalov, Sophia; Tenckhoff, Solveig; Klose, Christina; Feisst, Manuel; Zimmermann, Samuel; Babic, Benjamin; Berlt, Felix; Bruns, Christiane; Gockel, Ines; Graf, Sandra; Grimminger, Peter; Gutschow, Christian; Hoeppner, Jens; Ludwig, Kaja; Mirow, Lutz; Mönig, Stefan; Reim, Daniel; Seyfried, Florian; Stange, Daniel; Billeter, Adrian; Nienhüser, Henrik; Probst, Pascal; Schmidt, Thomas; Müller-Stich, Beat

VERSION 1 – REVIEW

REVIEWER	Peterli, Ralph Clarunis University Center for Gastrointestinal and Liver Diseases, Visceral Surgery
REVIEW RETURNED	10-Jun-2022

GENERAL COMMENTS	General comment This is a multicentre RCT to compare postoperative morbidity following minimally invasive versus open total gastrectomy to treat gastric cancer. Specific comments: Page 4, line 92: numbers seem small to detect relevant differences in subgroup analysis between conventional laparoscopic vs Robotic total gastrectomy Page 4, line 94: 2x80 pts seems to be a sufficient patient number for the primary endpoint but it is not a “large group size”. In comparison KLASS-02-RCT had 2x>520 pts in each group, knowing that the prevalence in Europe is much lower compared to Asian population Page 7, line 162: inclusion criteria: the authors don’t mention neoadjuvant chemotherapy. I assume it is not an exclusion criterion. Page 10, line 229: I would add in the sentence on CCI:…..of the severity and individual burden of …. Table 2 Grading of Adverse events: What is the reason you define SAE as CD Grade IV and V and not f.ex. including IIIb? Page 15, line 342:2: relevant difference of CCI 10 point to be considered relevant: based on what?

	Page 16, line 353: 50% participation rate: this is very optimistic. Many series report 5-10% of patients being randomized to one or another surgical method, on what experience do you expect 50% to accept being randomized?

REVIEWER	Terashima , Masanori Shizuoka Cancer Center, Gastric Surgery
REVIEW RETURNED	17-Aug-2022

GENERAL COMMENTS	1. In Germany, perioperative FLOT maybe a standard of care. However, there is no description about preoperative treatment. Are patients with preoperative chemotherapy eligible or not eligible? It should be described in inclusion or exclusion criteria. 2. Are there any stratification factors in this trial?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Prof. Ralph Peterli, Clarunis University Center for Gastrointestinal and Liver Diseases
Comments to the Author:
General comment
This is a multicentre RCT to compare postoperative morbidity following minimally invasive versus open total gastrectomy to treat gastric cancer.

Specific comments:
Page 4, line 92: numbers seem small to detect relevant differences in subgroup analysis between conventional laparoscopic vs Robotic total gastrectomy.
This is exactly right. The sample size calculation has exclusively focused on the open and minimally-invasive approach (combining laparoscopic and robotic). Therefore, the statistical power might not be high enough to detect relevant differences in subgroups. However, this is also not the primary aim of this trial and the decision was consciously made in order to avoid prolongation of the answer of the clinically highly relevant research question this trial is designed to provide; namely, relevant differences between the open and minimally-invasive approach.

Page 4, line 94: 2x80 pts seems to be a sufficient patient number for the primary endpoint, but it is not a “large group size”. In comparison KLASS-02-RCT had 2x>520 pts in each group, knowing that the prevalence in Europe is much lower compared to Asian population
We have rephrased the wording into “well-powered group sizes”.

Page 7, line 162: inclusion criteria: the authors don’t mention neoadjuvant chemotherapy. I assume it is not an exclusion criterion.
Neoadjuvant chemotherapy is no exclusion criterion and we now added it explicitly in the text: “Neoadjuvant chemotherapy does explicitly not contribute to inclusion or exclusion criteria, but will of course be monitored”.

Page 10, line 229: I would add in the sentence on CCI:…..of the severity and individual burden of ….
We added the recommended phrase (“Usage of this index will enable a comparison of the severity and individual burden of postoperative complications with results from other trials”).

Table 2 Grading of Adverse events:
What is the reason you define SAE as CD Grade IV and V and not f.ex. including IIIb?
There is no uniform definition of serious adverse events in surgery. Therefore, we decided to follow the in-house-standards (Serious adverse event (SAE): Clavien-Dindo: IV-V; Major complication:

Clavien-Dindo: III-V). What is much more relevant in our opinion is the transparency of this wording, which is why we decided to add “Table 2: Grading of Adverse Events” for explicit clarification and transparency. Complications will be reported with exact Clavien-Dindo classification to guarantee maximum transparency and compatibility with other trials.

Page 15, line 342:2: relevant difference of CCI 10 point to be considered relevant: based on what?
A difference in CCI of 10 points is considered relevant according to one of the original publications (see below), where a 10-point difference corresponds to a 40% relative risk reduction in the traditional endpoints.
Slankamenac, K., Nederlof, N., Pessaux, P., de Jonge, J., Wijnhoven, B. P., Breitenstein, S., Oberkofler, C. E., Graf, R., Puhan, M. A., & Clavien, P. A. (2014). The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Annals of surgery, 260(5), 757–763.
https://doi.org/10.1097/SLA.0000000000000948

Page 16, line 353: 50% participation rate: this is very optimistic. Many series report 5-10% of patients being randomized to one or another surgical method, on what experience do you expect 50% to accept being randomized?
The assumption of a 50% participation rate has been based on previous in-house experience. Certain advantages may play an important role such as extensive experience and commitment through the Study Center of the German Society of Surgery (SDGC). The study center personnel has the resources and experience to optimize patient motivation, information, commitment and adherence.

Reviewer: 2
Dr. Masanori Terashima , Shizuoka Cancer Center
Comments to the Author:
1. In Germany, perioperative FLOT may be a standard of care. However, there is no description about preoperative treatment. Are patients with preoperative chemotherapy eligible or not eligible? It should be described in inclusion or exclusion criteria.
Neoadjuvant chemotherapy is no exclusion criterion and we now added it explicitly in the text: “Neoadjuvant chemotherapy does explicitly not contribute to inclusion or exclusion criteria, but will of course be monitored”.
(Already mentioned above)

2. Are there any stratification factors in this trial?
For the primary analysis of the primary endpoint, there are no stratification factors.
Stratification for the analysis of subgroups will include (but not be limited to) stratification for cancer stage, laparoscopic or robotic approach, age, gender, chemotherapy and more.
This will be specified in the statistical analysis plan, which will be defined and made public during recruitment and well before last-patient-in or any interim analyses.

VERSION 2 – REVIEW

REVIEWER	Peterli, Ralph Clarunis University Center for Gastrointestinal and Liver Diseases, Visceral Surgery
REVIEW RETURNED	22-Sep-2022

GENERAL COMMENTS	None

REVIEWER	Terashima , Masanori Shizuoka Cancer Center, Gastric Surgery
REVIEW RETURNED	05-Sep-2022

GENERAL COMMENTS	There are no furtehr comments.