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Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)

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Abstract

Introduction:

The only curative treatment for most gastric cancer is radical gastrectomy with D2 lymphadenectomy (LAD). Minimally invasive total gastrectomy (MIG) aims to reduce postoperative morbidity, but its use has not yet been widely established in Western

countries. MEGA is the first Western multicenter randomized controlled trial (RCT) to compare postoperative morbidity following MIG versus open total gastrectomy (OG).

Methods and analysis:

This superiority multicenter RCT compares MIG (intervention) to OG (control) for oncological total gastrectomy with D2 or D2+ LAD. Recruitment is expected to last for 2 years. Inclusion criteria comprise age between 18 and 84 years and planned total gastrectomy after initial diagnosis of gastric carcinoma. Exclusion criteria include ECOG performance status > 2 (**Appendix 1**), tumors requiring extended gastrectomy or less than total gastrectomy, previous abdominal surgery or extensive adhesions seriously complicating MIG, other active oncologic disease, advanced stages (T4 or M1), emergency setting, and pregnancy.

The sample size was calculated at 80 participants per group. The primary endpoint is 30-day postoperative morbidity as measured by the Comprehensive Complications Index (CCI). Secondary endpoints include postoperative morbidity and mortality, adherence to a fast-track protocol, and patient-reported quality of life (QoL) scores (QoR-15, EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADLs, and BIS). Oncologic endpoints include rate of R0 resection, lymph node yield, disease-free survival, and overall survival at 60-month follow-up.

Ethics and dissemination:

Ethical approval has been received by the independent Ethics Committee of the Medical Faculty, University of Heidelberg (S-816/2021) and will be received from each responsible ethics committee for each individual participating center prior to recruitment. Results will be published open access.

Trial registration: German Clinical Trials Register DRKS00025765. Registered on December 22nd, 2021.

Keywords: Minimally invasive gastrectomy, total gastrectomy, gastric cancer, Roux-Y reconstruction, linear stapled anastomosis, circular stapled anastomosis, randomized controlled trial, comprehensive complication index, fast-track, enhanced recovery after surgery

Strengths and limitations of this study

- MEGA is the first Western multicenter RCT to specifically compare OG with MIG in terms of postoperative morbidity using the comprehensive complication index (CCI).
- Usage of the CCI as a comprehensive outcome measure allows for objective comparisons with other trials.
- Differentiation between robotic and laparoscopic total gastrectomy will be made in the explorative subgroup analysis only.
- High levels of standardization, intraoperative photo documentation, large group sizes, and risk-based monitoring by the Study Center of the German Society of Surgery (SDGC) will guarantee objective data acquisition, increase patients' adherence to the protocol, and ultimately lead to exceptional data quality.

Introduction

Gastric cancer is the sixth most common tumor disease in the world and causes the second most deaths [1]. In 2018, approximately one million patients worldwide and approximately 15,000 patients in Germany were diagnosed with gastric cancer, of which an average of 76% die from the disease [1]. Gastric cancer causes one of the highest oncologic disease burdens as measured by lost disability-adjusted life years (DALY). This fact highlights the aggressiveness of the disease. Age-adjusted DALY rates per 100,000 reach 241 for men and 146 for women, ranking 4th after liver, lung, and breast cancer [2, 3].

Currently, the only therapy that offers a chance of cure is gastrectomy, with a 5-year survival rate of 20-30% and postoperative morbidity and mortality as high as 63% [4] and 11% [5-10], even at experienced centers [4-18]. Therefore, there is a great need to identify the optimal surgical approach using evidence from multicenter data in order to improve oncologic outcome and to decrease postoperative complications.

The current gold standard is open gastrectomy (OG) with D2 lymphadenectomy (LAD) (**Appendix 2**), but its highly invasive nature leads to potentially high complication rates, especially in elderly and obese patients. These frequent postoperative complications result in higher mortality, lower QoL, a longer hospital stay, and thus a higher burden on the health care system [6, 19]. In other fields of visceral surgery, such as appendectomy, cholecystectomy, obesity surgery, and esophagectomy, minimally invasive surgery has already replaced the open approach as the standard of care [7, 20-22]. Several randomized controlled trials (RCT) have demonstrated reduced postoperative complications following minimally invasive surgery compared to the open approach. This finding is due to the procedure's resulting smaller wounds, reduced operative trauma, lower blood loss, shorter hospital stay, and faster rehabilitation time [22-24].

Postoperative complications, however, are not only important for the immediate postoperative course, which is usually secondary in relevance, but can also affect long-term oncologic outcome [25-27]. In a study of 432 patients with curative gastrectomy and D2 LAD for treatment of gastric cancer, the occurrence of postoperative in-hospital complications was an independent predictor of worse 5-year survival (22% vs. 40%). This can be perceived as an indication that postoperative complications may lead to higher mortality in the long term [28]. Therefore, the trend towards favoring minimally invasive gastrectomy (MIG) for gastric cancer is increasing.

Methods and analysis

Setting

The MEGA trial is a prospective randomized, controlled, non-blinded, two-armed multicenter surgical superiority trial with a confirmatory character. It includes 14 surgical centers in Germany and Switzerland and is coordinated by the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital, in Germany. Recruitment is planned for 2 consecutive years. The study protocol was accepted by the Independent Ethics Committee of the Medical Faculty, University of Heidelberg (registration number S-816/2021) prior to recruitment. The trial was registered at DRKS under the registration number DRKS00025765 on December 22nd, 2021 [29]. No secondary identifying numbers such as a Universal Trial Number have been assigned. Recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist were followed [30].

Patient recruitment

Recruitment is planned to take place at 14 surgical centers in Germany and Switzerland. Certain eligibility criteria have to be met by the participating centers and surgeons in order to eliminate bias from inexperience or learning curves. Therefore, hospitals need to have a case load of ≥20 gastrectomies per year, and every trial surgeon has to provide evidence of at least 20 previously performed surgeries of the respective surgical procedure/s he or she wants to contribute [OG, laparoscopic gastrectomy (LAG) or robotic-assisted gastrectomy (RAG)]. Eligible patients will be screened consecutively to eliminate selection bias and will receive diagnostic staging laparoscopy prior to randomization.

Inclusion criteria:

- Age between 18 and 84 years
- Planned total gastrectomy after first diagnosis of gastric carcinoma
- Ability of patient to understand character and consequences of the trial
- Written informed consent

Exclusion criteria:

- ECOG performance status > 2
- Planned extended gastrectomy or less than total gastrectomy (e.g., adenocarcinoma of the esophagogastric junction (AEG) I and AEG II, or distal gastric tumors of an intestinal subtype)
- Previous gastric surgery or extensive adhesions seriously complicating MIG
- Other active oncologic disease or history of cancer limiting prognosis in comparison to the gastric cancer
- Emergency setting
- Language barriers rendering the patient unable to fill out patient-reported outcome questionnaires

- Participation in another intervention trial that might interfere with the intervention and/or outcome of this trial
- Pregnancy

Exclusion criteria previously or during staging laparoscopy:

- T4
- M1

Inclusion takes place after the staging laparoscopy, and patients will be randomized to the intervention arm (MIG) or the control arm (OG) (**Figure 1**).

Trial duration and schedule

Recruitment is planned to take 24 months. The duration of the trial for each patient is expected to be 1 month for the primary endpoint and 60 months for the secondary endpoints with long-term follow-up. Consequently, the duration of data collection is expected to be 25 months for the primary endpoint and 84 months for the secondary endpoints [first-patient-in (FPI) to last-patient-out (LPO)]. Trial analysis will take an additional 6 months. The actual overall duration or recruitment time may differ. Recruitment is planned to be active until both arms contain at least 80 patients in the intention-to-treat (ITT) dataset.

Trial visits

Patients will be monitored intraoperatively, on postoperative days (POD) 1, 3, and 5, and on the day of discharge. Follow-up will be conducted on POD 30, 90, and after postoperative months (POM) 6, 12, 24, 36, 48, and 60 (**Table 1**). Demographic and baseline clinical data, intraoperative findings, and postoperative results will be recorded. During follow-up, patients will complete established and validated questionnaires. To enhance participant retention and to avoid loss to follow-up,

patients will be contacted for the completion of questionnaires and to collect missing data. Informed consent will be obtained and trial data will be collected by trained assessors using electronic case report forms (eCRFs).

Table 1 | Trial visits and overview over documented parameters & outcomes

Activity & Documentation	Visit 1 (screening)	Visit 2 (laparosc.)	Visit 3 (surgery)	Visit 4-6 (POD 1, 3, 5)	Visit 7 (dis-charge)	Visit 8-9 (POD 30, 90)	Visit 10-15 (POM 6, 12, 24, 36, 48, 60)
inclusion & exclusion criteria	X						
informed consent	X						
medical history & preoperative assessment*	X						
randomization		X					
surgical & anaesthetic documentation**			X				
Postoperative morbidity measured with CCI (primary endpoint)	X		X	X	X	X	
scores / questionnaires							
EUROQOL EQ-5D-5L	X				X	X	X
EORTC QLQ-C30	X				X	X	X
EORTC QLQ-STO22	X				X	X	X
QoR-15				X (V5)			
ADLs	X			X	X	X	X
BIS							X (V13)
biological specimen retrieval							
EDTA blood samples	X						
formalin and paraffin tissue samples			X				
	Visit 1 (screening)	**Visit 2 (laparosc.)**	**Visit 3 (surgery)**	**Visit 4-6 (POD 1, 3, 5)**	**Visit 7 (dis-charge)**	**Visit 8-9 (POD 30, 90)**	**Visit 10-15 (POM 6, 12, 24, 36, 48, 60)**
Short-term clinical data							
Conversion rate			X				
Operation time			X				
Blood loss			X				
Length of stay in the ICU			X		X		
Length of hospital stay					X		
Pain and postoperative analgesic required				X	X		
Laboratory parameters (CRP, leucocytes)				X	X		
Mobilization of the patient				X			
Quality of the patient's recovery				X			
Quality of life	X				X	X	X
Adherence to a fast-track gastrectomy SOP			X	X	X		
Subjective evaluation of anastomoses			X				
First bowl function and mobilization				X			
Wound healing deficits				X	X	X (V8)	
Vegetative function						X	X
Necessity of interventions due to complications				X	X	X	X
Oncologic short-term data							
Number of lymph nodes removed and of tumor-positive lymph nodes			X				
Number of R0 resections			X				
Development of tumor markers			X				
Tumor histpathology			X				
Long-term clinical data (5-year follow-up)							
Changes of body weight					X	X	X
Quality of life	X				X	X	X
Incidence of incisional hernias						X	X
Incidence of reoperations				X	X	X	X
Incidence of stenosis						X	X
Cosmetic results and scar							X (V13)

	satisfaction							
Oncologic long-term data (5-year follow-up)								
	Oncologic treatment (adjuvant and consecutive therapy)						X	X
	Disease-free survival; DFS; recurrence free survival; RFS						X (V9)	X
	Local recurrence; LR						X (V9)	X
	Relapse-free survival; RFS						X (V9)	X
	Progression-free survival; PFS						X (V9)	X
	Time to progression; TTP						X (V9)	X
	Overall survival; OS						X (V9)	X

* Includes body mass index, ASA status, preoperative oncological status, prior surgical treatment, drug use and comorbidities. ** Includes surgical documentation (surgeons, procedures, complications, drains) & anesthesiology documentation. *** Includes dysphagia, reflux, and dumping syndromes. **** Includes entity, TNM, grading, and resection status. ASA American Society of Anesthesiologists classification, POD postoperative day, POM postoperative month, QoL quality of life, EUROQOL EQ-5D-5L EuroQol Group Questionnaire for Quality of Life with 5 dimensions and 5 levels, EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EORTC QLQ-STO22 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Gastric Cancer, QoR-15 Quality of Recovery 15, ADLs activities of daily living (**Appendix 3**), BIS Body Image Scale, ITT intention-to-treat, VAS visual analog scale of pain, need for ICU intermediate / intensive care unit, CCI Comprehensive Complication Index for complications & related interventions according to the Clavien-Dindo classification (**Appendix 4**).

Primary endpoint

The primary endpoint will be postoperative morbidity measured using the Comprehensive Complication Index (CCI) until postoperative day 30 [31]. Usage of this index will enable a comparison of the severity of postoperative complications with results from other trials [32, 33]. Postoperative morbidity is defined as any deviation

from the normal postoperative course according to the Clavien-Dindo classification [34]. This includes anastomotic insufficiency or loss of anastomotic integrity verified by either CT scan with detection of contrast agent external to the anastomosis, endoscopy, or the detection of methylene blue in a drain following oral intake.

Secondary endpoints

Secondary endpoints can be separated into short-term clinical and oncological endpoints as well as long-term clinical and oncological endpoints (at 5-year follow-up, as measured from the date of surgery) and can be found in **Table 1**.

Standardized therapy and trial interventions

Control: Total OG with D2/D2+ LAD**.**

Intervention: Total MIG with D2/D2+ LAD either as LAG or RAG. A mini-laparotomy or a Pfannenstiel incision (≤8 cm incision in both the skin and fascia) may be performed for specimen removal.

Modified cardia-preserving total gastrectomy (preservation of gastroesophageal junction) can also be accepted, but only if the short gastric vessels are dissected as well, and if LAD is the same as for total gastrectomy. Besides the open or minimally-invasive approach, the remaining treatment is identical in both groups. Any other form of gastrectomy, explicitly conventional subtotal gastrectomy (preserved short gastric vessels and limited LAD of station 2 and 4sa), extended gastrectomy, and distal gastrectomy with Billroth I or II reconstruction are not allowed. Reconstruction can be of any form including Roux-Y reconstruction, interposition, or pouch reconstruction. Any other step of the procedure such as antibiotic prophylaxis, placement of abdominal drains, and closure of the abdominal wall can be performed according to in-house standards. D2 LAD is defined according to the Japanese

classification [35], with stations 1, 2, 3a, 3b, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a obligatory for the MEGA trial (**Figure 2**). Station 10 is optional. Incomplete LAD is not allowed and has to be documented as a protocol deviation.

Removal of further stations (8b, 12b, 12p, 13, 14v, 14a, 15, 16a1, 16a2, 16b1, 16b2, 17, 18, 19, 20, 110, 111, and 112) is allowed when deemed appropriate, e.g., in case of assumed tumor invasion, and has to be documented as D2+.

Postoperative management

Postoperative management should be performed in a fast-track approach with short durations until patient mobilization, drainage removal, and first oralization of food. The patient should be extubated immediately after surgery and transferred to a normal ward, if possible. Further specifications for the postoperative course will be outlined in the provided standard operating procedure (SOP) for fast-track gastrectomy. The last in-hospital trial visit takes place on the day of discharge. Subsequent trial visits will be conducted via telephone. These will be questionnaire-based and focus on CCI (until POD 90), quality of life, and oncologic outcome.

Randomization and blinding

In order to ensure equal distribution of patient characteristics between both trial arms, randomization will be performed using a web-based randomization tool (www.randomizer.at). Randomization will take place following diagnostic laparoscopy (Visit 2). The allocation pattern is masked, block-randomized with variable block length, and stratified across centers. Due to the pragmatic character of the trial, blinding of the surgeon is not feasible.

