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BMJ Open

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

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Manuscripts

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3 1 **Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for**
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5 2 **a multicenter randomized controlled trial (DRKS00025765)**
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48
49 47 **Abstract**

50
51 48 **Introduction:**

52
53 49 The only curative treatment for most gastric cancer is radical gastrectomy with D2

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55 50 lymphadenectomy (LAD). Minimally invasive total gastrectomy (MIG) aims to reduce

56
57 51 postoperative morbidity, but its use has not yet been widely established in Western

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3 52 countries. MEGA is the first Western multicenter randomized controlled trial (RCT) to
4
5 53 compare postoperative morbidity following MIG versus open total gastrectomy (OG).
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10 55 **Methods and analysis:**

11
12 56 This superiority multicenter RCT compares MIG (intervention) to OG (control) for
13
14 57 oncological total gastrectomy with D2 or D2+ LAD. Recruitment is expected to last for
15
16 58 2 years. Inclusion criteria comprise age between 18 and 84 years and planned total
17
18 59 gastrectomy after initial diagnosis of gastric carcinoma. Exclusion criteria include
19
20 60 ECOG performance status > 2 (**Appendix 1**), tumors requiring extended gastrectomy
21
22 61 or less than total gastrectomy, previous abdominal surgery or extensive adhesions
23
24 62 seriously complicating MIG, other active oncologic disease, advanced stages (T4 or
25
26 63 M1), emergency setting, and pregnancy.

27
28
29 64 The sample size was calculated at 80 participants per group. The primary endpoint is
30
31 65 30-day postoperative morbidity as measured by the Comprehensive Complications
32
33 66 Index (CCI). Secondary endpoints include postoperative morbidity and mortality,
34
35 67 adherence to a fast-track protocol, and patient-reported quality of life (QoL) scores
36
37 68 (QoR-15, EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADLs,
38
39 69 and BIS). Oncologic endpoints include rate of R0 resection, lymph node yield,
40
41 70 disease-free survival, and overall survival at 60-month follow-up.
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49 72 **Ethics and dissemination:**

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51 73 Ethical approval has been received by the independent Ethics Committee of the
52
53 74 Medical Faculty, University of Heidelberg (S-816/2021) and will be received from
54
55 75 each responsible ethics committee for each individual participating center prior to
56
57 76 recruitment. Results will be published open access.
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3 78 **Trial registration:** German Clinical Trials Register DRKS00025765. Registered on
4
5 79 December 22nd, 2021.
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8 80
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10 81 **Keywords:** Minimally invasive gastrectomy, total gastrectomy, gastric cancer, Roux-
11
12 82 Y reconstruction, linear stapled anastomosis, circular stapled anastomosis,
13
14 83 randomized controlled trial, comprehensive complication index, fast-track, enhanced
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16
17 84 recovery after surgery
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19 85

20
21 86 **Strengths and limitations of this study**
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- 23
24 87 - MEGA is the first Western multicenter RCT to specifically compare OG with
25
26 88 MIG in terms of postoperative morbidity using the comprehensive complication
27
28 89 index (CCI).
29
30 90 - Usage of the CCI as a comprehensive outcome measure allows for objective
31
32 91 comparisons with other trials.
33
34 92 - Differentiation between robotic and laparoscopic total gastrectomy will be
35
36 93 made in the explorative subgroup analysis only.
37
38 94 - High levels of standardization, intraoperative photo documentation, large
39
40 95 group sizes, and risk-based monitoring by the Study Center of the German
41
42 96 Society of Surgery (SDGC) will guarantee objective data acquisition, increase
43
44 97 patients' adherence to the protocol, and ultimately lead to exceptional data
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46 98 quality.
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100 Introduction

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

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

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

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2
3 126 Postoperative complications, however, are not only important for the immediate
4
5 127 postoperative course, which is usually secondary in relevance, but can also affect
6
7 128 long-term oncologic outcome [25-27]. In a study of 432 patients with curative
8
9 129 gastrectomy and D2 LAD for treatment of gastric cancer, the occurrence of
10
11 130 postoperative in-hospital complications was an independent predictor of worse 5-year
12
13 131 survival (22% vs. 40%). This can be perceived as an indication that postoperative
14
15 132 complications may lead to higher mortality in the long term [28]. Therefore, the trend
16
17 133 towards favoring minimally invasive gastrectomy (MIG) for gastric cancer is
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19 134 increasing.
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26 136 **Methods and analysis**

27 137 **Setting**

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29
30 138 The MEGA trial is a prospective randomized, controlled, non-blinded, two-armed
31
32 139 multicenter surgical superiority trial with a confirmatory character. It includes 14
33
34 140 surgical centers in Germany and Switzerland and is coordinated by the Department
35
36 141 of General, Visceral and Transplantation Surgery at Heidelberg University Hospital,
37
38 142 in Germany. Recruitment is planned for 2 consecutive years. The study protocol was
39
40 143 accepted by the Independent Ethics Committee of the Medical Faculty, University of
41
42 144 Heidelberg (registration number S-816/2021) prior to recruitment. The trial was
43
44 145 registered at DRKS under the registration number DRKS00025765 on December
45
46 146 22nd, 2021 [29]. No secondary identifying numbers such as a Universal Trial Number
47
48 147 have been assigned. Recommendations of the SPIRIT (Standard Protocol Items:
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50 148 Recommendations for Interventional Trials) checklist were followed [30].
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152 **Patient recruitment**

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

162 Inclusion criteria:

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

167 Exclusion criteria:

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

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3 178 - Participation in another intervention trial that might interfere with the
4
5 179 intervention and/or outcome of this trial
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8 180 - Pregnancy
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10 181 Exclusion criteria previously or during staging laparoscopy:

- 11
12 182 - T4
13
14 183 - M1
15
16

17 184 Inclusion takes place after the staging laparoscopy, and patients will be randomized
18
19 185 to the intervention arm (MIG) or the control arm (OG) (**Figure 1**).
20
21 186

23 187 **Trial duration and schedule**

24
25 188 Recruitment is planned to take 24 months. The duration of the trial for each patient is
26
27 189 expected to be 1 month for the primary endpoint and 60 months for the secondary
28
29 190 endpoints with long-term follow-up. Consequently, the duration of data collection is
30
31 191 expected to be 25 months for the primary endpoint and 84 months for the secondary
32
33 192 endpoints [first-patient-in (FPI) to last-patient-out (LPO)]. Trial analysis will take an
34
35 193 additional 6 months. The actual overall duration or recruitment time may differ.
36
37 194 Recruitment is planned to be active until both arms contain at least 80 patients in the
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39 195 intention-to-treat (ITT) dataset.
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47 197 **Trial visits**

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49 198 Patients will be monitored intraoperatively, on postoperative days (POD) 1, 3, and 5,
50
51 199 and on the day of discharge. Follow-up will be conducted on POD 30, 90, and after
52
53 200 postoperative months (POM) 6, 12, 24, 36, 48, and 60 (**Table 1**). Demographic and
54
55 201 baseline clinical data, intraoperative findings, and postoperative results will be
56
57 202 recorded. During follow-up, patients will complete established and validated
58
59 203 questionnaires. To enhance participant retention and to avoid loss to follow-up,
60

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

207

208 **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 histopathology			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

209

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

225

226 **Primary endpoint**

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

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3 231 from the normal postoperative course according to the Clavien-Dindo classification
4
5 232 [34]. This includes anastomotic insufficiency or loss of anastomotic integrity verified
6
7 233 by either CT scan with detection of contrast agent external to the anastomosis,
8
9 234 endoscopy, or the detection of methylene blue in a drain following oral intake.
10
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235

236 **Secondary endpoints**

17 237 Secondary endpoints can be separated into short-term clinical and oncological
18
19 238 endpoints as well as long-term clinical and oncological endpoints (at 5-year follow-up,
20
21 239 as measured from the date of surgery) and can be found in **Table 1**.
22
23

240

241 **Standardized therapy and trial interventions**

28 242 **Control:** Total OG with D2/D2+ LAD.