Quality assurance and quality management

Clinical data monitoring

Clinical monitoring will be performed by independent monitors at the Study Center of the German Society of Surgery (SDGC). The monitoring strategy will comprise a combination of centralized and onsite monitoring and will be described in a trial specific monitoring plan. To confirm site selection, pre-study visits will be performed. On-site monitoring will focus on patient informed consent, safety, and surgical procedures as well as the correct recording and documentation of the primary and secondary endpoints by source data verification (SDV).

Surgical quality control

Several steps are necessary to ensure and evaluate surgical quality:

1) Trial surgeons must have performed 20 surgeries in the respective approach (OG, LAG, or RAG), depending on the trial arm they will contribute to.
2) Each trial surgeon must provide photographic or video documentation of a former procedure.
3) Each trial surgeon has to provide photographic or video documentation of the trial procedures, which will be assessed by an expert. This photographic or video documentation is defined as follows:
    a. lymph node station 7 (left gastric artery) after dissection
    b. lymph node station 8a (common hepatic artery) after dissection
    c. lymph node station 9 (celiac artery) after dissection
    d. lymph node station 10 (splenic hilum) after dissection
    e. lymph node station 11p (proximal splenic artery) after dissection
    f. lymph node station 11d (distal splenic artery) after dissection
    g. lymph node station 12a (hepatoduodenal ligament along the hepatic artery) after dissection

h. duodenal stump

i. all anastomoses

j. incision for specimen retrieval in MIG

Assessment of safety

Since the primary endpoint is postoperative complications as measured by the CCI, adverse (AE) and serious adverse events (SAE) are already captured and no additional safety analysis will be performed (**Table 2**).

Table 2: Grading of Adverse Events

<table>
<tr><th>Clavien-Dindo</th><th>Adverse event (AE)</th><th>Serious adverse event (SAE)</th><th>Minor complication</th><th>Major complication</th></tr>
<tr><td>Grade I complication</td><td rowspan="5">AE</td><td></td><td rowspan="2">Minor complication</td><td></td></tr>
<tr><td>Grade II complication</td><td></td><td></td></tr>
<tr><td>Grade III complication</td><td></td><td></td><td rowspan="3">Major complication</td></tr>
<tr><td>Grade IV complication</td><td rowspan="2">SAE</td><td></td></tr>
<tr><td>Grade V complication</td><td></td></tr>
</table>

Data management

The Institute of Medical Biometry (IMBI) is responsible for data management within this trial. An eCRF will be used for data collection. To assure safe and secure data use and storage, data transmission is encrypted with secure socket layer (SSL) technology. Only authorized users are able to enter or edit data, and access is further restricted to data of the patients in that user's respective center only. All changes to data are logged with a computerized timestamp in an audit trail. All data will be

pseudonymized. To guarantee high data quality, data validation rules will be defined in a data validation plan. Completeness, validity, and plausibility of data will be checked at the time of data entry (edit-checks) and using validating programs, which will generate queries. If no further corrections are to be made in the database, eCRF data will be locked. Data will finally be downloaded and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the IMBI that guarantee efficient conduct in compliance with Good Clinical Practice (GCP). At the end of the study, the data will be transformed into different data formats (e.g., csv-files) for archiving and to ensure that it can be re-used.

Statistical methods

Sample size

The sample size calculation is based on the primary endpoint "postoperative morbidity as measured with the CCI until POD 30." A decrease of the CCI by 10 points between OG and MIG is considered relevant by patients and clinicians, and a conservative standard deviation of 20 is assumed based on existing literature for upper GI surgery [36], leading to an effect size of d=0.5. Based on a t-test with a two-sided significance level of $\alpha=0.05$, a sample size of n=128 patients (64 per group) has to be recruited to achieve a power of 80%. The primary endpoint will be analyzed with a linear mixed regression model, which leads to equal or even increased power when compared to a two-sided t-test. To compensate for drop-outs and patients lost to follow-up, a further 20% of patients will be randomized, leading to a total sample size of n=160 (80 per group; 80 x 0,8 = 64.8). The number of patients to be screened

(n=400 to be assessed for eligibility; 400 x 0.5 x 0.8 = 160) was calculated with an assumed 50% participation rate and an exclusion rate of 20%.

Randomized & allocated (n = 160; 80 per group)

Intention-to-treat dataset (n = 160; 80 per group)

Per-protocol dataset (n = 136; 72 and 64)

Statistical analysis

For the examination of the primary endpoint "postoperative morbidity measured with the CCI until POD 30," the hypotheses to be assessed in the primary analysis are as follows: H_0: $\mu_1 = \mu_2$ vs H_1: $\mu_1 \neq \mu_2$, where μ_1 and μ_2 denote the mean CCI in the control and intervention groups, respectively. The significance level is set to a two-sided α=0.05. Therefore, the primary endpoint will be examined using a linear mixed model adjusting for the variables age and treatment group, as well as the surgical center as a random effect (due to the stratified randomization and relatively large number of centers in relation to the sample size, inclusion of center as a random effect is recommended). Details of the primary model (e.g., handling of missing values, sensitivity analyses) will be fully described in the statistical analysis plan.

The number of patients included in the primary analysis is determined as the full analysis set. Patients will be analyzed in the group they were randomized to (converted patients remain in their group). This reflects an analysis according to the intention to treat (ITT) principle. Specific events (e.g., death) that can occur after randomization will be handled within the primary endpoint definition, reflecting a composite strategy [according to the ICH E9 (R1) addendum]. Other post randomization events will not be considered. This choice reflects our treatment policy approach.

In general, for the full analysis set, all baseline values and secondary outcomes will be evaluated descriptively, with p-values reported alongside 95% confidence intervals for the corresponding effects. Furthermore, secondary endpoints will be evaluated descriptively, using appropriate regression models. Time-to-event endpoints will be evaluated by methods of survival analysis including Kaplan-Meier methods and Cox proportional hazards models. In addition, subgroup analyses (including age, gender, tumor stage, tumor grade, histological tumor type, linear vs. circular stapler for proximal anastomosis, linear vs. hand-sewn for distal anastomosis, type of retrieval incision, and intraoperative conversion) will be carried out. A detailed and comprehensive statistical analysis plan will be written shortly after the first patient is recruited. All analyses will be performed using SAS version 9.4 or higher.

Discussion

We performed a systematic literature search prior to planning this trial and identified 974 publications. Of those, 17 RCTs comparing LAG with OG [7, 37-55] and two RCTs comparing RAG with OG [56, 57] were found to be relevant. The studies showed comparable oncologic and short-term postoperative outcomes for MIG and OG. However, 16 of the 19 studies were conducted in China, Korea, and Japan [7, 38-50, 56, 57]. These countries have a significantly higher incidence of gastric cancer, which consequently leads to significantly higher surgical volume and expertise among the participating centers [58]. In addition, the body constitution of Asian patients is often different from that of Western patients, which limits the direct transferability of study results. Also, the incidence of gastric cancer is lower in Western populations and advanced disease stages are more frequently detected,

because screening is less common. Therefore, it is unclear whether these results would be reproducible in a Western population.

Currently, there have only been three non-Asian RCTs directly comparing LAG and OG. The first RCT, by Huscher et al., focused exclusively on distal gastrectomy, did not define any specific primary or secondary endpoints, and included a total of 59 patients [37]. Due to the missing differentiation between primary and secondary endpoints, the trial can be perceived as methodically limited and was most likely underpowered. However, no significant difference was found in perioperative outcome, oncologic outcome, or mortality [morbidity rates: 26.7% (LAG) and 27.6% (OG), lymph nodes harvested: 30.0 ± 14.9 (LAG) and 33.4 ± 17.4 (OG), operative mortality rates: 3.3% (LG) and 6.7% (OG), 5-year survival rate: 54.8% (LAG) and 55.7% (OG)].

The only two currently existing relevant Western multicenter RCTs comparing open versus minimally invasive oncologic total gastrectomy are the LOGICA trial [52, 53] and the STOMACH trial [51, 54, 55], which were both puplished in 2021.

The LOGICA trial is a non-blinded, multicenter superiority trial with 227 patients with postoperative hospital stay as the primary endpoint. The study identified significant differences regarding blood loss [150 ml (LAG) and 300 ml (OG), p<0.001] and operating time [216 min (LAG) and 182 min (OG), p<0.001], but no significant differences in hospital stay (p=0.34), postoperative complications [44% (LAG) and 42% (OG), p=0.91], in-hospital mortality [4% (LAG) and 7% (OG), p=0.40], R0 resections [95% (LAG) and 95% (OG), p=1.00], median lymph node yield [29 (LAG) and 29 (OG), p=0.49], 1-year overall survival [76% (LAG) and 78% (OG), p=0.74], and health-related quality of life [+1.5 (LAG) and +3.6 (OG) on a 1-100 scale].

The STOMACH trial is an observer-blinded, multicenter, non-inferiority trial with 96 patients following neoadjuvant chemotherapy with quality of oncological resection

(radicality of surgery and number of retrieved lymph nodes) as the primary endpoint. Mean number of resected lymph nodes [41.7±16.1 (LAG) and 43.4±17.3 (OG), p=0.612), number of R0 resections (44/47 (LAG) and 48/49 (OG), p=0.617], 1-year survival (85.5% (LAG) and 90.4% (OG), p=0.701], postoperative complications [16/47 (LAG) and 21/49 (OG), p=0.408], and postoperative QoL [measured with EQ5D, EORTC-QLQ-C30, and EORTC-QLQ-STO22] were not significantly different.

In a regular setting with a diagnosed carcinoma, patients should usually be advised to make their decision for or against a certain treatment option with regards to a combination of highest expected overall survival and simultaneous conservation of long-term QoL. Short-term postoperative complications should only be treated as secondary deciding factors. However, if postoperative complications might impair long-term QoL or even overall survival, they become equally relevant. In general, postoperative complications can have negative effects on QoL or overall survival; however, this is much more the case for gastric cancer, as time to continuation of peroperative chemotherapy can be prolonged and the prognosis therefore worsened.

The STOMACH trial provides evidence that MIG is non-inferior to OG in terms of oncologic quality of resection, which is a necessary requirement for the MEGA trial, as postoperative morbidity and complications can only be decisive factors in the case of oncological non-inferiority for an oncological resection with curative intent.

While both the STOMACH and LOGICA trials suggest that postoperative complications might not be significantly different between both groups, a premature confirmative statement must be avoided as complications have only been investigated as secondary endpoints so far. Consequently, a multicenter RCT comparing total MIG and OG for gastric cancer in terms of postoperative complications is needed to decide whether MIG should be established as the new standard treatment for resectable gastric cancer in Europe.

The MEGA trial has strict quality control measures and will be conducted in line with all relevant guidelines. Therefore, it will provide the highest level of evidence on this very relevant clinical research question.

Ethics and dissemination

The MEGA trial conforms to the Declaration of Helsinki [59]. The Independent Ethics Committee of the Medical Faculty, University of Heidelberg, approved the MEGA trial protocol (registration number S-816/2021). For other trial centers, recruitment will only be initiated after receiving approval from their respective local ethics committees. Study objectives and procedures will be communitated clearly to all qualifying patients and written informed consent will be obtained from those who agree to participate. Results will be presented at scientific meetings and published in international peer-reviewed journals. Summaries will be provided to the funders of the study and results will be published in open-access journals.

Patient and Public Involvement

Patients are involved in the design and conduction of this trial. Priority of the research question, outcome measures, and recruitment methods were discussed with patients during the initial planning stage. Patients have stated an uneventful postoperative course as a very notable feature, and every possible intervention contributing to lower postoperative morbidity was rated to be of great importance.

The chairman of one of Germany's largest patient self-aid groups concerning minimally invasive surgery (SHG Frankfurt Sachsenhausen) will be a member of the data safety and monitoring board as a patient representative. Therefore, this study will continue to take the patient's perspective into account.

Modification of the protocol

The current protocol version (1.2) will be utilized during trial initiation. In case of protocol amendments, these will be submitted to the relevant ethics committees for approval.

Additional file

Additional file 1: SPIRIT checklist.

Abbreviations

ADLs	Activities of daily living
AE	Adverse event
AEG	Adenocarcinoma of esophagogastric junction
ASA	American Society of Anesthesiologists Classification
BIS	Body Image Scale
BMBF	Federal Ministry of Education and Research
CA	Carbohydrate antigen
CEA	Carcinoembryonic antigen
CCI	Comprehensive Complication Index according to Clavien-Dindo classification
eCRF	Electronic Case Report Forms
CRP	C-reactive protein
DALY	Disability-adjusted life years
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
DSMB	Data Safety and Monitoring Board
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Gastric Cancer
EUROQOL EQ-5D-5L	EuroQol Group Questionnaire for Quality of Life with 5 dimensions and 5 levels
FPI	First-patient-in
FU	Follow-up
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intermediate / intensive care unit
IMBI	Institute of Medical Biometry

ITT	Intention-to-treat
LAG	Laparoscopic gastrectomy
LPO	Last-patient-out
MIG	Minimally invasive gastrectomy
OG	Open gastrectomy
POD	Postoperative day
POM	Postoperative month
PRO	Patient-reported outcome
QoL	Quality of life
QoR-15	Quality of Recovery 15 questionnaire
RAG	Robotic-assisted gastrectomy
RCT	Randomized controlled trial
SAE	Serious adverse event
SDGC	Study Center of the German Society of Surgery
SDV	Source data verification
SOP	Standard operating procedure
V	Visit

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Funding statement

The MEGA trial is funded by the Federal Ministry of Education and Research (BMBF), funding number 01KG2029. All trial aspects will be performed independently from the funding source, including trial design and conduction, analysis, and interpretation of data, as well as submission of the report for publication. The funder does not have any influence in study design or collection, management, analysis, and interpretation of data.

Authors' contributions

BPMS, FN and ASF developed the original concept of the trial and applied for funding. FN, ASF, DH, CK, MF, SZ and BPMS developed the design and methodology. BPMS and FN recruited all participating trial centers. FN, ASF, CK, MF, SZ and BPMS performed initial statistical steps to develop the analysis plan. FN, ASF, RK, SVA, ST, PP, AB and HN contributed to drafting the protocol. DH, CK, MF, SZ, BB, FB, CB, IG, SG, PG, CG, JH, KL, LM, SM, DR, FS, DS, PP, TS and BPMS contributed to the revision of the final protocol. All authors have read and approved of the final manuscript.

Responsibilities

Prof. Dr. Müller-Stich, Coordinating Investigator, is involved in every aspect of the trial and has ultimate authority over study design, data collection, interpretation of data, and oversight of the intermittent and final written reports. PD Dr. Nickel, MME, is Deputy Coordinating Investigator. Alexander Studier-Fischer, MD, is Trial Organizer. The Clinical Trial Committee consists of the Coordinating Investigator, the Deputy Coordinating Investigator, and the Trial Organizer, originating from the Division of Minimally Invasive and Robotic-assisted Surgery in the Department of General, Visceral, and Transplantation Surgery at Heidelberg University Hospital. To ensure objectivity, the third-party Institute of Medical Biometry (IMBI) is responsible for data management, statistical planning, and analysis. Project management and monitoring are handled by the SDGC (Study Center of the German Society of Surgery), in Heidelberg. Additionally, a Data Safety and Monitoring Board (DSMB) consisting of independent experts will advise on the continuation, modification, or

termination of the trial and a steering committee will supervise the conduction of the trial and make decisions based on DSMB recommendations.

Data availability

The full protocol, participant-level dataset, and statistical code will be made available by the corresponding authors upon reasonable request.

Conflict of interest statements

The authors declare that they have no conflicts of interest or relevant financial ties to disclose. Felix Nickel reports support for courses and travel from Johnson and Johnson, Medtronic, Intuitive Surgical, Cambridge Medical Robotics, and KARL STORZ as well as consultancy fees from KARL STORZ.

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Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

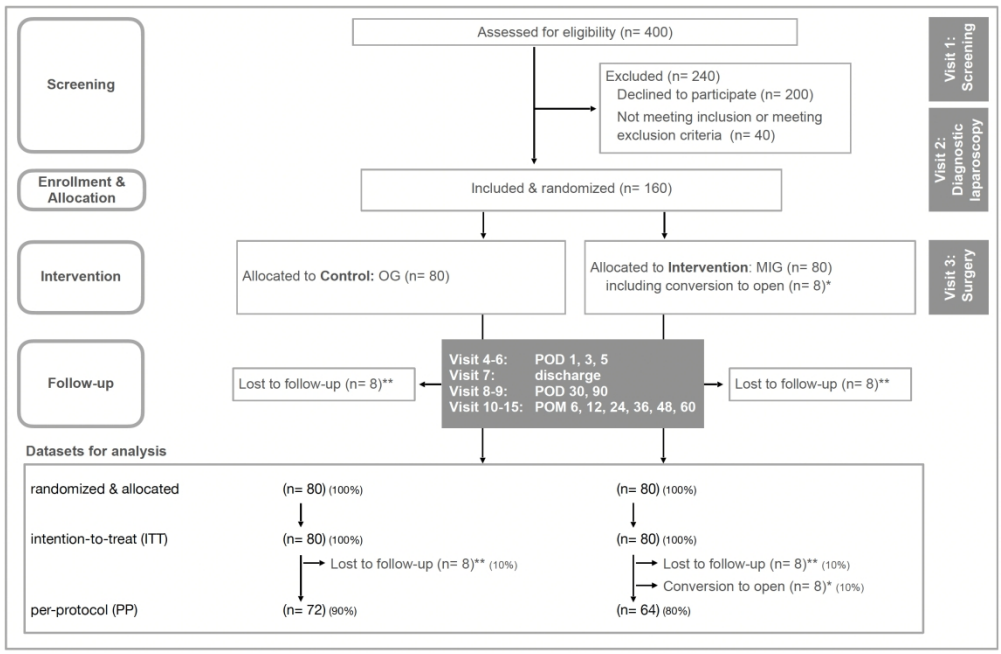

Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

473x306mm (144 x 144 DPI)

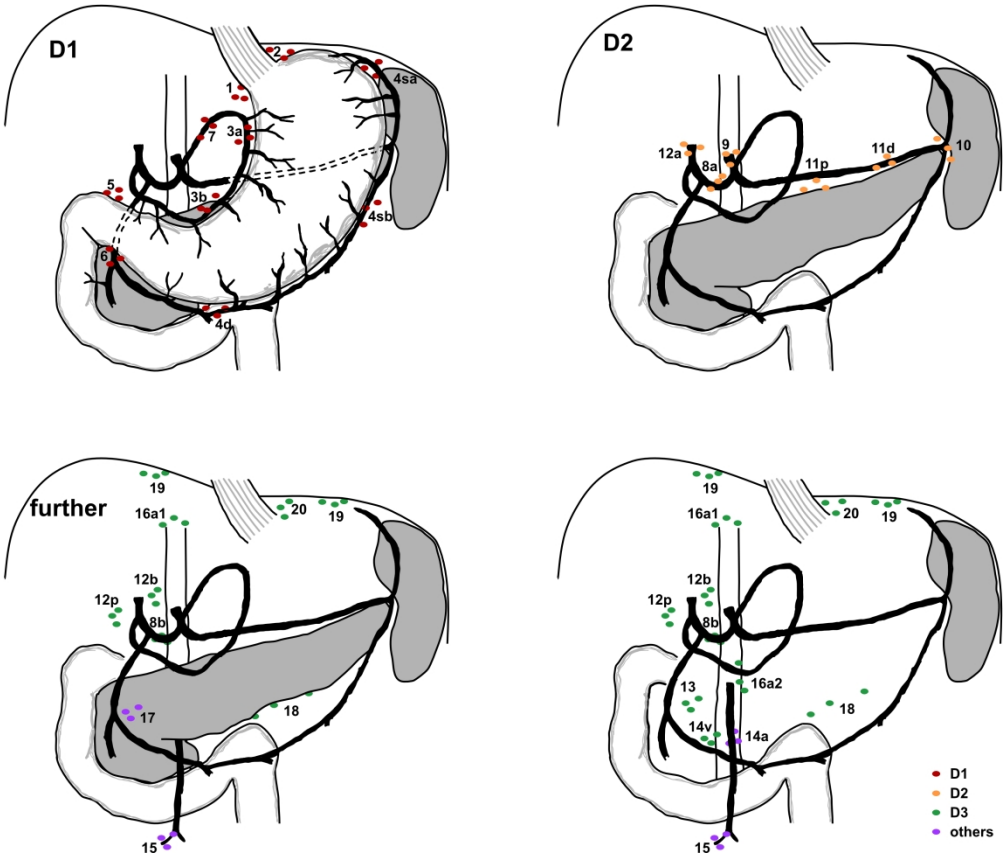

Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

750x636mm (118 x 118 DPI)

Appendices

Appendix 1: ECOG & KARNOFSKY Performance Status

ECOG PERFORMANCE STATUS* **		KARNOFSKY PERFORMANCE STATUS***	
GRADE	Description	GRADE	Description
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do active work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated although death not imminent
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20	Very ill; hospitalization and active supportive care necessary
		10	Moribund
5	Dead	0	Dead

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https://ecog-acrin.org/resources/ecog-performance-status

Appendix 2: Documentation of lymphadenectomy during total gastrectomy

Japanese classification of gastric carcinoma: 3rd English edition Gastric Cancer (2011) 14:101–112			D2 Lymphadenectomy
No.	Location		completed lymphadenectomy = ☐
1*	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.	☐
2*	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	☐
3a*	Left gastric vessel	Lesser curvature LNs along the branches of the left gastric artery	☐
3b*	Right gastric vessel	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery	☐
4sa*	Short gastric vessel	Left greater curvature LNs along the short gastric arteries (perigastric area)	☐
4sb*	Left gastroepiploic	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	☐
4d*	Right gastroepiploic	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	☐
5*	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	☐
6*	Infrapyloric	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein	☐
7*	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	☐
8a**	Common hepatic artery	Anterosuperior LNs along the common hepatic artery	☐
8b	Common hepatic artery	Posterior LNs along the common hepatic artery	☐
9**	Celiac artery	Celiac artery LNs	☐
10**	Splenic hilum	Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch	(☐)
11p**	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	☐
11d**	Distal splenic artery	Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail	☐
12a**	Hepatoduodenal ligament along the hepatic artery	Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	☐
12b	Hepatoduodenal ligament along the bile duct	Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	☐
12p	Hepatoduodenal ligament along behind the portal vein	Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	☐
13	Posterior surface of pancreatic head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla	☐
14v	Superior mesenteric vein	LNs along the superior mesenteric vein	☐
14a	Superior mesenteric artery	-	☐
15	Middle colic vessels	LNs along the middle colic vessels	☐
16a1	Aortic hiatus	Paraaortic LNs in the diaphragmatic aortic hiatus	☐
16a2	Abdominal aorta (celiac trunk to left renal vein)	Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein	☐
16b1	Abdominal aorta (left renal vein to IMA)	Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery	☐
16b2	Abdominal aorta (IMA to aortic bifurcation	Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation	☐
17	Anterior surface of pancreatic head	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath	☐
18	Inferior margin of pancreas	LNs along the inferior border of the pancreatic body	☐
19	Infradiaphragmatic	Infradiaphragmatic LNs predominantly along the subphrenic artery	☐
20	Esophageal hiatus of the diaphragm	Paraesophageal LNs in the diaphragmatic esophageal hiatus	☐
110	Paraesophageal lower thorax	Paraesophageal LNs in the lower thorax	☐
111	Supradiaphragmatic	Supradiaphragmatic LNs separate from the esophagus	☐
112	Posterior mediastinal	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus	☐

*required for D1 lymphadenectomy

**required for D2 lymphadenectomy

	Not required for MEGA trial
	Optional for MEGA trial
	Required for MEGA trial; if not explain why

Appendix 3: Katz Activities of Daily Living

Activities Points (1 or 0)	**Independence** **(1 Point)** NO supervision, direction or personal assistance.	**Dependence** **(0 Points)** WITH supervision, direction, personal assistance or total care.
BATHING Points: _____	Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING Points: _____	Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	Exercises complete self control over urination and defecation.	Is partially or totally incontinent of bowel or bladder.
FEEDING Points: _____	Gets food from plate into mouth without help. Preparation of food may be done by another person.	Needs partial or total help with feeding or requires parenteral feeding.

Appendix 4: Clavien-Dindo-Classification

https://www.assessurgery.com/about_cci-calculator/

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-213.

Grades		**Definition**
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Intervention not under general anesthesia
	IIIb	Intervention under general anesthesia
IV		Life-threatening complication (including CNS complications)* requiring IC/ICU-management
	IVa	single organ dysfunction (including dialysis)
	IVb	multiorgandysfunction
V		Death of a patient

*brain hemorrhage, ischemic stroke, subarrachnoidalbleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	across whole protocol
Protocol version	3	Date and version identifier	22
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 24
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5, 11, 19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11, 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11, 12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16, 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	21, 22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7, 9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24, 25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 1

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)

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Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)

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Abstract

Introduction:

The only curative treatment for most gastric cancer is radical gastrectomy with D2 lymphadenectomy (LAD). Minimally invasive total gastrectomy (MIG) aims to reduce postoperative morbidity, but its use has not yet been widely established in Western

countries. MEGA is the first Western multicenter randomized controlled trial (RCT) to compare postoperative morbidity following MIG versus open total gastrectomy (OG).

Methods and analysis:

This superiority multicenter RCT compares MIG (intervention) to OG (control) for oncological total gastrectomy with D2 or D2+ LAD. Recruitment is expected to last for 2 years. Inclusion criteria comprise age between 18 and 84 years and planned total gastrectomy after initial diagnosis of gastric carcinoma. Exclusion criteria include ECOG performance status > 2 (**Appendix 1**), tumors requiring extended gastrectomy or less than total gastrectomy, previous abdominal surgery or extensive adhesions seriously complicating MIG, other active oncologic disease, advanced stages (T4 or M1), emergency setting, and pregnancy.

The sample size was calculated at 80 participants per group. The primary endpoint is 30-day postoperative morbidity as measured by the Comprehensive Complications Index (CCI). Secondary endpoints include postoperative morbidity and mortality, adherence to a fast-track protocol, and patient-reported quality of life (QoL) scores (QoR-15, EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADLs, and BIS). Oncologic endpoints include rate of R0 resection, lymph node yield, disease-free survival, and overall survival at 60-month follow-up.

Ethics and dissemination:

Ethical approval has been received by the independent Ethics Committee of the Medical Faculty, University of Heidelberg (S-816/2021) and will be received from each responsible ethics committee for each individual participating center prior to recruitment. Results will be published open access.

Trial registration: German Clinical Trials Register DRKS00025765. Registered on December 22nd, 2021.

Keywords: Minimally invasive gastrectomy, total gastrectomy, gastric cancer, Roux-Y reconstruction, linear stapled anastomosis, circular stapled anastomosis, randomized controlled trial, comprehensive complication index, fast-track, enhanced recovery after surgery

Strengths and limitations of this study

- MEGA is the first Western multicenter RCT to specifically compare OG with MIG in terms of postoperative morbidity using the comprehensive complication index (CCI).
- Usage of the CCI as a comprehensive outcome measure allows for objective comparisons with other trials.
- Differentiation between robotic and laparoscopic total gastrectomy will be made in the explorative subgroup analysis only.
- High levels of standardization, intraoperative photo documentation, well-powered group sizes, and risk-based monitoring by the Study Center of the German Society of Surgery (SDGC) will guarantee objective data acquisition, increase patients' adherence to the protocol, and ultimately lead to exceptional data quality.

Introduction

Gastric cancer is the sixth most common tumor disease in the world and causes the second most deaths [1]. In 2018, approximately one million patients worldwide and approximately 15,000 patients in Germany were diagnosed with gastric cancer, of which an average of 76% die from the disease [1]. Gastric cancer causes one of the highest oncologic disease burdens as measured by lost disability-adjusted life years (DALY). This fact highlights the aggressiveness of the disease. Age-adjusted DALY rates per 100,000 reach 241 for men and 146 for women, ranking 4th after liver, lung, and breast cancer [2, 3].

Currently, the only therapy that offers a chance of cure is gastrectomy, with a 5-year survival rate of 20-30% and postoperative morbidity and mortality as high as 63% [4] and 11% [5-10], even at experienced centers [4-18]. Therefore, there is a great need to identify the optimal surgical approach using evidence from multicenter data in order to improve oncologic outcome and to decrease postoperative complications.

The current gold standard is open gastrectomy (OG) with D2 lymphadenectomy (LAD) (**Appendix 2**), but its highly invasive nature leads to potentially high complication rates, especially in elderly and obese patients. These frequent postoperative complications result in higher mortality, lower QoL, a longer hospital stay, and thus a higher burden on the health care system [6, 19]. In other fields of visceral surgery, such as appendectomy, cholecystectomy, obesity surgery, and esophagectomy, minimally invasive surgery has already replaced the open approach as the standard of care [7, 20-22]. Several randomized controlled trials (RCT) have demonstrated reduced postoperative complications following minimally invasive surgery compared to the open approach. This finding is due to the procedure's resulting smaller wounds, reduced operative trauma, lower blood loss, shorter hospital stay, and faster rehabilitation time [22-24].

Postoperative complications, however, are not only important for the immediate postoperative course, which is usually secondary in relevance, but can also affect long-term oncologic outcome [25-27]. In a study of 432 patients with curative gastrectomy and D2 LAD for treatment of gastric cancer, the occurrence of postoperative in-hospital complications was an independent predictor of worse 5-year survival (22% vs. 40%). This can be perceived as an indication that postoperative complications may lead to higher mortality in the long term [28]. Therefore, the trend towards favoring minimally invasive gastrectomy (MIG) for gastric cancer is increasing.