30 243 **Intervention:** Total MIG with D2/D2+ LAD either as LAG or RAG. A mini-laparotomy
31
32 244 or a Pfannenstiel incision (≤ 8 cm incision in both the skin and fascia) may be
33
34 245 performed for specimen removal.
35
36

37 246 Modified cardia-preserving total gastrectomy (preservation of gastroesophageal
38
39 247 junction) can also be accepted, but only if the short gastric vessels are dissected as
40
41 248 well, and if LAD is the same as for total gastrectomy. Besides the open or minimally-
42
43 249 invasive approach, the remaining treatment is identical in both groups. Any other
44
45 250 form of gastrectomy, explicitly conventional subtotal gastrectomy (preserved short
46
47 251 gastric vessels and limited LAD of station 2 and 4sa), extended gastrectomy, and
48
49 252 distal gastrectomy with Billroth I or II reconstruction are not allowed. Reconstruction
50
51 253 can be of any form including Roux-Y reconstruction, interposition, or pouch
52
53 254 reconstruction. Any other step of the procedure such as antibiotic prophylaxis,
54
55 255 placement of abdominal drains, and closure of the abdominal wall can be performed
56
57 256 according to in-house standards. D2 LAD is defined according to the Japanese
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3 257 classification [35], with stations 1, 2, 3a, 3b, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and
4
5 258 12a obligatory for the MEGA trial (**Figure 2**). Station 10 is optional. Incomplete LAD
6
7 259 is not allowed and has to be documented as a protocol deviation.

8
9
10 260 Removal of further stations (8b, 12b, 12p, 13, 14v, 14a, 15, 16a1, 16a2, 16b1, 16b2,
11
12 261 17, 18, 19, 20, 110, 111, and 112) is allowed when deemed appropriate, e.g., in case
13
14 262 of assumed tumor invasion, and has to be documented as D2+.

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18 19 264 **Postoperative management**

20
21 265 Postoperative management should be performed in a fast-track approach with short
22
23 266 durations until patient mobilization, drainage removal, and first oralization of food.

24 267 The patient should be extubated immediately after surgery and transferred to a
25
26 268 normal ward, if possible. Further specifications for the postoperative course will be
27
28 269 outlined in the provided standard operating procedure (SOP) for fast-track
29
30 270 gastrectomy. The last in-hospital trial visit takes place on the day of discharge.
31
32 271 Subsequent trial visits will be conducted via telephone. These will be questionnaire-
33
34 272 based and focus on CCI (until POD 90), quality of life, and oncologic outcome.

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36
37 273

38 39 274 **Randomization and blinding**

40
41
42 275 In order to ensure equal distribution of patient characteristics between both trial arms,
43
44 276 randomization will be performed using a web-based randomization tool
45
46 277 (www.randomizer.at). Randomization will take place following diagnostic laparoscopy
47
48 278 (Visit 2). The allocation pattern is masked, block-randomized with variable block
49
50 279 length, and stratified across centers. Due to the pragmatic character of the trial,
51
52 280 blinding of the surgeon is not feasible.

53
54
55 281

56 57 282 **Quality assurance and quality management**

283 **Clinical data monitoring**

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

291

292 **Surgical quality control**

293 Several steps are necessary to ensure and evaluate surgical quality:

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

- 1
2
3 309 h. duodenal stump
4
5 310 i. all anastomoses
6
7 311 j. incision for specimen retrieval in MIG
8
9

10 312

11
12 313 **Assessment of safety**

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14 314 Since the primary endpoint is postoperative complications as measured by the CCI,
15
16 315 adverse (AE) and serious adverse events (SAE) are already captured and no
17
18 316 additional safety analysis will be performed (**Table 2**).
19
20

21 317

22
23
24 318 **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				

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46 320 **Data management**

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48 321 The Institute of Medical Biometry (IMBI) is responsible for data management within
49
50 322 this trial. An eCRF will be used for data collection. To assure safe and secure data
51
52 323 use and storage, data transmission is encrypted with secure socket layer (SSL)
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54 324 technology. Only authorized users are able to enter or edit data, and access is further
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56 325 restricted to data of the patients in that user's respective center only. All changes to
57
58 326 data are logged with a computerized timestamp in an audit trail. All data will be
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3 327 pseudonymized. To guarantee high data quality, data validation rules will be defined
4
5 328 in a data validation plan. Completeness, validity, and plausibility of data will be
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7 329 checked at the time of data entry (edit-checks) and using validating programs, which
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9 330 will generate queries. If no further corrections are to be made in the database, eCRF
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11 331 data will be locked. Data will finally be downloaded and used for statistical analysis.
12
13 332 All data management procedures will be conducted according to written defined
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15 333 standard operating procedures (SOPs) of the IMBI that guarantee efficient conduct in
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17 334 compliance with Good Clinical Practice (GCP). At the end of the study, the data will
18
19 335 be transformed into different data formats (e.g., csv-files) for archiving and to ensure
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21 336 that it can be re-used.
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31 339 **Statistical methods**

32 340 **Sample size**

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34
35 341 The sample size calculation is based on the primary endpoint “postoperative
36
37 342 morbidity as measured with the CCI until POD 30.” A decrease of the CCI by 10
38
39 343 points between OG and MIG is considered relevant by patients and clinicians, and a
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41 344 conservative standard deviation of 20 is assumed based on existing literature for
42
43 345 upper GI surgery [36], leading to an effect size of $d=0.5$. Based on a t-test with a two-
44
45 346 sided significance level of $\alpha=0.05$, a sample size of $n=128$ patients (64 per group)
46
47 347 has to be recruited to achieve a power of 80%. The primary endpoint will be analyzed
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49 348 with a linear mixed regression model, which leads to equal or even increased power
50
51 349 when compared to a two-sided t-test. To compensate for drop-outs and patients lost
52
53 350 to follow-up, a further 20% of patients will be randomized, leading to a total sample
54
55 351 size of $n=160$ (80 per group; $80 \times 0,8 = 64.8$). The number of patients to be screened
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3 352 (n=400 to be assessed for eligibility; $400 \times 0.5 \times 0.8 = 160$) was calculated with an
4
5 353 assumed 50% participation rate and an exclusion rate of 20%.

6
7 354 Randomized & allocated (n = 160; 80 per group)

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9
10 355 Intention-to-treat dataset (n = 160; 80 per group)

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12 356 Per-protocol dataset (n = 136; 72 and 64)

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15 357

16 17 358 **Statistical analysis**

18
19 359 For the examination of the primary endpoint “postoperative morbidity measured with
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21 360 the CCI until POD 30,” the hypotheses to be assessed in the primary analysis are as
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23 361 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
24
25 362 control and intervention groups, respectively. The significance level is set to a two-
26
27 363 sided $\alpha=0.05$. Therefore, the primary endpoint will be examined using a linear mixed
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29 364 model adjusting for the variables age and treatment group, as well as the surgical
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31 365 center as a random effect (due to the stratified randomization and relatively large
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33 366 number of centers in relation to the sample size, inclusion of center as a random
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35 367 effect is recommended). Details of the primary model (e.g., handling of missing
36
37 368 values, sensitivity analyses) will be fully described in the statistical analysis plan.