Methods and analysis

Setting

The MEGA trial is a prospective randomized, controlled, non-blinded, two-armed multicenter surgical superiority trial with a confirmatory character. It includes 14 surgical centers in Germany and Switzerland and is coordinated by the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital, in Germany. Recruitment is planned for 2 consecutive years. The study protocol was accepted by the Independent Ethics Committee of the Medical Faculty, University of Heidelberg (registration number S-816/2021) prior to recruitment. The trial was registered at DRKS under the registration number DRKS00025765 on December 22nd, 2021 [29]. No secondary identifying numbers such as a Universal Trial Number have been assigned. Recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist were followed [30].

Patient recruitment

Recruitment is planned to take place at 14 surgical centers in Germany and Switzerland. Certain eligibility criteria have to be met by the participating centers and surgeons in order to eliminate bias from inexperience or learning curves. Therefore, hospitals need to have a case load of ≥20 gastrectomies per year, and every trial surgeon has to provide evidence of at least 20 previously performed surgeries of the respective surgical procedure/s he or she wants to contribute [OG, laparoscopic gastrectomy (LAG) or robotic-assisted gastrectomy (RAG)]. Eligible patients will be screened consecutively to eliminate selection bias and will receive diagnostic staging laparoscopy prior to randomization.

Inclusion criteria:

- Age between 18 and 84 years
- Planned total gastrectomy after first diagnosis of gastric carcinoma
- Ability of patient to understand character and consequences of the trial
- Written informed consent

Exclusion criteria:

- ECOG performance status > 2
- Planned extended gastrectomy or less than total gastrectomy (e.g., adenocarcinoma of the esophagogastric junction (AEG) I and AEG II, or distal gastric tumors of an intestinal subtype)
- Previous gastric surgery or extensive adhesions seriously complicating MIG
- Other active oncologic disease or history of cancer limiting prognosis in comparison to the gastric cancer
- Emergency setting
- Language barriers rendering the patient unable to fill out patient-reported outcome questionnaires

- Participation in another intervention trial that might interfere with the intervention and/or outcome of this trial
- Pregnancy

Exclusion criteria previously or during staging laparoscopy:

- T4
- M1

Neoadjuvant chemotherapy does explicitly not contribute to inclusion or exclusion criteria, but will of course be monitored. Inclusion takes place after the staging laparoscopy, and patients will be randomized to the intervention arm (MIG) or the control arm (OG) (**Figure 1**).

Trial duration and schedule

Recruitment is planned to take 24 months. The duration of the trial for each patient is expected to be 1 month for the primary endpoint and 60 months for the secondary endpoints with long-term follow-up. Consequently, the duration of data collection is expected to be 25 months for the primary endpoint and 84 months for the secondary endpoints [first-patient-in (FPI) to last-patient-out (LPO)]. FPI is planned for September 2022 and Last-patient-in (LPI) is planned for September 2024. LPO is consequently planned for September 2029. Trial analysis will take an additional 6 months. The actual overall duration or recruitment time may differ. Recruitment is planned to be active until both arms contain at least 80 patients in the intention-to-treat (ITT) dataset.

Trial visits

Patients will be monitored intraoperatively, on postoperative days (POD) 1, 3, and 5, and on the day of discharge. Follow-up will be conducted on POD 30, 90, and after

postoperative months (POM) 6, 12, 24, 36, 48, and 60 (**Table 1**). Demographic and baseline clinical data, intraoperative findings, and postoperative results will be recorded. During follow-up, patients will complete established and validated questionnaires. To enhance participant retention and to avoid loss to follow-up, patients will be contacted for the completion of questionnaires and to collect missing data. Informed consent will be obtained and trial data will be collected by trained assessors using electronic case report forms (eCRFs).

Table 1 | Trial visits and overview over documented parameters & outcomes

Activity & Documentation	**Visit 1** (screening)	**Visit 2** (laparosc.)	**Visit 3** (surgery)	**Visit 4-6** (POD 1, 3, 5)	**Visit 7** (dis-charge)	**Visit 8-9** (POD 30, 90)	**Visit 10-15** (POM 6, 12, 24, 36, 48, 60)
inclusion & exclusion criteria	X						
informed consent	X						
medical history & preoperative assessment*	X						
randomization		X					
surgical & anaesthetic documentation**			X				
Postoperative morbidity measured with CCI (primary endpoint)	X		X	X	X	X	
scores / questionnaires							
EUROQOL EQ-5D-5L	X				X	X	X
EORTC QLQ-C30	X				X	X	X
EORTC QLQ-STO22	X				X	X	X
QoR-15				X (V5)			
ADLs	X			X	X	X	X
BIS							X (V13)
biological specimen retrieval							
EDTA blood samples	X						
formalin and paraffin tissue samples			X				
	Visit 1 (screening)	**Visit 2** (laparosc.)	**Visit 3** (surgery)	**Visit 4-6** (POD 1, 3, 5)	**Visit 7** (dis-charge)	**Visit 8-9** (POD 30, 90)	**Visit 10-15** (POM 6, 12, 24, 36, 48, 60)
Short-term clinical data							
Conversion rate			X				
Operation time			X				
Blood loss			X				
Length of stay in the ICU			X		X		
Length of hospital stay					X		
Pain and postoperative analgesic required				X	X		
Laboratory parameters (CRP, leucocytes)				X	X		
Mobilization of the patient				X			
Quality of the patient's recovery				X			
Quality of life	X				X	X	X
Adherence to a fast-track gastrectomy SOP			X	X	X		
Subjective evaluation of anastomoses			X				
First bowl function and mobilization				X			
Wound healing deficits				X	X	X (V8)	
Vegetative function						X	X
Necessity of interventions due to complications				X	X	X	X
Oncologic short-term data							
Number of lymph nodes removed and of tumor-positive			X				

	lymph nodes							
	Number of R0 resections			X				
	Development of tumor markers			X				
	Tumor histpathology			X				
Long-term clinical data (5-year follow-up)								
	Changes of body weight					X	X	X
	Quality of life	X				X	X	X
	Incidence of incisional hernias						X	X
	Incidence of reoperations				X	X	X	X
	Incidence of stenosis						X	X
	Cosmetic results and scar satisfaction							X (V13)
Oncologic long-term data (5-year follow-up)								
	Oncologic treatment (adjuvant and consecutive therapy)						X	X
	Disease-free survival; DFS; recurrence free survival; RFS						X (V9)	X
	Local recurrence; LR						X (V9)	X
	Relapse-free survival; RFS						X (V9)	X
	Progression-free survival; PFS						X (V9)	X
	Time to progression; TTP						X (V9)	X
	Overall survival; OS						X (V9)	X

* Includes body mass index, ASA status, preoperative oncological status, prior surgical treatment, drug use and comorbidities. ** Includes surgical documentation (surgeons, procedures, complications, drains) & anesthesiology documentation. *** Includes dysphagia, reflux, and dumping syndromes. **** Includes entity, TNM, grading, and resection status. ASA American Society of Anesthesiologists classification, POD postoperative day, POM postoperative month, QoL quality of life, EUROQOL EQ-5D-5L EuroQol Group Questionnaire for Quality of Life with 5 dimensions and 5 levels, EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EORTC QLQ-STO22 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Gastric Cancer, QoR-15 Quality of Recovery 15, ADLs activities of daily living (**Appendix 3**), BIS Body Image Scale, ITT intention-to-treat, VAS visual analog scale of pain, need for ICU intermediate / intensive care unit, CCI Comprehensive Complication Index for complications & related interventions according to the Clavien-Dindo classification (**Appendix 4**).

Primary endpoint

The primary endpoint will be postoperative morbidity measured using the Comprehensive Complication Index (CCI) until postoperative day 30 [31]. Usage of this index will enable a comparison of the severity and individual burden of postoperative complications with results from other trials [32, 33]. Postoperative morbidity is defined as any deviation from the normal postoperative course according to the Clavien-Dindo classification [34]. This includes anastomotic insufficiency or loss of anastomotic integrity verified by either CT scan with detection of contrast agent external to the anastomosis, endoscopy, or the detection of methylene blue in a drain following oral intake.

Secondary endpoints

Secondary endpoints can be separated into short-term clinical and oncological endpoints as well as long-term clinical and oncological endpoints (at 5-year follow-up, as measured from the date of surgery) and can be found in **Table 1**.

Standardized therapy and trial interventions

Control: Total OG with D2/D2+ LAD**.**

Intervention: Total MIG with D2/D2+ LAD either as LAG or RAG. A mini-laparotomy or a Pfannenstiel incision (≤8 cm incision in both the skin and fascia) may be performed for specimen removal.

Modified cardia-preserving total gastrectomy (preservation of gastroesophageal junction) can also be accepted, but only if the short gastric vessels are dissected as well, and if LAD is the same as for total gastrectomy. Besides the open or minimally-invasive approach, the remaining treatment is identical in both groups. Any other form of gastrectomy, explicitly conventional subtotal gastrectomy (preserved short

gastric vessels and limited LAD of station 2 and 4sa), extended gastrectomy, and distal gastrectomy with Billroth I or II reconstruction are not allowed. Reconstruction can be of any form including Roux-Y reconstruction, interposition, or pouch reconstruction. Any other step of the procedure such as antibiotic prophylaxis, placement of abdominal drains, and closure of the abdominal wall can be performed according to in-house standards. D2 LAD is defined according to the Japanese classification [35], with stations 1, 2, 3a, 3b, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a obligatory for the MEGA trial (**Figure 2**). Station 10 is optional. Incomplete LAD is not allowed and has to be documented as a protocol deviation.

Removal of further stations (8b, 12b, 12p, 13, 14v, 14a, 15, 16a1, 16a2, 16b1, 16b2, 17, 18, 19, 20, 110, 111, and 112) is allowed when deemed appropriate, e.g., in case of assumed tumor invasion, and has to be documented as D2+.

Postoperative management

Postoperative management should be performed in a fast-track approach with short durations until patient mobilization, drainage removal, and first oralization of food. The patient should be extubated immediately after surgery and transferred to a normal ward, if possible. Further specifications for the postoperative course will be outlined in the provided standard operating procedure (SOP) for fast-track gastrectomy. The last in-hospital trial visit takes place on the day of discharge. Subsequent trial visits will be conducted via telephone. These will be questionnaire-based and focus on CCI (until POD 90), quality of life, and oncologic outcome.

Randomization and blinding

In order to ensure equal distribution of patient characteristics between both trial arms, randomization will be performed using a web-based randomization tool

(www.randomizer.at). Randomization will take place following diagnostic laparoscopy (Visit 2). The allocation pattern is masked, block-randomized with variable block length, and stratified across centers. Due to the pragmatic character of the trial, blinding of the surgeon is not feasible.

Quality assurance and quality management

Clinical data monitoring

Clinical monitoring will be performed by independent monitors at the Study Center of the German Society of Surgery (SDGC). The monitoring strategy will comprise a combination of centralized and onsite monitoring and will be described in a trial specific monitoring plan. To confirm site selection, pre-study visits will be performed. On-site monitoring will focus on patient informed consent, safety, and surgical procedures as well as the correct recording and documentation of the primary and secondary endpoints by source data verification (SDV).

Surgical quality control

Several steps are necessary to ensure and evaluate surgical quality:

1) Trial surgeons must have performed 20 surgeries in the respective approach (OG, LAG, or RAG), depending on the trial arm they will contribute to.
2) Each trial surgeon must provide photographic or video documentation of a former procedure.
3) Each trial surgeon has to provide photographic or video documentation of the trial procedures, which will be assessed by an expert. This photographic or video documentation is defined as follows:
    a. lymph node station 7 (left gastric artery) after dissection
    b. lymph node station 8a (common hepatic artery) after dissection

c. lymph node station 9 (celiac artery) after dissection

d. lymph node station 10 (splenic hilum) after dissection

e. lymph node station 11p (proximal splenic artery) after dissection

f. lymph node station 11d (distal splenic artery) after dissection

g. lymph node station 12a (hepatoduodenal ligament along the hepatic artery) after dissection

h. duodenal stump

i. all anastomoses

j. incision for specimen retrieval in MIG

Assessment of safety

Since the primary endpoint is postoperative complications as measured by the CCI, adverse (AE) and serious adverse events (SAE) are already captured and no additional safety analysis will be performed (**Table 2**).

Table 2: Grading of Adverse Events

Clavien-Dindo	Adverse event (AE)	Serious adverse event (SAE)	Minor complication	Major complication
Grade I complication	AE		Minor complication	
Grade II complication				
Grade III complication				Major complication
Grade IV complication		SAE		
Grade V complication				

Data management

The Institute of Medical Biometry (IMBI) is responsible for data management within this trial. An eCRF will be used for data collection. To assure safe and secure data use and storage, data transmission is encrypted with secure socket layer (SSL) technology. Only authorized users are able to enter or edit data, and access is further restricted to data of the patients in that user's respective center only. All changes to data are logged with a computerized timestamp in an audit trail. All data will be pseudonymized. To guarantee high data quality, data validation rules will be defined in a data validation plan. Completeness, validity, and plausibility of data will be checked at the time of data entry (edit-checks) and using validating programs, which will generate queries. If no further corrections are to be made in the database, eCRF data will be locked. Data will finally be downloaded and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the IMBI that guarantee efficient conduct in compliance with Good Clinical Practice (GCP). At the end of the study, the data will be transformed into different data formats (e.g., csv-files) for archiving and to ensure that it can be re-used.

Statistical methods

Sample size

The sample size calculation is based on the primary endpoint "postoperative morbidity as measured with the CCI until POD 30." A decrease of the CCI by 10 points between OG and MIG is considered relevant by patients and clinicians, and a conservative standard deviation of 20 is assumed based on existing literature for

upper GI surgery [36], leading to an effect size of d=0.5. Based on a t-test with a two-sided significance level of α=0.05, a sample size of n=128 patients (64 per group) has to be recruited to achieve a power of 80%. The primary endpoint will be analyzed with a linear mixed regression model, which leads to equal or even increased power when compared to a two-sided t-test. To compensate for drop-outs and patients lost to follow-up, a further 20% of patients will be randomized, leading to a total sample size of n=160 (80 per group; 80 x 0,8 = 64.8). The number of patients to be screened (n=400 to be assessed for eligibility; 400 x 0.5 x 0.8 = 160) was calculated with an assumed 50% participation rate and an exclusion rate of 20%.

Randomized & allocated (n = 160; 80 per group)

Intention-to-treat dataset (n = 160; 80 per group)

Per-protocol dataset (n = 136; 72 and 64)

Statistical analysis

For the examination of the primary endpoint "postoperative morbidity measured with the CCI until POD 30," the hypotheses to be assessed in the primary analysis are as follows: H_0: $\mu_1 = \mu_2$ vs H_1: $\mu_1 \neq \mu_2$, where μ_1 and μ_2 denote the mean CCI in the control and intervention groups, respectively. The significance level is set to a two-sided α=0.05. Therefore, the primary endpoint will be examined using a linear mixed model adjusting for the variables age and treatment group, as well as the surgical center as a random effect (due to the stratified randomization and relatively large number of centers in relation to the sample size, inclusion of center as a random effect is recommended). Details of the primary model (e.g., handling of missing values, sensitivity analyses) will be fully described in the statistical analysis plan.