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39
40 369 The number of patients included in the primary analysis is determined as the full
41
42 370 analysis set. Patients will be analyzed in the group they were randomized to
43
44 371 (converted patients remain in their group). This reflects an analysis according to the
45
46 372 intention to treat (ITT) principle. Specific events (e.g., death) that can occur after
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48 373 randomization will be handled within the primary endpoint definition, reflecting a
49
50 374 composite strategy [according to the ICH E9 (R1) addendum]. Other post
51
52 375 randomization events will not be considered. This choice reflects our treatment policy
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54 376 approach.

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2
3 377 In general, for the full analysis set, all baseline values and secondary outcomes will
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5 378 be evaluated descriptively, with p-values reported alongside 95% confidence
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7 379 intervals for the corresponding effects. Furthermore, secondary endpoints will be
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9
10 380 evaluated descriptively, using appropriate regression models. Time-to-event
11
12 381 endpoints will be evaluated by methods of survival analysis including Kaplan-Meier
13
14 382 methods and Cox proportional hazards models. In addition, subgroup analyses
15
16 383 (including age, gender, tumor stage, tumor grade, histological tumor type, linear vs.
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18 384 circular stapler for proximal anastomosis, linear vs. hand-sewn for distal
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20 385 anastomosis, type of retrieval incision, and intraoperative conversion) will be carried
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22
23 386 out. A detailed and comprehensive statistical analysis plan will be written shortly after
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25 387 the first patient is recruited. All analyses will be performed using SAS version 9.4 or
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27
28 388 higher.

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32 391 **Discussion**

33 392 We performed a systematic literature search prior to planning this trial and identified
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35 393 974 publications. Of those, 17 RCTs comparing LAG with OG [7, 37-55] and two
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37 394 RCTs comparing RAG with OG [56, 57] were found to be relevant. The studies
38
39 395 showed comparable oncologic and short-term postoperative outcomes for MIG and
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41 396 OG. However, 16 of the 19 studies were conducted in China, Korea, and Japan [7,
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43 397 38-50, 56, 57]. These countries have a significantly higher incidence of gastric
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45 398 cancer, which consequently leads to significantly higher surgical volume and
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47 399 expertise among the participating centers [58]. In addition, the body constitution of
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49 400 Asian patients is often different from that of Western patients, which limits the direct
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51 401 transferability of study results. Also, the incidence of gastric cancer is lower in
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53 402 Western populations and advanced disease stages are more frequently detected,

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3 403 because screening is less common. Therefore, it is unclear whether these results
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5 404 would be reproducible in a Western population.
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8 405 Currently, there have only been three non-Asian RCTs directly comparing LAG and
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10 406 OG. The first RCT, by Huscher et al., focused exclusively on distal gastrectomy, did
11
12 407 not define any specific primary or secondary endpoints, and included a total of 59
13
14 408 patients [37]. Due to the missing differentiation between primary and secondary
15
16 409 endpoints, the trial can be perceived as methodically limited and was most likely
17
18 410 underpowered. However, no significant difference was found in perioperative
19
20 411 outcome, oncologic outcome, or mortality [morbidity rates: 26.7% (LAG) and 27.6%
21
22 412 (OG), lymph nodes harvested: 30.0 ± 14.9 (LAG) and 33.4 ± 17.4 (OG), operative
23
24 413 mortality rates: 3.3% (LAG) and 6.7% (OG), 5-year survival rate: 54.8% (LAG) and
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26 414 55.7% (OG)].
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31 415 The only two currently existing relevant Western multicenter RCTs comparing open
32
33 416 versus minimally invasive oncologic total gastrectomy are the LOGICA trial [52, 53]
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35 417 and the STOMACH trial [51, 54, 55], which were both published in 2021.
36

37
38 418 The LOGICA trial is a non-blinded, multicenter superiority trial with 227 patients with
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40 419 postoperative hospital stay as the primary endpoint. The study identified significant
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42 420 differences regarding blood loss [150 ml (LAG) and 300 ml (OG), $p < 0.001$] and
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44 421 operating time [216 min (LAG) and 182 min (OG), $p < 0.001$], but no significant
45
46 422 differences in hospital stay ($p = 0.34$), postoperative complications [44% (LAG) and
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48 423 42% (OG), $p = 0.91$], in-hospital mortality [4% (LAG) and 7% (OG), $p = 0.40$], R0
49
50 424 resections [95% (LAG) and 95% (OG), $p = 1.00$], median lymph node yield [29 (LAG)
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52 425 and 29 (OG), $p = 0.49$], 1-year overall survival [76% (LAG) and 78% (OG), $p = 0.74$],
53
54 426 and health-related quality of life [+1.5 (LAG) and +3.6 (OG) on a 1-100 scale].
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57
58 427 The STOMACH trial is an observer-blinded, multicenter, non-inferiority trial with 96
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60 428 patients following neoadjuvant chemotherapy with quality of oncological resection

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3 429 (radicality of surgery and number of retrieved lymph nodes) as the primary endpoint.
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5 430 Mean number of resected lymph nodes [41.7±16.1 (LAG) and 43.4±17.3 (OG),
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7 431 p=0.612), number of R0 resections (44/47 (LAG) and 48/49 (OG), p=0.617], 1-year
8
9 432 survival (85.5% (LAG) and 90.4% (OG), p=0.701], postoperative complications
10
11 433 [16/47 (LAG) and 21/49 (OG), p=0.408], and postoperative QoL [measured with
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13 434 EQ5D, EORTC-QLQ-C30, and EORTC-QLQ-STO22] were not significantly different.
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15
16 435 In a regular setting with a diagnosed carcinoma, patients should usually be advised
17
18 436 to make their decision for or against a certain treatment option with regards to a
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20 437 combination of highest expected overall survival and simultaneous conservation of
21
22 438 long-term QoL. Short-term postoperative complications should only be treated as
23
24 439 secondary deciding factors. However, if postoperative complications might impair
25
26 440 long-term QoL or even overall survival, they become equally relevant. In general,
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28 441 postoperative complications can have negative effects on QoL or overall survival;
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30 442 however, this is much more the case for gastric cancer, as time to continuation of
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32 443 peroperative chemotherapy can be prolonged and the prognosis therefore worsened.
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34 444 The STOMACH trial provides evidence that MIG is non-inferior to OG in terms of
35
36 445 oncologic quality of resection, which is a necessary requirement for the MEGA trial,
37
38 446 as postoperative morbidity and complications can only be decisive factors in the case
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40 447 of oncological non-inferiority for an oncological resection with curative intent.
41
42 448 While both the STOMACH and LOGICA trials suggest that postoperative
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44 449 complications might not be significantly different between both groups, a premature
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46 450 confirmative statement must be avoided as complications have only been
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48 451 investigated as secondary endpoints so far. Consequently, a multicenter RCT
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50 452 comparing total MIG and OG for gastric cancer in terms of postoperative
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52 453 complications is needed to decide whether MIG should be established as the new
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54 454 standard treatment for resectable gastric cancer in Europe.
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3 455 The MEGA trial has strict quality control measures and will be conducted in line with
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5 456 all relevant guidelines. Therefore, it will provide the highest level of evidence on this
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7 457 very relevant clinical research question.
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11 459 **Ethics and dissemination**

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14 460 The MEGA trial conforms to the Declaration of Helsinki [59]. The Independent Ethics
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16 461 Committee of the Medical Faculty, University of Heidelberg, approved the MEGA trial
17
18 462 protocol (registration number S-816/2021). For other trial centers, recruitment will
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20 463 only be initiated after receiving approval from their respective local ethics
21
22 464 committees. Study objectives and procedures will be communicated clearly to all
23
24 465 qualifying patients and written informed consent will be obtained from those who
25
26 466 agree to participate. Results will be presented at scientific meetings and published in
27
28 467 international peer-reviewed journals. Summaries will be provided to the funders of
29
30 468 the study and results will be published in open-access journals.
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36 470 **Patient and Public Involvement**

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38 471 Patients are involved in the design and conduction of this trial. Priority of the research
39
40 472 question, outcome measures, and recruitment methods were discussed with patients
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42 473 during the initial planning stage. Patients have stated an uneventful postoperative
43
44 474 course as a very notable feature, and every possible intervention contributing to
45
46 475 lower postoperative morbidity was rated to be of great importance.
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50 476 The chairman of one of Germany's largest patient self-aid groups concerning
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52 477 minimally invasive surgery (SHG Frankfurt Sachsenhausen) will be a member of the
53
54 478 data safety and monitoring board as a patient representative. Therefore, this study
55
56 479 will continue to take the patient's perspective into account.
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3 481 **Modification of the protocol**
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5 482 The current protocol version (1.2) will be utilized during trial initiation. In case of
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7 483 protocol amendments, these will be submitted to the relevant ethics committees for
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9 484 approval.
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14 486 **Additional file**

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17 487 Additional file 1: SPIRIT checklist.
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21 489 **Abbreviations**
22

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

490

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 494 Surgery at Heidelberg University Hospital for its assistance in coordinating this RCT.
 495 We would also like to thank the other centers that have committed to participating in
 496 the trial.

497

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

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3 5054
5 **506 Authors' contributions**

7 507 BPMS, FN and ASF developed the original concept of the trial and applied for
8 funding. FN, ASF, DH, CK, MF, SZ and BPMS developed the design and
9 methodology. BPMS and FN recruited all participating trial centers. FN, ASF, CK,
10 MF, SZ and BPMS performed initial statistical steps to develop the analysis plan. FN,
11 ASF, RK, SVA, ST, PP, AB and HN contributed to drafting the protocol. DH, CK, MF,
12 SZ, BB, FB, CB, IG, SG, PG, CG, JH, KL, LM, SM, DR, FS, DS, PP, TS and BPMS
13 contributed to the revision of the final protocol. All authors have read and approved of
14 the final manuscript.
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31 **517 Responsibilities**

32 Prof. Dr. Müller-Stich, Coordinating Investigator, is involved in every aspect of the
33 trial and has ultimate authority over study design, data collection, interpretation of
34 data, and oversight of the intermittent and final written reports. PD Dr. Nickel, MME,
35 is Deputy Coordinating Investigator. Alexander Studier-Fischer, MD, is Trial
36 Organizer. The Clinical Trial Committee consists of the Coordinating Investigator, the
37 Deputy Coordinating Investigator, and the Trial Organizer, originating from the
38 Division of Minimally Invasive and Robotic-assisted Surgery in the Department of
39 General, Visceral, and Transplantation Surgery at Heidelberg University Hospital. To
40 ensure objectivity, the third-party Institute of Medical Biometry (IMBI) is responsible
41 for data management, statistical planning, and analysis. Project management and
42 monitoring are handled by the SDGC (Study Center of the German Society of
43 Surgery), in Heidelberg. Additionally, a Data Safety and Monitoring Board (DSMB)
44 consisting of independent experts will advise on the continuation, modification, or
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3 531 termination of the trial and a steering committee will supervise the conduction of the
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5 532 trial and make decisions based on DSMB recommendations.
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10 534 **Data availability**

11
12 535 The full protocol, participant-level dataset, and statistical code will be made available
13
14 536 by the corresponding authors upon reasonable request.
15
16

17 537

18
19 538 **Conflict of interest statements**

20
21 539 The authors declare that they have no conflicts of interest or relevant financial ties to
22
23 540 disclose. Felix Nickel reports support for courses and travel from Johnson and
24
25 541 Johnson, Medtronic, Intuitive Surgical, Cambridge Medical Robotics, and KARL
26
27 542 STORZ as well as consultancy fees from KARL STORZ.
28
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28 717 **Figure 1 | Trial design flow chart.** * Intraoperative conversion from MIG to OG, e.g.,
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30 718 due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day
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32 719 (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

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37 721 **Figure 2 | Schematic lymphadenectomy.** Stations for lymphadenectomy (LAD) as
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39 722 required for total gastrectomy according to the cited Japanese classification.
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41 723 Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

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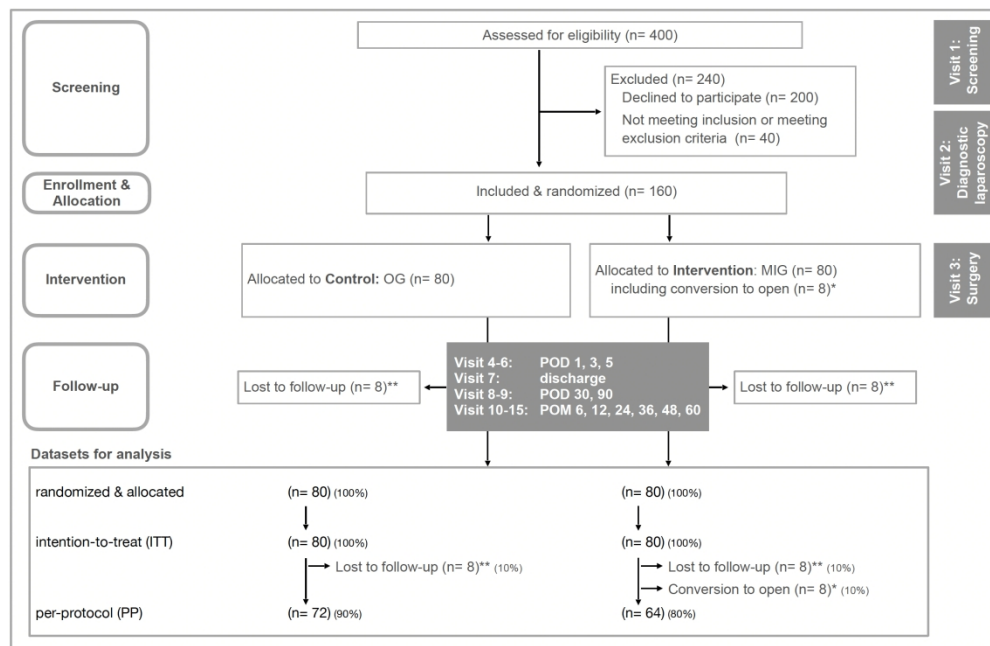


Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

473x306mm (144 x 144 DPI)