The number of patients included in the primary analysis is determined as the full analysis set. Patients will be analyzed in the group they were randomized to

(converted patients remain in their group). This reflects an analysis according to the intention to treat (ITT) principle. Specific events (e.g., death) that can occur after randomization will be handled within the primary endpoint definition, reflecting a composite strategy [according to the ICH E9 (R1) addendum]. Other post randomization events will not be considered. This choice reflects our treatment policy approach.

In general, for the full analysis set, all baseline values and secondary outcomes will be evaluated descriptively, with p-values reported alongside 95% confidence intervals for the corresponding effects. Furthermore, secondary endpoints will be evaluated descriptively, using appropriate regression models. Time-to-event endpoints will be evaluated by methods of survival analysis including Kaplan-Meier methods and Cox proportional hazards models. In addition, subgroup analyses (including age, gender, tumor stage, tumor grade, histological tumor type, linear vs. circular stapler for proximal anastomosis, linear vs. hand-sewn for distal anastomosis, type of retrieval incision, and intraoperative conversion) will be carried out. A detailed and comprehensive statistical analysis plan will be written shortly after the first patient is recruited. All analyses will be performed using SAS version 9.4 or higher.

Discussion

We performed a systematic literature search prior to planning this trial and identified 974 publications. Of those, 17 RCTs comparing LAG with OG [7, 37-55] and two RCTs comparing RAG with OG [56, 57] were found to be relevant. The studies showed comparable oncologic and short-term postoperative outcomes for MIG and OG. However, 16 of the 19 studies were conducted in China, Korea, and Japan [7,

38-50, 56, 57]. These countries have a significantly higher incidence of gastric cancer, which consequently leads to significantly higher surgical volume and expertise among the participating centers [58]. In addition, the body constitution of Asian patients is often different from that of Western patients, which limits the direct transferability of study results. Also, the incidence of gastric cancer is lower in Western populations and advanced disease stages are more frequently detected, because screening is less common. Therefore, it is unclear whether these results would be reproducible in a Western population.

Currently, there have only been three non-Asian RCTs directly comparing LAG and OG. The first RCT, by Huscher et al., focused exclusively on distal gastrectomy, did not define any specific primary or secondary endpoints, and included a total of 59 patients [37]. Due to the missing differentiation between primary and secondary endpoints, the trial can be perceived as methodically limited and was most likely underpowered. However, no significant difference was found in perioperative outcome, oncologic outcome, or mortality [morbidity rates: 26.7% (LAG) and 27.6% (OG), lymph nodes harvested: 30.0 ± 14.9 (LAG) and 33.4 ± 17.4 (OG), operative mortality rates: 3.3% (LG) and 6.7% (OG), 5-year survival rate: 54.8% (LAG) and 55.7% (OG)].

The only two currently existing relevant Western multicenter RCTs comparing open versus minimally invasive oncologic total gastrectomy are the LOGICA trial [52, 53] and the STOMACH trial [51, 54, 55], which were both puplished in 2021.

The LOGICA trial is a non-blinded, multicenter superiority trial with 227 patients with postoperative hospital stay as the primary endpoint. The study identified significant differences regarding blood loss [150 ml (LAG) and 300 ml (OG), $p<0.001$] and operating time [216 min (LAG) and 182 min (OG), $p<0.001$], but no significant differences in hospital stay ($p=0.34$), postoperative complications [44% (LAG) and

42% (OG), p=0.91], in-hospital mortality [4% (LAG) and 7% (OG), p=0.40], R0 resections [95% (LAG) and 95% (OG), p=1.00], median lymph node yield [29 (LAG) and 29 (OG), p=0.49], 1-year overall survival [76% (LAG) and 78% (OG), p=0.74], and health-related quality of life [+1.5 (LAG) and +3.6 (OG) on a 1-100 scale].

The STOMACH trial is an observer-blinded, multicenter, non-inferiority trial with 96 patients following neoadjuvant chemotherapy with quality of oncological resection (radicality of surgery and number of retrieved lymph nodes) as the primary endpoint. Mean number of resected lymph nodes [41.7±16.1 (LAG) and 43.4±17.3 (OG), p=0.612), number of R0 resections (44/47 (LAG) and 48/49 (OG), p=0.617], 1-year survival (85.5% (LAG) and 90.4% (OG), p=0.701], postoperative complications [16/47 (LAG) and 21/49 (OG), p=0.408], and postoperative QoL [measured with EQ5D, EORTC-QLQ-C30, and EORTC-QLQ-STO22] were not significantly different.

In a regular setting with a diagnosed carcinoma, patients should usually be advised to make their decision for or against a certain treatment option with regards to a combination of highest expected overall survival and simultaneous conservation of long-term QoL. Short-term postoperative complications should only be treated as secondary deciding factors. However, if postoperative complications might impair long-term QoL or even overall survival, they become equally relevant. In general, postoperative complications can have negative effects on QoL or overall survival; however, this is much more the case for gastric cancer, as time to continuation of peroperative chemotherapy can be prolonged and the prognosis therefore worsened.

The STOMACH trial provides evidence that MIG is non-inferior to OG in terms of oncologic quality of resection, which is a necessary requirement for the MEGA trial, as postoperative morbidity and complications can only be decisive factors in the case of oncological non-inferiority for an oncological resection with curative intent.

While both the STOMACH and LOGICA trials suggest that postoperative complications might not be significantly different between both groups, a premature confirmative statement must be avoided as complications have only been investigated as secondary endpoints so far. Consequently, a multicenter RCT comparing total MIG and OG for gastric cancer in terms of postoperative complications is needed to decide whether MIG should be established as the new standard treatment for resectable gastric cancer in Europe.

The MEGA trial has strict quality control measures and will be conducted in line with all relevant guidelines. Therefore, it will provide the highest level of evidence on this very relevant clinical research question.

Ethics and dissemination

The MEGA trial conforms to the Declaration of Helsinki [59]. The Independent Ethics Committee of the Medical Faculty, University of Heidelberg, approved the MEGA trial protocol (registration number S-816/2021). For other trial centers, recruitment will only be initiated after receiving approval from their respective local ethics committees. Study objectives and procedures will be communitated clearly to all qualifying patients and written informed consent will be obtained from those who agree to participate. Results will be presented at scientific meetings and published in international peer-reviewed journals. Summaries will be provided to the funders of the study and results will be published in open-access journals.

Patient and Public Involvement

Patients are involved in the design and conduction of this trial. Priority of the research question, outcome measures, and recruitment methods were discussed with patients during the initial planning stage. Patients have stated an uneventful postoperative

course as a very notable feature, and every possible intervention contributing to lower postoperative morbidity was rated to be of great importance.

The chairman of one of Germany's largest patient self-aid groups concerning minimally invasive surgery (SHG Frankfurt Sachsenhausen) will be a member of the data safety and monitoring board as a patient representative. Therefore, this study will continue to take the patient's perspective into account.

Modification of the protocol

The current protocol version (1.2) will be utilized during trial initiation. In case of protocol amendments, these will be submitted to the relevant ethics committees for approval.

Additional file

Additional file 1: SPIRIT checklist.

Abbreviations

ADLs	Activities of daily living
AE	Adverse event
AEG	Adenocarcinoma of esophagogastric junction
ASA	American Society of Anesthesiologists Classification
BIS	Body Image Scale
BMBF	Federal Ministry of Education and Research
CA	Carbohydrate antigen
CEA	Carcinoembryonic antigen
CCI	Comprehensive Complication Index according to Clavien-Dindo classification
eCRF	Electronic Case Report Forms
CRP	C-reactive protein
DALY	Disability-adjusted life years
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
DSMB	Data Safety and Monitoring Board
EORTC QLQ-	European Organisation for Research and Treatment of Cancer Quality of Life

C30	Questionnaire Core 30
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Gastric Cancer
EUROQOL EQ-5D-5L	EuroQol Group Questionnaire for Quality of Life with 5 dimensions and 5 levels
FPI	First-patient-in
FU	Follow-up
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intermediate / intensive care unit
IMBI	Institute of Medical Biometry
ITT	Intention-to-treat
LAG	Laparoscopic gastrectomy
LPI	Last-patient-in
LPO	Last-patient-out
MIG	Minimally invasive gastrectomy
OG	Open gastrectomy
POD	Postoperative day
POM	Postoperative month
PRO	Patient-reported outcome
QoL	Quality of life
QoR-15	Quality of Recovery 15 questionnaire
RAG	Robotic-assisted gastrectomy
RCT	Randomized controlled trial
SAE	Serious adverse event
SDGC	Study Center of the German Society of Surgery
SDV	Source data verification
SOP	Standard operating procedure
V	Visit

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The MEGA trial is funded by the Federal Ministry of Education and Research (BMBF), funding number 01KG2029. All trial aspects will be performed independently from the funding source, including trial design and conduction, analysis, and interpretation of data, as well as submission of the report for publication. The funder does not have any influence in study design or collection, management, analysis, and interpretation of data.

Authors' contributions

BPMS, FN and ASF developed the original concept of the trial and applied for funding. FN, ASF, DH, CK, MF, SZ and BPMS developed the design and methodology. BPMS and FN recruited all participating trial centers. FN, ASF, CK, MF, SZ and BPMS performed initial statistical steps to develop the analysis plan. FN, ASF, RK, SVA, ST, PP, AB and HN contributed to drafting the protocol. DH, CK, MF, SZ, BB, FB, CB, IG, SG, PG, CG, JH, KL, LM, SM, DR, FS, DS, PP, TS and BPMS contributed to the revision of the final protocol. All authors have read and approved of the final manuscript.

Responsibilities

Prof. Dr. Müller-Stich, Coordinating Investigator, is involved in every aspect of the trial and has ultimate authority over study design, data collection, interpretation of data, and oversight of the intermittent and final written reports. PD Dr. Nickel, MME, is Deputy Coordinating Investigator. Alexander Studier-Fischer, MD, is Trial Organizer. The Clinical Trial Committee consists of the Coordinating Investigator, the

Deputy Coordinating Investigator, and the Trial Organizer, originating from the Division of Minimally Invasive and Robotic-assisted Surgery in the Department of General, Visceral, and Transplantation Surgery at Heidelberg University Hospital. To ensure objectivity, the third-party Institute of Medical Biometry (IMBI) is responsible for data management, statistical planning, and analysis. Project management and monitoring are handled by the SDGC (Study Center of the German Society of Surgery), in Heidelberg. Additionally, a Data Safety and Monitoring Board (DSMB) consisting of independent experts will advise on the continuation, modification, or termination of the trial and a steering committee will supervise the conduction of the trial and make decisions based on DSMB recommendations.

Data availability

The full protocol, results and statistical code will be made available by the corresponding authors upon reasonable request.

Conflict of interest statements

The authors declare that they have no conflicts of interest or relevant financial ties to disclose. Felix Nickel reports support for courses and travel from Johnson and Johnson, Medtronic, Intuitive Surgical, Cambridge Medical Robotics, and KARL STORZ as well as consultancy fees from KARL STORZ.

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Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

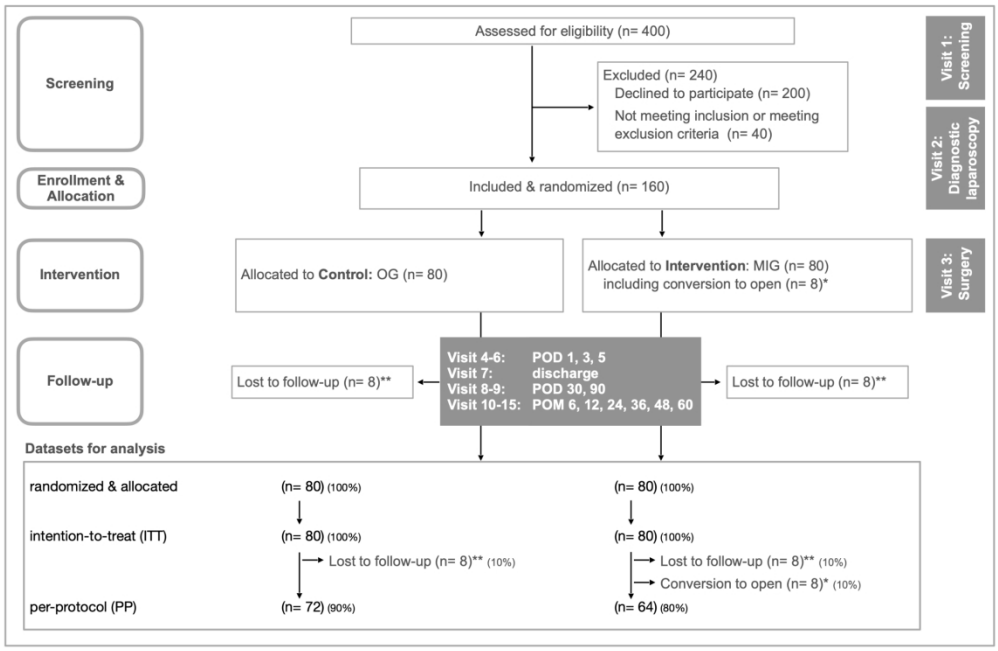

Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

200x129mm (300 x 300 DPI)

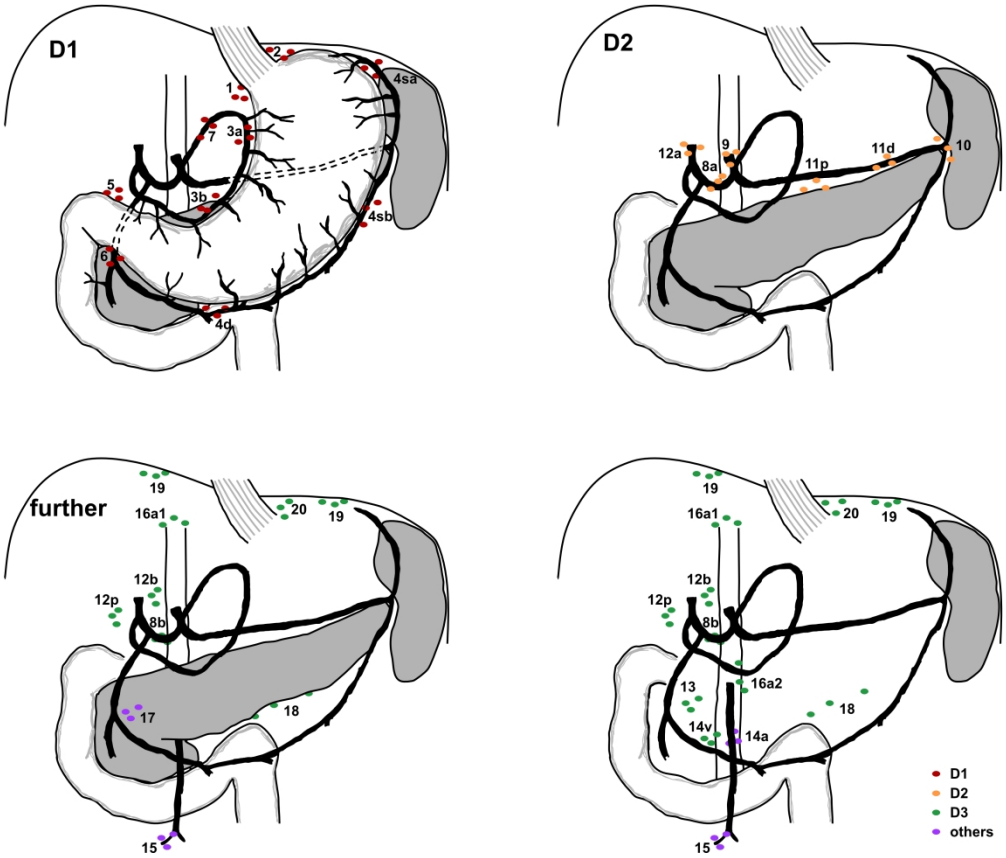

Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

295x250mm (300 x 300 DPI)