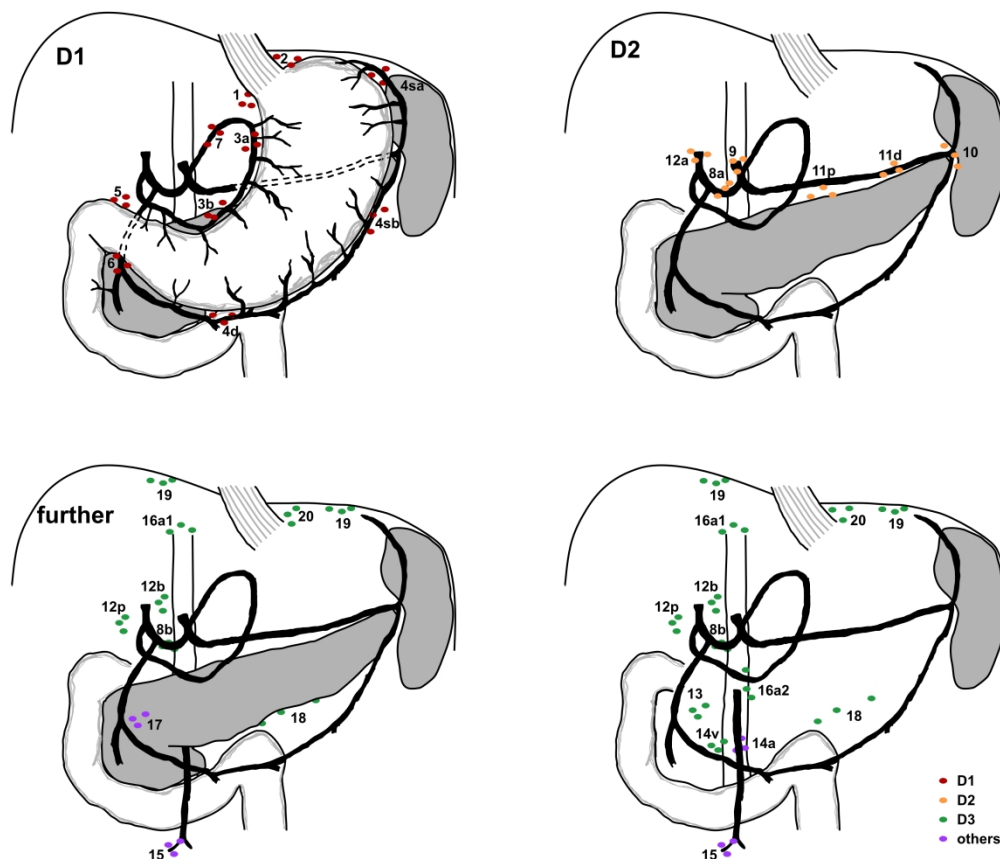


Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

750x636mm (118 x 118 DPI)

1 Appendices

3 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>

13 **Appendix 2: Documentation of lymphadenectomy during total gastrectomy**

Japanese classification of gastric carcinoma: 3rd English edition Gastric Cancer (2011) 14:101–112			D2 Lymphadenectomy completed lymphadenectomy = <input type="checkbox"/>
No.	Location		
1*	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.	<input type="checkbox"/>
2*	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	<input type="checkbox"/>
3a*	Left gastric vessel	Lesser curvature LNs along the branches of the left gastric artery	<input type="checkbox"/>
3b*	Right gastric vessel	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery	<input type="checkbox"/>
4sa*	Short gastric vessel	Left greater curvature LNs along the short gastric arteries (perigastric area)	<input type="checkbox"/>
4sb*	Left gastroepiploic	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	<input type="checkbox"/>
4d*	Right gastroepiploic	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	<input type="checkbox"/>
5*	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	<input type="checkbox"/>
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 pancreaticoduodenal vein	<input type="checkbox"/>
7*	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	<input type="checkbox"/>
8a**	Common hepatic artery	Anterosuperior LNs along the common hepatic artery	<input type="checkbox"/>
8b	Common hepatic artery	Posterior LNs along the common hepatic artery	<input type="checkbox"/>
9**	Celiac artery	Celiac artery LNs	<input type="checkbox"/>
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	(<input type="checkbox"/>)
11p**	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
13	Posterior surface of pancreatic head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla	<input type="checkbox"/>
14v	Superior mesenteric vein	LNs along the superior mesenteric vein	<input type="checkbox"/>
14a	Superior mesenteric artery	-	<input type="checkbox"/>
15	Middle colic vessels	LNs along the middle colic vessels	<input type="checkbox"/>
16a1	Aortic hiatus	Paraaortic LNs in the diaphragmatic aortic hiatus	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
17	Anterior surface of pancreatic head	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath	<input type="checkbox"/>
18	Inferior margin of pancreas	LNs along the inferior border of the pancreatic body	<input type="checkbox"/>
19	Infradiaphragmatic	Infradiaphragmatic LNs predominantly along the subphrenic artery	<input type="checkbox"/>
20	Esophageal hiatus of the diaphragm	Paraesophageal LNs in the diaphragmatic esophageal hiatus	<input type="checkbox"/>
110	Paraesophageal lower thorax	Paraesophageal LNs in the lower thorax	<input type="checkbox"/>
111	Supradiaphragmatic	Supradiaphragmatic LNs separate from the esophagus	<input type="checkbox"/>
112	Posterior mediastinal	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus	<input type="checkbox"/>

*required for D1 lymphadenectomy

**required for D2 lymphadenectomy

<input type="checkbox"/>	Not required for MEGA trial
<input type="checkbox"/>	Optional for MEGA trial
<input type="checkbox"/>	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 transfusions and total parenteral nutrition are 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 multiorgan dysfunction
V	Death of a patient

*brain hemorrhage, ischemic stroke, subarachnoidal bleeding, 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

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	5
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	5, 11, 19
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	
17			be collected. Reference to where list of study sites can be obtained	6
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	
23			administered	11, 12
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	
26			change in response to harms, participant request, or improving/worsening disease)	15
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	
29			(eg, drug tablet return, laboratory tests)	4, 16
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
32				11, 12
33				
34	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	
35			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
36			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
37			efficacy and harm outcomes is strongly recommended	11
38				
39				
40	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	
41			participants. A schematic diagram is highly recommended (see Figure)	Figure 1
42				
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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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence	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
11	generation			
12				
13				
14				
15				
16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	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
34	methods			
35				
36				
37				
38		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
39				
40				
41				
42				

1	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
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
9				
10		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
11				
12				
13				
14	Methods: Monitoring			
15				
16	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
17				
18				
19				
20				
21				
22		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
23				
24				
25	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
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
35				
36				
37	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
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24, 25
11				
12				
13	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
14				
15				
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
17				
18				
19				
20	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
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	24
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
32				
33				
34	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
35				
36				

*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”](https://creativecommons.org/licenses/by-nc-nd/3.0/) 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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Manuscripts

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3 1 **Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for**
4
5 2 **a multicenter randomized controlled trial (DRKS00025765)**
6

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45
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47 46

48
49 47 **Abstract**

50
51 48 **Introduction:**

52
53 49 The only curative treatment for most gastric cancer is radical gastrectomy with D2
54
55 50 lymphadenectomy (LAD). Minimally invasive total gastrectomy (MIG) aims to reduce
56
57 51 postoperative morbidity, but its use has not yet been widely established in Western
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3 52 countries. MEGA is the first Western multicenter randomized controlled trial (RCT) to
4
5 53 compare postoperative morbidity following MIG versus open total gastrectomy (OG).
6
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8 54

9
10 55 **Methods and analysis:**

11
12 56 This superiority multicenter RCT compares MIG (intervention) to OG (control) for
13
14 57 oncological total gastrectomy with D2 or D2+ LAD. Recruitment is expected to last for
15
16 58 2 years. Inclusion criteria comprise age between 18 and 84 years and planned total
17
18 59 gastrectomy after initial diagnosis of gastric carcinoma. Exclusion criteria include
19
20 60 ECOG performance status > 2 (**Appendix 1**), tumors requiring extended gastrectomy
21
22 61 or less than total gastrectomy, previous abdominal surgery or extensive adhesions
23
24 62 seriously complicating MIG, other active oncologic disease, advanced stages (T4 or
25
26 63 M1), emergency setting, and pregnancy.

27
28
29 64 The sample size was calculated at 80 participants per group. The primary endpoint is
30
31 65 30-day postoperative morbidity as measured by the Comprehensive Complications
32
33 66 Index (CCI). Secondary endpoints include postoperative morbidity and mortality,
34
35 67 adherence to a fast-track protocol, and patient-reported quality of life (QoL) scores
36
37 68 (QoR-15, EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADLs,
38
39 69 and BIS). Oncologic endpoints include rate of R0 resection, lymph node yield,
40
41 70 disease-free survival, and overall survival at 60-month follow-up.
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49 72 **Ethics and dissemination:**

50
51 73 Ethical approval has been received by the independent Ethics Committee of the
52
53 74 Medical Faculty, University of Heidelberg (S-816/2021) and will be received from
54
55 75 each responsible ethics committee for each individual participating center prior to
56
57 76 recruitment. Results will be published open access.
58
59
60

77

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2
3 78 **Trial registration:** German Clinical Trials Register DRKS00025765. Registered on
4
5 79 December 22nd, 2021.
6
7
8 80
9

10 81 **Keywords:** Minimally invasive gastrectomy, total gastrectomy, gastric cancer, Roux-
11
12 82 Y reconstruction, linear stapled anastomosis, circular stapled anastomosis,
13
14 83 randomized controlled trial, comprehensive complication index, fast-track, enhanced
15
16
17 84 recovery after surgery
18
19 85

20
21 86 **Strengths and limitations of this study**
22

- 23
24 87 - MEGA is the first Western multicenter RCT to specifically compare OG with
25
26 88 MIG in terms of postoperative morbidity using the comprehensive complication
27
28 89 index (CCI).
29
30 90 - Usage of the CCI as a comprehensive outcome measure allows for objective
31
32 91 comparisons with other trials.
33
34 92 - Differentiation between robotic and laparoscopic total gastrectomy will be
35
36 93 made in the explorative subgroup analysis only.
37
38 94 - High levels of standardization, intraoperative photo documentation, well-
39
40 95 powered group sizes, and risk-based monitoring by the Study Center of the
41
42 96 German Society of Surgery (SDGC) will guarantee objective data acquisition,
43
44 97 increase patients' adherence to the protocol, and ultimately lead to exceptional
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46 98 data quality.
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100 Introduction

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

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

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

1
2
3 126 Postoperative complications, however, are not only important for the immediate
4
5 127 postoperative course, which is usually secondary in relevance, but can also affect
6
7 128 long-term oncologic outcome [25-27]. In a study of 432 patients with curative
8
9 129 gastrectomy and D2 LAD for treatment of gastric cancer, the occurrence of
10
11 130 postoperative in-hospital complications was an independent predictor of worse 5-year
12
13 131 survival (22% vs. 40%). This can be perceived as an indication that postoperative
14
15 132 complications may lead to higher mortality in the long term [28]. Therefore, the trend
16
17 133 towards favoring minimally invasive gastrectomy (MIG) for gastric cancer is
18
19 134 increasing.
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26 136 **Methods and analysis**

27 137 **Setting**

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29
30 138 The MEGA trial is a prospective randomized, controlled, non-blinded, two-armed
31
32 139 multicenter surgical superiority trial with a confirmatory character. It includes 14
33
34 140 surgical centers in Germany and Switzerland and is coordinated by the Department
35
36 141 of General, Visceral and Transplantation Surgery at Heidelberg University Hospital,
37
38 142 in Germany. Recruitment is planned for 2 consecutive years. The study protocol was
39
40 143 accepted by the Independent Ethics Committee of the Medical Faculty, University of
41
42 144 Heidelberg (registration number S-816/2021) prior to recruitment. The trial was
43
44 145 registered at DRKS under the registration number DRKS00025765 on December
45
46 146 22nd, 2021 [29]. No secondary identifying numbers such as a Universal Trial Number
47
48 147 have been assigned. Recommendations of the SPIRIT (Standard Protocol Items:
49
50 148 Recommendations for Interventional Trials) checklist were followed [30].
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152 **Patient recruitment**

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

162 Inclusion criteria:

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

167 Exclusion criteria:

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

- 1
2
3 178 - Participation in another intervention trial that might interfere with the
4
5 179 intervention and/or outcome of this trial
6
7
8 180 - Pregnancy
9

10 181 Exclusion criteria previously or during staging laparoscopy:

- 11
12 182 - T4
13
14 183 - M1
15
16

17 184 Neoadjuvant chemotherapy does explicitly not contribute to inclusion or exclusion
18
19 185 criteria, but will of course be monitored. Inclusion takes place after the staging
20
21 186 laparoscopy, and patients will be randomized to the intervention arm (MIG) or the
22
23 187 control arm (OG) (**Figure 1**).
24
25

26 188

27 28 189 **Trial duration and schedule**

29
30 190 Recruitment is planned to take 24 months. The duration of the trial for each patient is
31
32 191 expected to be 1 month for the primary endpoint and 60 months for the secondary
33
34 192 endpoints with long-term follow-up. Consequently, the duration of data collection is
35
36 193 expected to be 25 months for the primary endpoint and 84 months for the secondary
37
38 194 endpoints [first-patient-in (FPI) to last-patient-out (LPO)]. FPI is planned for
39
40 195 September 2022 and Last-patient-in (LPI) is planned for September 2024. LPO is
41
42 196 consequently planned for September 2029. Trial analysis will take an additional 6
43
44 197 months. The actual overall duration or recruitment time may differ. Recruitment is
45
46 198 planned to be active until both arms contain at least 80 patients in the intention-to-
47
48 199 treat (ITT) dataset.
49
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53 200

54 55 201 **Trial visits**

56
57 202 Patients will be monitored intraoperatively, on postoperative days (POD) 1, 3, and 5,
58
59 203 and on the day of discharge. Follow-up will be conducted on POD 30, 90, and after
60

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

211
 212 **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 histopathology			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

213

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

229

230

231

232 **Primary endpoint**

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

243 **Secondary endpoints**

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

248 **Standardized therapy and trial interventions**

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

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

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

1
2
3 258 gastric vessels and limited LAD of station 2 and 4sa), extended gastrectomy, and
4
5 259 distal gastrectomy with Billroth I or II reconstruction are not allowed. Reconstruction
6
7 260 can be of any form including Roux-Y reconstruction, interposition, or pouch
8
9
10 261 reconstruction. Any other step of the procedure such as antibiotic prophylaxis,
11
12 262 placement of abdominal drains, and closure of the abdominal wall can be performed
13
14 263 according to in-house standards. D2 LAD is defined according to the Japanese
15
16 264 classification [35], with stations 1, 2, 3a, 3b, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and
17
18 265 12a obligatory for the MEGA trial (**Figure 2**). Station 10 is optional. Incomplete LAD
19
20 266 is not allowed and has to be documented as a protocol deviation.
21
22
23 267 Removal of further stations (8b, 12b, 12p, 13, 14v, 14a, 15, 16a1, 16a2, 16b1, 16b2,
24
25 268 17, 18, 19, 20, 110, 111, and 112) is allowed when deemed appropriate, e.g., in case
26
27 269 of assumed tumor invasion, and has to be documented as D2+.
28
29
30
31 270
32

33 271 **Postoperative management**

34
35 272 Postoperative management should be performed in a fast-track approach with short
36
37 273 durations until patient mobilization, drainage removal, and first oralization of food.
38
39 274 The patient should be extubated immediately after surgery and transferred to a
40
41 275 normal ward, if possible. Further specifications for the postoperative course will be
42
43 276 outlined in the provided standard operating procedure (SOP) for fast-track
44
45 277 gastrectomy. The last in-hospital trial visit takes place on the day of discharge.
46
47 278 Subsequent trial visits will be conducted via telephone. These will be questionnaire-
48
49 279 based and focus on CCI (until POD 90), quality of life, and oncologic outcome.
50
51
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53 280
54
55