Appendices

Appendix 1: ECOG & KARNOFSKY Performance Status

ECOG PERFORMANCE STATUS* **		KARNOFSKY PERFORMANCE STATUS***	
GRADE	Description	GRADE	Description
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do active work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated although death not imminent
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20	Very ill; hospitalization and active supportive care necessary
		10	Moribund
5	Dead	0	Dead

*Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.
**Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.
***Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
https://ecog-acrin.org/resources/ecog-performance-status

Appendix 2: Documentation of lymphadenectomy during total gastrectomy

Japanese classification of gastric carcinoma: 3rd English edition Gastric Cancer (2011) 14:101–112			D2 Lymphadenectomy
No.	Location		completed lymphadenectomy = □
1*	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.	□
2*	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	□
3a*	Left gastric vessel	Lesser curvature LNs along the branches of the left gastric artery	□
3b*	Right gastric vessel	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery	□
4sa*	Short gastric vessel	Left greater curvature LNs along the short gastric arteries (perigastric area)	□
4sb*	Left gastroepiploic	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	□
4d*	Right gastroepiploic	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	□
5*	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	□
6*	Infrapyloric	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein	□
7*	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	□
8a**	Common hepatic artery	Anterosuperior LNs along the common hepatic artery	□
8b	Common hepatic artery	Posterior LNs along the common hepatic artery	□
9**	Celiac artery	Celiac artery LNs	□
10**	Splenic hilum	Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch	(□)
11p**	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	□
11d**	Distal splenic artery	Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail	□
12a**	Hepatoduodenal ligament along the hepatic artery	Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	□
12b	Hepatoduodenal ligament along the bile duct	Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	□
12p	Hepatoduodenal ligament along behind the portal vein	Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	□
13	Posterior surface of pancreatic head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla	□
14v	Superior mesenteric vein	LNs along the superior mesenteric vein	□
14a	Superior mesenteric artery	-	□
15	Middle colic vessels	LNs along the middle colic vessels	□
16a1	Aortic hiatus	Paraaortic LNs in the diaphragmatic aortic hiatus	□
16a2	Abdominal aorta (celiac trunk to left renal vein)	Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein	□
16b1	Abdominal aorta (left renal vein to IMA)	Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery	□
16b2	Abdominal aorta (IMA to aortic bifurcation	Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation	□
17	Anterior surface of pancreatic head	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath	□
18	Inferior margin of pancreas	LNs along the inferior border of the pancreatic body	□
19	Infradiaphragmatic	Infradiaphragmatic LNs predominantly along the subphrenic artery	□
20	Esophageal hiatus of the diaphragm	Paraesophageal LNs in the diaphragmatic esophageal hiatus	□
110	Paraesophageal lower thorax	Paraesophageal LNs in the lower thorax	□
111	Supradiaphragmatic	Supradiaphragmatic LNs separate from the esophagus	□
112	Posterior mediastinal	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus	□

*required for D1 lymphadenectomy
**required for D2 lymphadenectomy

	Not required for MEGA trial
	Optional for MEGA trial
	Required for MEGA trial; if not explain why

Appendix 3: Katz Activities of Daily Living

Activities Points (1 or 0)	**Independence** **(1 Point)** NO supervision, direction or personal assistance.	**Dependence** **(0 Points)** WITH supervision, direction, personal assistance or total care.
BATHING Points: _____	Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING Points: _____	Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	Exercises complete self control over urination and defecation.	Is partially or totally incontinent of bowel or bladder.
FEEDING Points: _____	Gets food from plate into mouth without help. Preparation of food may be done by another person.	Needs partial or total help with feeding or requires parenteral feeding.

Appendix 4: Clavien-Dindo-Classification

https://www.assessurgery.com/about_cci-calculator/

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-213.

Grades		**Definition**
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Intervention not under general anesthesia
	IIIb	Intervention under general anesthesia
IV		Life-threatening complication (including CNS complications)* requiring IC/ICU-management
	IVa	single organ dysfunction (including dialysis)
	IVb	multiorgandysfunction
V		Death of a patient

*brain hemorrhage, ischemic stroke, subarrachnoidalbleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	across whole protocol
Protocol version	3	Date and version identifier	22
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 24
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5, 11, 19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11, 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11, 12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16, 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	21, 22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7, 9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24, 25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 1

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	SURGERY, ONCOLOGY, Gastrointestinal tumours < ONCOLOGY

Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)

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Abstract

Introduction:

The only curative treatment for most gastric cancer is radical gastrectomy with D2 lymphadenectomy (LAD). Minimally invasive total gastrectomy (MIG) aims to reduce postoperative morbidity, but its use has not yet been widely established in Western countries. MEGA is the first Western multicenter randomized controlled trial (RCT) to compare postoperative morbidity following MIG versus open total gastrectomy (OG).

Methods and analysis:

This superiority multicenter RCT compares MIG (intervention) to OG (control) for oncological total gastrectomy with D2 or D2+ LAD. Recruitment is expected to last for 2 years. Inclusion criteria comprise age between 18 and 84 years and planned total gastrectomy after initial diagnosis of gastric carcinoma. Exclusion criteria include ECOG performance status > 2 (**Appendix 1**), tumors requiring extended gastrectomy or less than total gastrectomy, previous abdominal surgery or extensive adhesions seriously complicating MIG, other active oncologic disease, advanced stages (T4 or M1), emergency setting, and pregnancy.

The sample size was calculated at 80 participants per group. The primary endpoint is 30-day postoperative morbidity as measured by the Comprehensive Complications Index (CCI). Secondary endpoints include postoperative morbidity and mortality, adherence to a fast-track protocol, and patient-reported quality of life (QoL) scores (QoR-15, EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADLs, and BIS). Oncologic endpoints include rate of R0 resection, lymph node yield, disease-free survival, and overall survival at 60-month follow-up.

Ethics and dissemination:

Ethical approval has been received by the independent Ethics Committee of the Medical Faculty, University of Heidelberg (S-816/2021) and will be received from each responsible ethics committee for each individual participating center prior to recruitment. Results will be published open access.

Trial registration: German Clinical Trials Register DRKS00025765. Registered on December 22nd, 2021.

Keywords: Minimally invasive gastrectomy, total gastrectomy, gastric cancer, Roux-Y reconstruction, linear stapled anastomosis, circular stapled anastomosis, randomized controlled trial, comprehensive complication index, fast-track, enhanced recovery after surgery

Strengths and limitations of this study

- MEGA is the first Western multicenter RCT to specifically compare OG with MIG in terms of postoperative morbidity using the comprehensive complication index (CCI).
- Usage of the CCI as a comprehensive outcome measure allows for objective comparisons with other trials.
- Differentiation between robotic and laparoscopic total gastrectomy will be made in the explorative subgroup analysis only.
- High levels of standardization, intraoperative photo documentation, well-powered group sizes, and risk-based monitoring by the Study Center of the German Society of Surgery (SDGC) will guarantee objective data acquisition, increase patients' adherence to the protocol, and ultimately lead to exceptional data quality.

Introduction

Gastric cancer is the sixth most common tumor disease in the world and causes the second most deaths [1]. In 2018, approximately one million patients worldwide and approximately 15,000 patients in Germany were diagnosed with gastric cancer, of which an average of 76% die from the disease [1]. Gastric cancer causes one of the highest oncologic disease burdens as measured by lost disability-adjusted life years (DALY). This fact highlights the aggressiveness of the disease. Age-adjusted DALY rates per 100,000 reach 241 for men and 146 for women, ranking 4th after liver, lung, and breast cancer [2, 3].

Currently, the only therapy that offers a chance of cure is gastrectomy, with a 5-year survival rate of 20-30% and postoperative morbidity and mortality as high as 63% [4] and 11% [5-10], even at experienced centers [4-18]. Therefore, there is a great need to identify the optimal surgical approach using evidence from multicenter data in order to improve oncologic outcome and to decrease postoperative complications.

The current gold standard is open gastrectomy (OG) with D2 lymphadenectomy (LAD) (**Appendix 2**), but its highly invasive nature leads to potentially high complication rates, especially in elderly and obese patients. These frequent postoperative complications result in higher mortality, lower QoL, a longer hospital stay, and thus a higher burden on the health care system [6, 19]. In other fields of visceral surgery, such as appendectomy, cholecystectomy, obesity surgery, and esophagectomy, minimally invasive surgery has already replaced the open approach as the standard of care [7, 20-22]. Several randomized controlled trials (RCT) have demonstrated reduced postoperative complications following minimally invasive surgery compared to the open approach. This finding is due to the procedure's resulting smaller wounds, reduced operative trauma, lower blood loss, shorter hospital stay, and faster rehabilitation time [22-24].

Postoperative complications, however, are not only important for the immediate postoperative course, which is usually secondary in relevance, but can also affect long-term oncologic outcome [25-27]. In a study of 432 patients with curative gastrectomy and D2 LAD for treatment of gastric cancer, the occurrence of postoperative in-hospital complications was an independent predictor of worse 5-year survival (22% vs. 40%). This can be perceived as an indication that postoperative complications may lead to higher mortality in the long term [28]. Therefore, the trend towards favoring minimally invasive gastrectomy (MIG) for gastric cancer is increasing.

Methods and analysis

Setting

The MEGA trial is a prospective randomized, controlled, non-blinded, two-armed multicenter surgical superiority trial with a confirmatory character. It includes 14 surgical centers in Germany and Switzerland and is coordinated by the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital, in Germany. Recruitment is planned for 2 consecutive years. The study protocol was accepted by the Independent Ethics Committee of the Medical Faculty, University of Heidelberg (registration number S-816/2021) prior to recruitment. The trial was registered at DRKS under the registration number DRKS00025765 on December 22nd, 2021 [29]. No secondary identifying numbers such as a Universal Trial Number have been assigned. Recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist were followed [30].

Patient recruitment

Recruitment is planned to take place at 14 surgical centers in Germany and Switzerland. Certain eligibility criteria have to be met by the participating centers and

surgeons in order to eliminate bias from inexperience or learning curves. Therefore, hospitals need to have a case load of ≥20 gastrectomies per year, and every trial surgeon has to provide evidence of at least 20 previously performed surgeries of the respective surgical procedure/s he or she wants to contribute [OG, laparoscopic gastrectomy (LAG) or robotic-assisted gastrectomy (RAG)]. Eligible patients will be screened consecutively to eliminate selection bias and will receive diagnostic staging laparoscopy prior to randomization.

Inclusion criteria:

- Age between 18 and 84 years
- Planned total gastrectomy after first diagnosis of gastric carcinoma
- Ability of patient to understand character and consequences of the trial
- Written informed consent

Exclusion criteria:

- ECOG performance status > 2
- Planned extended gastrectomy or less than total gastrectomy (e.g., adenocarcinoma of the esophagogastric junction (AEG) I and AEG II, or distal gastric tumors of an intestinal subtype)
- Previous gastric surgery or extensive adhesions seriously complicating MIG
- Other active oncologic disease or history of cancer limiting prognosis in comparison to the gastric cancer
- Emergency setting
- Language barriers rendering the patient unable to fill out patient-reported outcome questionnaires
- Participation in another intervention trial that might interfere with the intervention and/or outcome of this trial
- Pregnancy

Exclusion criteria previously or during staging laparoscopy:

- T4
- M1

Neoadjuvant chemotherapy does explicitly not contribute to inclusion or exclusion criteria, but will of course be monitored. Inclusion takes place after the staging laparoscopy, and patients will be randomized to the intervention arm (MIG) or the control arm (OG) (**Figure 1**).

Trial duration and schedule

Recruitment is planned to take 24 months. The duration of the trial for each patient is expected to be 1 month for the primary endpoint and 60 months for the secondary endpoints with long-term follow-up. Consequently, the duration of data collection is expected to be 25 months for the primary endpoint and 84 months for the secondary endpoints [first-patient-in (FPI) to last-patient-out (LPO)]. FPI is planned for September 2022 and Last-patient-in (LPI) is planned for September 2024. LPO is consequently planned for September 2029. Trial analysis will take an additional 6 months. The actual overall duration or recruitment time may differ. Recruitment is planned to be active until both arms contain at least 80 patients in the intention-to-treat (ITT) dataset.

Trial visits

Patients will be monitored intraoperatively, on postoperative days (POD) 1, 3, and 5, and on the day of discharge. Follow-up will be conducted on POD 30, 90, and after postoperative months (POM) 6, 12, 24, 36, 48, and 60 (**Table 1**). Demographic and baseline clinical data, intraoperative findings, and postoperative results will be recorded. During follow-up, patients will complete established and validated questionnaires. To enhance participant retention and to avoid loss to follow-up,

patients will be contacted for the completion of questionnaires and to collect missing data. Informed consent will be obtained and trial data will be collected by trained assessors using electronic case report forms (eCRFs).