56 281 **Randomization and blinding**

57
58 282 In order to ensure equal distribution of patient characteristics between both trial arms,
59
60 283 randomization will be performed using a web-based randomization tool

1
2
3 284 (www.randomizer.at). Randomization will take place following diagnostic laparoscopy
4
5 285 (Visit 2). The allocation pattern is masked, block-randomized with variable block
6
7 286 length, and stratified across centers. Due to the pragmatic character of the trial,
8
9
10 287 blinding of the surgeon is not feasible.
11

12 288

14 289 **Quality assurance and quality management**

16 290 **Clinical data monitoring**

17
18
19 291 Clinical monitoring will be performed by independent monitors at the Study Center of
20
21 292 the German Society of Surgery (SDGC). The monitoring strategy will comprise a
22
23 293 combination of centralized and onsite monitoring and will be described in a trial
24
25 294 specific monitoring plan. To confirm site selection, pre-study visits will be performed.
26
27
28 295 On-site monitoring will focus on patient informed consent, safety, and surgical
29
30 296 procedures as well as the correct recording and documentation of the primary and
31
32
33 297 secondary endpoints by source data verification (SDV).
34

35 298

37 299 **Surgical quality control**

38
39
40 300 Several steps are necessary to ensure and evaluate surgical quality:

- 41
42 301 1) Trial surgeons must have performed 20 surgeries in the respective approach
43
44 302 (OG, LAG, or RAG), depending on the trial arm they will contribute to.
- 45
46 303 2) Each trial surgeon must provide photographic or video documentation of a
47
48 304 former procedure.
- 49
50 305 3) Each trial surgeon has to provide photographic or video documentation of the
51
52 306 trial procedures, which will be assessed by an expert. This photographic or
53
54 307 video documentation is defined as follows:
 - 55
56 308 a. lymph node station 7 (left gastric artery) after dissection
 - 57
58 309 b. lymph node station 8a (common hepatic artery) after dissection

- 1
2
3 310 c. lymph node station 9 (celiac artery) after dissection
4
5 311 d. lymph node station 10 (splenic hilum) after dissection
6
7 312 e. lymph node station 11p (proximal splenic artery) after dissection
8
9 313 f. lymph node station 11d (distal splenic artery) after dissection
10
11 314 g. lymph node station 12a (hepatoduodenal ligament along the hepatic
12
13 315 artery) after dissection
14
15 316 h. duodenal stump
16
17 317 i. all anastomoses
18
19 318 j. incision for specimen retrieval in MIG
20
21
22
23
24
25

320 **Assessment of safety**

321 Since the primary endpoint is postoperative complications as measured by the CCI,
322 adverse (AE) and serious adverse events (SAE) are already captured and no
323 additional safety analysis will be performed (**Table 2**).
324

325 **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				
Grade IV complication		SAE		Major complication
Grade V complication				

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327

328 **Data management**

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

345

346

347 **Statistical methods**

348 **Sample size**

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

1
2
3 353 upper GI surgery [36], leading to an effect size of $d=0.5$. Based on a t-test with a two-
4
5 354 sided significance level of $\alpha=0.05$, a sample size of $n=128$ patients (64 per group)
6
7
8 355 has to be recruited to achieve a power of 80%. The primary endpoint will be analyzed
9
10 356 with a linear mixed regression model, which leads to equal or even increased power
11
12 357 when compared to a two-sided t-test. To compensate for drop-outs and patients lost
13
14 358 to follow-up, a further 20% of patients will be randomized, leading to a total sample
15
16
17 359 size of $n=160$ (80 per group; $80 \times 0,8 = 64.8$). The number of patients to be screened
18
19 360 ($n=400$ to be assessed for eligibility; $400 \times 0.5 \times 0.8 = 160$) was calculated with an
20
21 361 assumed 50% participation rate and an exclusion rate of 20%.

22
23
24 362 Randomized & allocated (n = 160; 80 per group)

25
26 363 Intention-to-treat dataset (n = 160; 80 per group)

27
28 364 Per-protocol dataset (n = 136; 72 and 64)

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31 365

32 33 366 **Statistical analysis**

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35 367 For the examination of the primary endpoint “postoperative morbidity measured with
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37 368 the CCI until POD 30,” the hypotheses to be assessed in the primary analysis are as
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39
40 369 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
41
42 370 control and intervention groups, respectively. The significance level is set to a two-
43
44 371 sided $\alpha=0.05$. Therefore, the primary endpoint will be examined using a linear mixed
45
46
47 372 model adjusting for the variables age and treatment group, as well as the surgical
48
49 373 center as a random effect (due to the stratified randomization and relatively large
50
51 374 number of centers in relation to the sample size, inclusion of center as a random
52
53 375 effect is recommended). Details of the primary model (e.g., handling of missing
54
55 376 values, sensitivity analyses) will be fully described in the statistical analysis plan.

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57
58 377 The number of patients included in the primary analysis is determined as the full
59
60 378 analysis set. Patients will be analyzed in the group they were randomized to

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2
3 379 (converted patients remain in their group). This reflects an analysis according to the
4
5 380 intention to treat (ITT) principle. Specific events (e.g., death) that can occur after
6
7 381 randomization will be handled within the primary endpoint definition, reflecting a
8
9 382 composite strategy [according to the ICH E9 (R1) addendum]. Other post
10
11 383 randomization events will not be considered. This choice reflects our treatment policy
12
13 384 approach.

14
15
16 385 In general, for the full analysis set, all baseline values and secondary outcomes will
17
18 386 be evaluated descriptively, with p-values reported alongside 95% confidence
19
20 387 intervals for the corresponding effects. Furthermore, secondary endpoints will be
21
22 388 evaluated descriptively, using appropriate regression models. Time-to-event
23
24 389 endpoints will be evaluated by methods of survival analysis including Kaplan-Meier
25
26 390 methods and Cox proportional hazards models. In addition, subgroup analyses
27
28 391 (including age, gender, tumor stage, tumor grade, histological tumor type, linear vs.
29
30 392 circular stapler for proximal anastomosis, linear vs. hand-sewn for distal
31
32 393 anastomosis, type of retrieval incision, and intraoperative conversion) will be carried
33
34 394 out. A detailed and comprehensive statistical analysis plan will be written shortly after
35
36 395 the first patient is recruited. All analyses will be performed using SAS version 9.4 or
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38 396 higher.

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47 399 **Discussion**

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49 400 We performed a systematic literature search prior to planning this trial and identified
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51 401 974 publications. Of those, 17 RCTs comparing LAG with OG [7, 37-55] and two
52
53 402 RCTs comparing RAG with OG [56, 57] were found to be relevant. The studies
54
55 403 showed comparable oncologic and short-term postoperative outcomes for MIG and
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57 404 OG. However, 16 of the 19 studies were conducted in China, Korea, and Japan [7,

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2
3 405 38-50, 56, 57]. These countries have a significantly higher incidence of gastric
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5 406 cancer, which consequently leads to significantly higher surgical volume and
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7 407 expertise among the participating centers [58]. In addition, the body constitution of
8
9 408 Asian patients is often different from that of Western patients, which limits the direct
10
11 409 transferability of study results. Also, the incidence of gastric cancer is lower in
12
13 410 Western populations and advanced disease stages are more frequently detected,
14
15 411 because screening is less common. Therefore, it is unclear whether these results
16
17 412 would be reproducible in a Western population.