Table 1 | Trial visits and overview over documented parameters & outcomes

Activity & Documentation	Visit 1 (screening)	Visit 2 (laparosc.)	Visit 3 (surgery)	Visit 4-6 (POD 1, 3, 5)	Visit 7 (dis-charge)	Visit 8-9 (POD 30, 90)	Visit 10-15 (POM 6, 12, 24, 36, 48, 60)
inclusion & exclusion criteria	X						
informed consent	X						
medical history & preoperative assessment*	X						
randomization		X					
surgical & anaesthetic documentation**			X				
Postoperative morbidity measured with CCI (primary endpoint) until POD 30	X		X	X	X	X (V8)	
biological specimen retrieval							
EDTA blood samples	X						
formalin and paraffin tissue samples			X				
	Visit 1 (screening)	**Visit 2 (laparosc.)**	**Visit 3 (surgery)**	**Visit 4-6 (POD 1, 3, 5)**	**Visit 7 (dis-charge)**	**Visit 8-9 (POD 30, 90)**	**Visit 10-15 (POM 6, 12, 24, 36, 48, 60)**
Short-term clinical endpoints							
Postoperative morbidity measured with the CCI until POD 90			X	X	X	X	
Major complications (Clavien-Dindo ≥ 3) unitl POD 90			X	X	X	X	
Conversion rate			X				
Operation time			X				
Blood loss			X				
Length of stay in the ICU			X		X		
Length of hospital stay					X		
Pain and postoperative analgesic required				X	X		
Laboratory parameters (CRP, leucocytes)				X	X		
Mobilization of the patient				X			
Quality of the patient's recovery (QoR-15)				X (V5)			
Quality of life (EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADL)	X				X	X	X
Adherence to a fast-track gastrectomy SOP			X	X	X		
Objective evaluation of anastomoses			X				
First bowl function				X			
Wound healing deficits				X	X	X (V8)	
Vegetative function***						X	X
Necessity of interventions due to complications				X	X	X	X
Oncologic short-term data							
Number of lymph nodes removed and of tumor-positive lymph nodes			X				
Number of R0 resections			X				
Development of tumor markers (CA 125, CA 19-9, CA 72-4, CEA)			X				

	Tumor histpathology****			X				
Long-term clinical data (5-year follow-up)								
	Changes of body weight					X	X	X
	Quality of life (EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADL, BIS)	X				X	X	X
	Incidence of incisional hernias						X	X
	Incidence of reoperations				X	X	X	X
	Incidence of stenosis						X	X
	Cosmetic results and scar satisfaction (BIS)							X (V13)
Oncologic long-term data (5-year follow-up)								
	Oncologic treatment (adjuvant and consecutive therapy)						X	X
	Disease-free survival; DFS; recurrence free survival; RFS						X (V9)	X
	Local recurrence; LR						X (V9)	X
	Relapse-free survival; RFS						X (V9)	X
	Progression-free survival; PFS						X (V9)	X
	Time to progression; TTP						X (V9)	X
	Overall survival; OS						X (V9)	X

* Includes body mass index, ASA status, preoperative oncological status, prior surgical treatment, drug use and comorbidities. ** Includes surgical documentation (surgeons, procedures, complications, drains) & anesthesiology documentation. *** Includes dysphagia, reflux, and dumping syndromes. **** Includes entity, TNM, grading, and resection status. ASA American Society of Anesthesiologists classification, POD postoperative day, POM postoperative month, CCI Comprehensive Complication Index for complications & related interventions according to the Clavien-Dindo classification (**Appendix 3**), EDTA ethylenediaminetetraacetic acid, need for ICU intermediate / intensive care unit, CRP C-reactive protein, EUROQOL EQ-5D-5L EuroQol Group Questionnaire for Quality of Life with 5 dimensions and 5 levels, EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EORTC QLQ-STO22 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Gastric Cancer, QoR-15 Quality of Recovery 15, ADLs activities of daily living (**Appendix 4**), BIS Body Image Scale, SOP standard operating procedure, CA carbohydrate antigen, CEA carcinoembryonic antigen.

Primary endpoint

The primary endpoint will be postoperative morbidity measured using the Comprehensive Complication Index (CCI) until postoperative day 30 [31]. Usage of this index will enable a comparison of the severity and individual burden of postoperative complications with results from other trials [32, 33]. Postoperative morbidity is defined as any deviation from the normal postoperative course according to the Clavien-Dindo classification [34]. This includes anastomotic insufficiency or loss of anastomotic integrity verified by either CT scan with detection of contrast agent external to the anastomosis, endoscopy, or the detection of methylene blue in a drain following oral intake.

Secondary endpoints

Secondary endpoints can be separated into short-term clinical and oncological endpoints as well as long-term clinical and oncological endpoints (at 5-year follow-up, as measured from the date of surgery) and can be found in **Table 1**. Hyperspectral imaging (HSI) of the surgical site intraoperatively (visit 3) will be performed in Heidelberg only.

Standardized therapy and trial interventions

Control: Total OG with D2/D2+ LAD**.**

Intervention: Total MIG with D2/D2+ LAD either as LAG or RAG. A mini-laparotomy or a Pfannenstiel incision (≤8 cm incision in both the skin and fascia) may be performed for specimen removal.

Modified cardia-preserving total gastrectomy (preservation of gastroesophageal junction) can also be accepted, but only if the short gastric vessels are dissected as well, and if LAD is the same as for total gastrectomy. Besides the open or minimally-

invasive approach, the remaining treatment is identical in both groups. Any other form of gastrectomy, explicitly conventional subtotal gastrectomy (preserved short gastric vessels and limited LAD of station 2 and 4sa), extended gastrectomy, and distal gastrectomy with Billroth I or II reconstruction are not allowed. Reconstruction can be of any form including Roux-Y reconstruction, interposition, or pouch reconstruction. Any other step of the procedure such as antibiotic prophylaxis, placement of abdominal drains, and closure of the abdominal wall can be performed according to in-house standards. D2 LAD is defined according to the Japanese classification [35], with stations 1, 2, 3a, 3b, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a obligatory for the MEGA trial (**Figure 2**). Station 10 is optional. Incomplete LAD is not allowed and has to be documented as a protocol deviation.

Removal of further stations (8b, 12b, 12p, 13, 14v, 14a, 15, 16a1, 16a2, 16b1, 16b2, 17, 18, 19, 20, 110, 111, and 112) is allowed when deemed appropriate, e.g., in case of assumed tumor invasion, and has to be documented as D2+.

Postoperative management

Postoperative management should be performed in a fast-track approach with short durations until patient mobilization, drainage removal, and first oralization of food. The patient should be extubated immediately after surgery and transferred to a normal ward, if possible. Further specifications for the postoperative course will be outlined in the provided standard operating procedure (SOP) for fast-track gastrectomy. The last in-hospital trial visit takes place on the day of discharge. Subsequent trial visits will be conducted via telephone. These will be questionnaire-based and focus on CCI (until POD 90), quality of life, and oncologic outcome.

Randomization and blinding

In order to ensure equal distribution of patient characteristics between both trial arms, randomization will be performed using a web-based randomization tool (www.randomizer.at). Randomization will take place following diagnostic laparoscopy (Visit 2). The allocation pattern is masked, block-randomized with variable block length, and stratified across centers. Due to the pragmatic character of the trial, blinding of the surgeon is not feasible.

Quality assurance and quality management

Clinical data monitoring

Clinical monitoring will be performed by independent monitors at the Study Center of the German Society of Surgery (SDGC). The monitoring strategy will comprise a combination of centralized and onsite monitoring and will be described in a trial specific monitoring plan. To confirm site selection, pre-study visits will be performed. On-site monitoring will focus on patient informed consent, safety, and surgical procedures as well as the correct recording and documentation of the primary and secondary endpoints by source data verification (SDV).

Surgical quality control

Several steps are necessary to ensure and evaluate surgical quality:

1) Trial surgeons must have performed 20 surgeries in the respective approach (OG, LAG, or RAG), depending on the trial arm they will contribute to.
2) Each trial surgeon must provide photographic or video documentation of a former procedure.

3) Each trial surgeon has to provide photographic or video documentation of the trial procedures, which will be assessed by an expert. This photographic or video documentation is defined as follows:
    a. lymph node station 7 (left gastric artery) after dissection
    b. lymph node station 8a (common hepatic artery) after dissection
    c. lymph node station 9 (celiac artery) after dissection
    d. lymph node station 10 (splenic hilum) after dissection
    e. lymph node station 11p (proximal splenic artery) after dissection
    f. lymph node station 11d (distal splenic artery) after dissection
    g. lymph node station 12a (hepatoduodenal ligament along the hepatic artery) after dissection
    h. duodenal stump
    i. all anastomoses
    j. incision for specimen retrieval in MIG

Assessment of safety

Since the primary endpoint is postoperative complications as measured by the CCI, adverse (AE) and serious adverse events (SAE) are already captured and no additional safety analysis will be performed (**Table 2**).

Table 2: Grading of Adverse Events

Clavien-Dindo	Adverse event (AE)	Serious adverse event (SAE)	Minor complication	Major complication
Grade I complication	AE		Minor complication	
Grade II complication				

<table>
<tr><td>Grade III complication</td><td rowspan="3"></td><td></td><td></td><td rowspan="3">Major complication</td></tr>
<tr><td>Grade IV complication</td><td rowspan="2">SAE</td><td></td></tr>
<tr><td>Grade V complication</td><td></td></tr>
</table>

Data management

The Institute of Medical Biometry (IMBI) is responsible for data management within this trial. An eCRF will be used for data collection. To assure safe and secure data use and storage, data transmission is encrypted with secure socket layer (SSL) technology. Only authorized users are able to enter or edit data, and access is further restricted to data of the patients in that user's respective center only. All changes to data are logged with a computerized timestamp in an audit trail. All data will be pseudonymized. To guarantee high data quality, data validation rules will be defined in a data validation plan. Completeness, validity, and plausibility of data will be checked at the time of data entry (edit-checks) and using validating programs, which will generate queries. If no further corrections are to be made in the database, eCRF data will be locked. Data will finally be downloaded and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the IMBI that guarantee efficient conduct in compliance with Good Clinical Practice (GCP). At the end of the study, the data will be transformed into different data formats (e.g., csv-files) for archiving and to ensure that it can be re-used.

Statistical methods

Sample size

The sample size calculation is based on the primary endpoint “postoperative morbidity as measured with the CCI until POD 30.” A decrease of the CCI by 10 points between OG and MIG is considered relevant by patients and clinicians, and a conservative standard deviation of 20 is assumed based on existing literature for upper GI surgery [36], leading to an effect size of d=0.5. Based on a t-test with a two-sided significance level of α=0.05, a sample size of n=128 patients (64 per group) has to be recruited to achieve a power of 80%. The primary endpoint will be analyzed with a linear mixed regression model, which leads to equal or even increased power when compared to a two-sided t-test. To compensate for drop-outs and patients lost to follow-up, a further 20% of patients will be randomized, leading to a total sample size of n=160 (80 per group; 80 x 0,8 = 64.8). The number of patients to be screened (n=400 to be assessed for eligibility; 400 x 0.5 x 0.8 = 160) was calculated with an assumed 50% participation rate and an exclusion rate of 20%.

Randomized & allocated (n = 160; 80 per group)

Intention-to-treat dataset (n = 160; 80 per group)

Per-protocol dataset (n = 136; 72 and 64)

Statistical analysis

For the examination of the primary endpoint “postoperative morbidity measured with the CCI until POD 30,” the hypotheses to be assessed in the primary analysis are as follows: H_0: $\mu_1 = \mu_2$ vs H_1: $\mu_1 \neq \mu_2$, where μ_1 and μ_2 denote the mean CCI in the control and intervention groups, respectively. The significance level is set to a two-sided α=0.05. Therefore, the primary endpoint will be examined using a linear mixed model adjusting for the variables age and treatment group, as well as the surgical center as

a random effect (due to the stratified randomization and relatively large number of centers in relation to the sample size, inclusion of center as a random effect is recommended). Details of the primary model (e.g., handling of missing values, sensitivity analyses) will be fully described in the statistical analysis plan.

The number of patients included in the primary analysis is determined as the full analysis set. Patients will be analyzed in the group they were randomized to (converted patients remain in their group). This reflects an analysis according to the intention to treat (ITT) principle. Specific events (e.g., death) that can occur after randomization will be handled within the primary endpoint definition, reflecting a composite strategy [according to the ICH E9 (R1) addendum]. Other post randomization events will not be considered. This choice reflects our treatment policy approach.

In general, for the full analysis set, all baseline values and secondary outcomes will be evaluated descriptively, with p-values reported alongside 95% confidence intervals for the corresponding effects. Furthermore, secondary endpoints will be evaluated descriptively, using appropriate regression models. Time-to-event endpoints will be evaluated by methods of survival analysis including Kaplan-Meier methods and Cox proportional hazards models. In addition, subgroup analyses (including age, gender, tumor stage, tumor grade, histological tumor type, linear vs. circular stapler for proximal anastomosis, linear vs. hand-sewn for distal anastomosis, type of retrieval incision, and intraoperative conversion) will be carried out. A detailed and comprehensive statistical analysis plan will be written shortly after the first patient is recruited. All analyses will be performed using SAS version 9.4 or higher.

Discussion

We performed a systematic literature search prior to planning this trial and identified 974 publications. Of those, 17 RCTs comparing LAG with OG [7, 37-55] and two RCTs

comparing RAG with OG [56, 57] were found to be relevant. The studies showed comparable oncologic and short-term postoperative outcomes for MIG and OG. However, 16 of the 19 studies were conducted in China, Korea, and Japan [7, 38-50, 56, 57]. These countries have a significantly higher incidence of gastric cancer, which consequently leads to significantly higher surgical volume and expertise among the participating centers [58]. In addition, the body constitution of Asian patients is often different from that of Western patients, which limits the direct transferability of study results. Also, the incidence of gastric cancer is lower in Western populations and advanced disease stages are more frequently detected, because screening is less common. Therefore, it is unclear whether these results would be reproducible in a Western population.

Currently, there have only been three non-Asian RCTs directly comparing LAG and OG. The first RCT, by Huscher et al., focused exclusively on distal gastrectomy, did not define any specific primary or secondary endpoints, and included a total of 59 patients [37]. Due to the missing differentiation between primary and secondary endpoints, the trial can be perceived as methodically limited and was most likely underpowered. However, no significant difference was found in perioperative outcome, oncologic outcome, or mortality [morbidity rates: 26.7% (LAG) and 27.6% (OG), lymph nodes harvested: 30.0 ± 14.9 (LAG) and 33.4 ± 17.4 (OG), operative mortality rates: 3.3% (LG) and 6.7% (OG), 5-year survival rate: 54.8% (LAG) and 55.7% (OG)].

The only two currently existing relevant Western multicenter RCTs comparing open versus minimally invasive oncologic total gastrectomy are the LOGICA trial [52, 53] and the STOMACH trial [51, 54, 55], which were both puplished in 2021.

The LOGICA trial is a non-blinded, multicenter superiority trial with 227 patients with postoperative hospital stay as the primary endpoint. The study identified significant differences regarding blood loss [150 ml (LAG) and 300 ml (OG), p<0.001] and

operating time [216 min (LAG) and 182 min (OG), p<0.001], but no significant differences in hospital stay (p=0.34), postoperative complications [44% (LAG) and 42% (OG), p=0.91], in-hospital mortality [4% (LAG) and 7% (OG), p=0.40], R0 resections [95% (LAG) and 95% (OG), p=1.00], median lymph node yield [29 (LAG) and 29 (OG), p=0.49], 1-year overall survival [76% (LAG) and 78% (OG), p=0.74], and health-related quality of life [+1.5 (LAG) and +3.6 (OG) on a 1-100 scale].

The STOMACH trial is an observer-blinded, multicenter, non-inferiority trial with 96 patients following neoadjuvant chemotherapy with quality of oncological resection (radicality of surgery and number of retrieved lymph nodes) as the primary endpoint. Mean number of resected lymph nodes [41.7±16.1 (LAG) and 43.4±17.3 (OG), p=0.612), number of R0 resections (44/47 (LAG) and 48/49 (OG), p=0.617], 1-year survival (85.5% (LAG) and 90.4% (OG), p=0.701], postoperative complications [16/47 (LAG) and 21/49 (OG), p=0.408], and postoperative QoL [measured with EQ5D, EORTC-QLQ-C30, and EORTC-QLQ-STO22] were not significantly different.

In a regular setting with a diagnosed carcinoma, patients should usually be advised to make their decision for or against a certain treatment option with regards to a combination of highest expected overall survival and simultaneous conservation of long-term QoL. Short-term postoperative complications should only be treated as secondary deciding factors. However, if postoperative complications might impair long-term QoL or even overall survival, they become equally relevant. In general, postoperative complications can have negative effects on QoL or overall survival; however, this is much more the case for gastric cancer, as time to continuation of peroperative chemotherapy can be prolonged and the prognosis therefore worsened.

The STOMACH trial provides evidence that MIG is non-inferior to OG in terms of oncologic quality of resection, which is a necessary requirement for the MEGA trial, as

postoperative morbidity and complications can only be decisive factors in the case of oncological non-inferiority for an oncological resection with curative intent.

While both the STOMACH and LOGICA trials suggest that postoperative complications might not be significantly different between both groups, a premature confirmative statement must be avoided as complications have only been investigated as secondary endpoints so far. Consequently, a multicenter RCT comparing total MIG and OG for gastric cancer in terms of postoperative complications is needed to decide whether MIG should be established as the new standard treatment for resectable gastric cancer in Europe.

The MEGA trial has strict quality control measures and will be conducted in line with all relevant guidelines. Therefore, it will provide the highest level of evidence on this very relevant clinical research question.

Ethics and dissemination

The MEGA trial conforms to the Declaration of Helsinki [59]. The Independent Ethics Committee of the Medical Faculty, University of Heidelberg, approved the MEGA trial protocol (registration number S-816/2021). For other trial centers, recruitment will only be initiated after receiving approval from their respective local ethics committees. **Additional file 1** provides the SPIRIT checklist for interventional trials [60].

Study objectives and procedures will be communitated clearly to all qualifying patients and written informed consent will be obtained from those who agree to participate. Results will be presented at scientific meetings and published in international peer-reviewed journals. Summaries will be provided to the funders of the study and results will be published in open-access journals.

Patient and Public Involvement

Patients are involved in the design and conduction of this trial. Priority of the research question, outcome measures, and recruitment methods were discussed with patients during the initial planning stage. Patients have stated an uneventful postoperative course as a very notable feature, and every possible intervention contributing to lower postoperative morbidity was rated to be of great importance.

The chairman of one of Germany's largest patient self-aid groups concerning minimally invasive surgery (SHG Frankfurt Sachsenhausen) will be a member of the data safety and monitoring board as a patient representative. Therefore, this study will continue to take the patient's perspective into account.

Modification of the protocol

The current protocol version (1.2) will be utilized during trial initiation. In case of protocol amendments, these will be submitted to the relevant ethics committees for approval.

Additional file

Additional file 1: SPIRIT checklist.

Abbreviations

ADLs	Activities of daily living
AE	Adverse event
AEG	Adenocarcinoma of esophagogastric junction
ASA	American Society of Anesthesiologists Classification
BIS	Body Image Scale
BMBF	Federal Ministry of Education and Research

CA	Carbohydrate antigen
CEA	Carcinoembryonic antigen
CCI	Comprehensive Complication Index according to Clavien-Dindo classification
eCRF	Electronic Case Report Forms
CRP	C-reactive protein
DALY	Disability-adjusted life years
DRKS	Deutsches Register Klinischer Studien (German Clinical Trials Register)
DSMB	Data Safety and Monitoring Board
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Gastric Cancer
EUROQOL EQ-5D-5L	EuroQol Group Questionnaire for Quality of Life with 5 dimensions and 5 levels
FPI	First-patient-in
FU	Follow-up
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intermediate / intensive care unit
IMBI	Institute of Medical Biometry
ITT	Intention-to-treat
LAG	Laparoscopic gastrectomy
LPI	Last-patient-in

LPO	Last-patient-out
MIG	Minimally invasive gastrectomy
OG	Open gastrectomy
POD	Postoperative day
POM	Postoperative month
PRO	Patient-reported outcome
QoL	Quality of life
QoR-15	Quality of Recovery 15 questionnaire
RAG	Robotic-assisted gastrectomy
RCT	Randomized controlled trial
SAE	Serious adverse event
SDGC	Study Center of the German Society of Surgery
SDV	Source data verification
SOP	Standard operating procedure
V	Visit

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data, as well as submission of the report for publication. The funder does not have any influence in study design or collection, management, analysis, and interpretation of data.

Authors' contributions

FN and ASF have contributed equally as first authors. BPMS, FN and ASF developed the original concept of the trial and applied for funding. FN, ASF, DH, CK, MF, SZ and BPMS developed the design and methodology. BPMS and FN recruited all participating trial centers. FN, ASF, CK, MF, SZ and BPMS performed initial statistical steps to develop the analysis plan. FN, ASF, RK, SVA, ST, PP, AB and HN contributed to drafting the protocol. DH, CK, MF, SZ, BB, FB, CB, IG, SG, PG, CG, JH, KL, LM, SM, DR, FS, DS, PP, TS and BPMS contributed to the revision of the final protocol. All authors have read and approved of the final manuscript.

Responsibilities

Prof. Dr. Müller-Stich, Coordinating Investigator, is involved in every aspect of the trial and has ultimate authority over study design, data collection, interpretation of data, and oversight of the intermittent and final written reports. PD Dr. Nickel, MME, is Deputy Coordinating Investigator. Alexander Studier-Fischer, MD, is Trial Organizer. The Clinical Trial Committee consists of the Coordinating Investigator, the Deputy Coordinating Investigator, and the Trial Organizer, originating from the Division of Minimally Invasive and Robotic-assisted Surgery in the Department of General, Visceral, and Transplantation Surgery at Heidelberg University Hospital. To ensure objectivity, the third-party Institute of Medical Biometry (IMBI) is responsible for data management, statistical planning, and analysis. Project management and monitoring are handled by the SDGC (Study Center of the German Society of Surgery), in

Heidelberg. Additionally, a Data Safety and Monitoring Board (DSMB) consisting of independent experts will advise on the continuation, modification, or termination of the trial and a steering committee will supervise the conduction of the trial and make decisions based on DSMB recommendations.

Data availability

The full protocol, results and statistical code will be made available by the corresponding authors upon reasonable request.

Conflict of interest statements

The authors declare that they have no conflicts of interest or relevant financial ties to disclose. Felix Nickel reports support for courses and travel from Johnson and Johnson, Medtronic, Intuitive Surgical, Cambridge Medical Robotics, and KARL STORZ as well as consultancy fees from KARL STORZ.

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Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

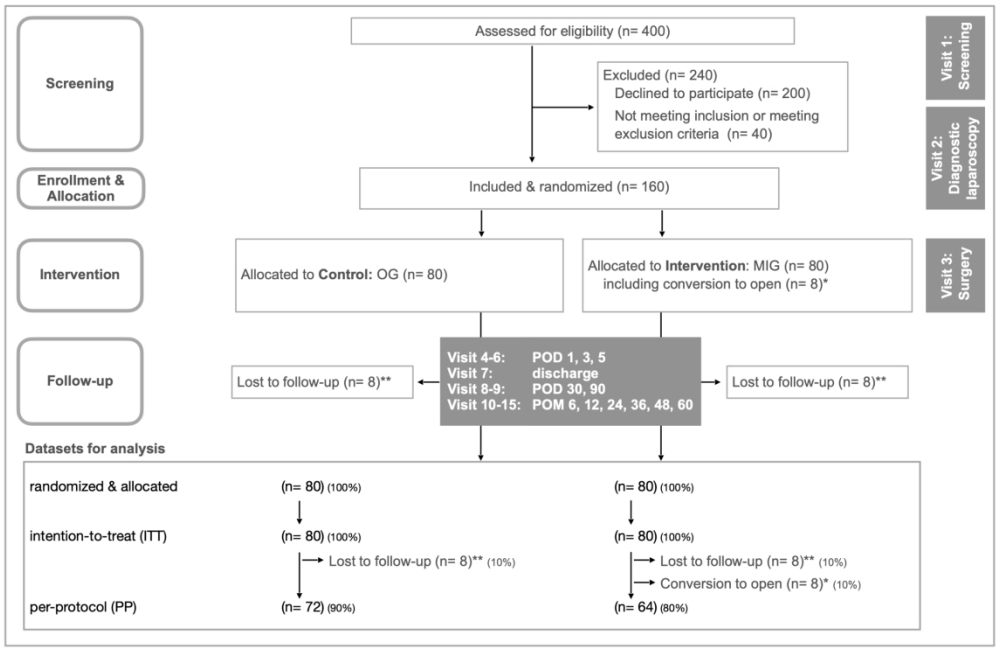

Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

200x129mm (300 x 300 DPI)

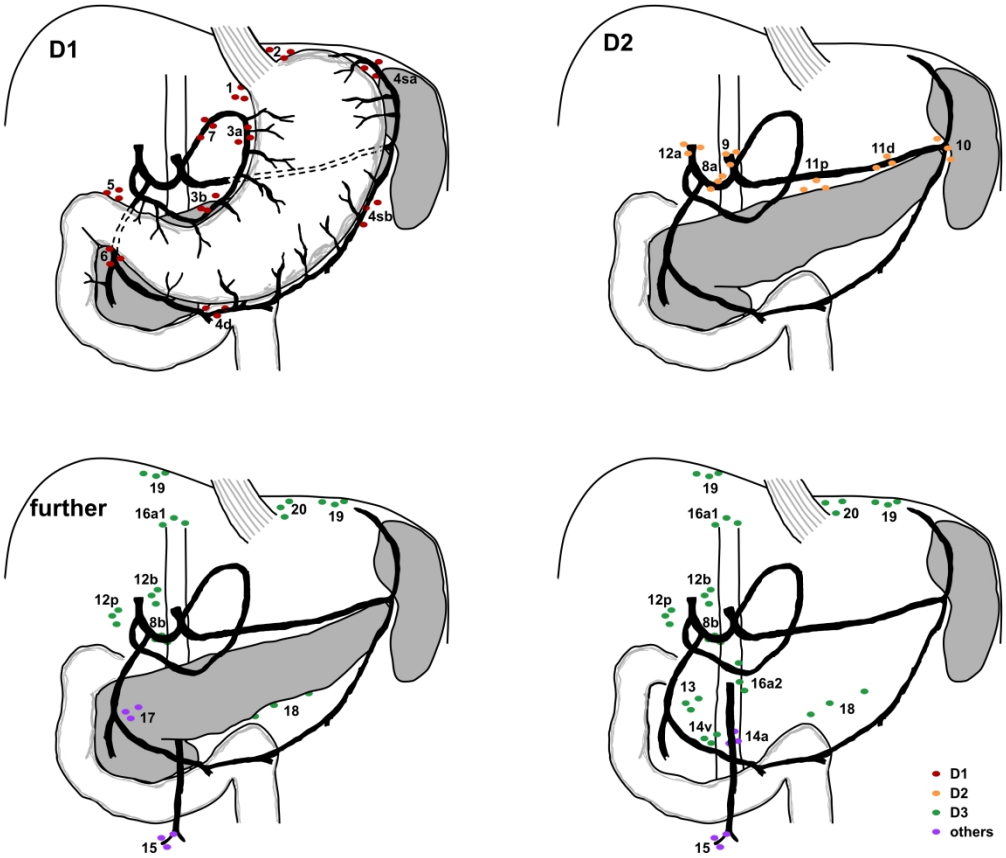

Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

295x250mm (300 x 300 DPI)

Appendices

Appendix 1: ECOG & KARNOFSKY Performance Status

ECOG PERFORMANCE STATUS [1] [2]		KARNOFSKY PERFORMANCE STATUS [3]	
GRADE	Description	GRADE	Description
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do active work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated although death not imminent
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20	Very ill; hospitalization and active supportive care necessary
		10	Moribund
5	Dead	0	Dead

Appendix 2: Documentation of lymphadenectomy during total gastrectomy [4]

			D2 Lymphadenectomy
No.	Location		completed lymphadenectomy = □
1*	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.	□
2*	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	□
3a*	Left gastric vessel	Lesser curvature LNs along the branches of the left gastric artery	□
3b*	Right gastric vessel	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery	□
4sa*	Short gastric vessel	Left greater curvature LNs along the short gastric arteries (perigastric area)	□
4sb*	Left gastroepiploic	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	□
4d*	Right gastroepiploic	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	□
5*	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	□
6*	Infrapyloric	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein	□
7*	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	□
8a**	Common hepatic artery	Anterosuperior LNs along the common hepatic artery	□
8b	Common hepatic artery	Posterior LNs along the common hepatic artery	□
9**	Celiac artery	Celiac artery LNs	□
10**	Splenic hilum	Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch	(□)
11p**	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	□
11d**	Distal splenic artery	Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail	□
12a**	Hepatoduodenal ligament along the hepatic artery	Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	□
12b	Hepatoduodenal ligament along the bile duct	Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	□
12p	Hepatoduodenal ligament along behind the portal vein	Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas	□
13	Posterior surface of pancreatic head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla	□
14v	Superior mesenteric vein	LNs along the superior mesenteric vein	□
14a	Superior mesenteric artery	-	□
15	Middle colic vessels	LNs along the middle colic vessels	□
16a1	Aortic hiatus	Paraaortic LNs in the diaphragmatic aortic hiatus	□
16a2	Abdominal aorta (celiac trunk to left renal vein)	Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein	□
16b1	Abdominal aorta (left renal vein to IMA)	Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery	□
16b2	Abdominal aorta (IMA to aortic bifurcation	Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation	□
17	Anterior surface of pancreatic head	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath	□
18	Inferior margin of pancreas	LNs along the inferior border of the pancreatic body	□
19	Infradiaphragmatic	Infradiaphragmatic LNs predominantly along the subphrenic artery	□
20	Esophageal hiatus of the diaphragm	Paraesophageal LNs in the diaphragmatic esophageal hiatus	□
110	Paraesophageal lower thorax	Paraesophageal LNs in the lower thorax	□
111	Supradiaphragmatic	Supradiaphragmatic LNs separate from the esophagus	□
112	Posterior mediastinal	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus	□

*required for D1 lymphadenectomy
**required for D2 lymphadenectomy

	Not required for MEGA trial
	Optional for MEGA trial
	Required for MEGA trial; if not explain why

Appendix 3: Clavien-Dindo-Classification [5]

Grades		Definition
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Intervention not under general anesthesia
	IIIb	Intervention under general anesthesia
IV		Life-threatening complication (including CNS complications)* requiring IC/ICU-management
	IVa	single organ dysfunction (including dialysis)
	IVb	multiorgandysfunction
V		Death of a patient

*brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

Appendix 4: Katz Activities of Daily Living

Activities Points (1 or 0)	**Independence** **(1 Point)** NO supervision, direction or personal assistance.	**Dependence** **(0 Points)** WITH supervision, direction, personal assistance or total care.
BATHING Points: _____	Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING Points: _____	Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable	Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	Exercises complete self control over urination and defecation.	Is partially or totally incontinent of bowel or bladder.
FEEDING Points: _____	Gets food from plate into mouth without help. Preparation of food may be done by another person.	Needs partial or total help with feeding or requires parenteral feeding.

Appendix References

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	across whole protocol
Protocol version	3	Date and version identifier	21
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 24
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5, 11, 19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11 - 12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4, 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11 - 12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6, 13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16 - 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16 - 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	24 - 25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16, 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14 - 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	24 - 25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	21 - 22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8 - 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8 - 9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8 - 9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23 - 25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16 - 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 1

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.