18
19 413 Currently, there have only been three non-Asian RCTs directly comparing LAG and
20
21 414 OG. The first RCT, by Huscher et al., focused exclusively on distal gastrectomy, did
22
23 415 not define any specific primary or secondary endpoints, and included a total of 59
24
25 416 patients [37]. Due to the missing differentiation between primary and secondary
26
27 417 endpoints, the trial can be perceived as methodically limited and was most likely
28
29 418 underpowered. However, no significant difference was found in perioperative
30
31 419 outcome, oncologic outcome, or mortality [morbidity rates: 26.7% (LAG) and 27.6%
32
33 420 (OG), lymph nodes harvested: 30.0 ± 14.9 (LAG) and 33.4 ± 17.4 (OG), operative
34
35 421 mortality rates: 3.3% (LAG) and 6.7% (OG), 5-year survival rate: 54.8% (LAG) and
36
37 422 55.7% (OG)].

38
39 423 The only two currently existing relevant Western multicenter RCTs comparing open
40
41 424 versus minimally invasive oncologic total gastrectomy are the LOGICA trial [52, 53]
42
43 425 and the STOMACH trial [51, 54, 55], which were both published in 2021.

44
45 426 The LOGICA trial is a non-blinded, multicenter superiority trial with 227 patients with
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47 427 postoperative hospital stay as the primary endpoint. The study identified significant
48
49 428 differences regarding blood loss [150 ml (LAG) and 300 ml (OG), $p < 0.001$] and
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51 429 operating time [216 min (LAG) and 182 min (OG), $p < 0.001$], but no significant
52
53 430 differences in hospital stay ($p = 0.34$), postoperative complications [44% (LAG) and

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3 431 42% (OG), p=0.91], in-hospital mortality [4% (LAG) and 7% (OG), p=0.40], R0
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5 432 resections [95% (LAG) and 95% (OG), p=1.00], median lymph node yield [29 (LAG)
6
7 433 and 29 (OG), p=0.49], 1-year overall survival [76% (LAG) and 78% (OG), p=0.74],
8
9 434 and health-related quality of life [+1.5 (LAG) and +3.6 (OG) on a 1-100 scale].

10 435 The STOMACH trial is an observer-blinded, multicenter, non-inferiority trial with 96
11
12 436 patients following neoadjuvant chemotherapy with quality of oncological resection
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14 437 (radicality of surgery and number of retrieved lymph nodes) as the primary endpoint.
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16 438 Mean number of resected lymph nodes [41.7±16.1 (LAG) and 43.4±17.3 (OG),
17
18 439 p=0.612], number of R0 resections (44/47 (LAG) and 48/49 (OG), p=0.617], 1-year
19
20 440 survival (85.5% (LAG) and 90.4% (OG), p=0.701], postoperative complications
21
22 441 [16/47 (LAG) and 21/49 (OG), p=0.408], and postoperative QoL [measured with
23
24 442 EQ5D, EORTC-QLQ-C30, and EORTC-QLQ-STO22] were not significantly different.

25
26 443 In a regular setting with a diagnosed carcinoma, patients should usually be advised
27
28 444 to make their decision for or against a certain treatment option with regards to a
29
30 445 combination of highest expected overall survival and simultaneous conservation of
31
32 446 long-term QoL. Short-term postoperative complications should only be treated as
33
34 447 secondary deciding factors. However, if postoperative complications might impair
35
36 448 long-term QoL or even overall survival, they become equally relevant. In general,
37
38 449 postoperative complications can have negative effects on QoL or overall survival;
39
40 450 however, this is much more the case for gastric cancer, as time to continuation of
41
42 451 peroperative chemotherapy can be prolonged and the prognosis therefore worsened.

43
44 452 The STOMACH trial provides evidence that MIG is non-inferior to OG in terms of
45
46 453 oncologic quality of resection, which is a necessary requirement for the MEGA trial,
47
48 454 as postoperative morbidity and complications can only be decisive factors in the case
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50 455 of oncological non-inferiority for an oncological resection with curative intent.
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3 456 While both the STOMACH and LOGICA trials suggest that postoperative
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5 457 complications might not be significantly different between both groups, a premature
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7 458 confirmative statement must be avoided as complications have only been
8
9 459 investigated as secondary endpoints so far. Consequently, a multicenter RCT
10
11 460 comparing total MIG and OG for gastric cancer in terms of postoperative
12
13 461 complications is needed to decide whether MIG should be established as the new
14
15 462 standard treatment for resectable gastric cancer in Europe.

16
17 463 The MEGA trial has strict quality control measures and will be conducted in line with
18
19 464 all relevant guidelines. Therefore, it will provide the highest level of evidence on this
20
21 465 very relevant clinical research question.
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27 28 467 **Ethics and dissemination**

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30 468 The MEGA trial conforms to the Declaration of Helsinki [59]. The Independent Ethics
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32 469 Committee of the Medical Faculty, University of Heidelberg, approved the MEGA trial
33
34 470 protocol (registration number S-816/2021). For other trial centers, recruitment will
35
36 471 only be initiated after receiving approval from their respective local ethics
37
38 472 committees. Study objectives and procedures will be communicated clearly to all
39
40 473 qualifying patients and written informed consent will be obtained from those who
41
42 474 agree to participate. Results will be presented at scientific meetings and published in
43
44 475 international peer-reviewed journals. Summaries will be provided to the funders of
45
46 476 the study and results will be published in open-access journals.
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52 53 478 **Patient and Public Involvement**

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55 479 Patients are involved in the design and conduction of this trial. Priority of the research
56
57 480 question, outcome measures, and recruitment methods were discussed with patients
58
59 481 during the initial planning stage. Patients have stated an uneventful postoperative
60

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

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

488

489 **Modification of the protocol**

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

493

494 **Additional file**

495 Additional file 1: SPIRIT checklist.

496

497 **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

498

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502 Surgery at Heidelberg University Hospital for its assistance in coordinating this RCT.
503 We would also like to thank the other centers that have committed to participating in
504 the trial.

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45 506 **Funding statement**

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8 (BMBF), funding number 01KG2029. All trial aspects will be performed independently
9
10 508 from the funding source, including trial design and conduction, analysis, and
11
12 509 interpretation of data, as well as submission of the report for publication. The funder
13
14 510 does not have any influence in study design or collection, management, analysis,
15
16 511 and interpretation of data.
17
18 512
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23 513

24 514 **Authors' contributions**

25
26 515 BPMS, FN and ASF developed the original concept of the trial and applied for
27
28 516 funding. FN, ASF, DH, CK, MF, SZ and BPMS developed the design and
29
30 517 methodology. BPMS and FN recruited all participating trial centers. FN, ASF, CK,
31
32 518 MF, SZ and BPMS performed initial statistical steps to develop the analysis plan. FN,
33
34 519 ASF, RK, SVA, ST, PP, AB and HN contributed to drafting the protocol. DH, CK, MF,
35
36 520 SZ, BB, FB, CB, IG, SG, PG, CG, JH, KL, LM, SM, DR, FS, DS, PP, TS and BPMS
37
38 521 contributed to the revision of the final protocol. All authors have read and approved of
39
40 522 the final manuscript.
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49 525 **Responsibilities**

50
51 526 Prof. Dr. Müller-Stich, Coordinating Investigator, is involved in every aspect of the
52
53 527 trial and has ultimate authority over study design, data collection, interpretation of
54
55 528 data, and oversight of the intermittent and final written reports. PD Dr. Nickel, MME,
56
57 529 is Deputy Coordinating Investigator. Alexander Studier-Fischer, MD, is Trial
58
59 530 Organizer. The Clinical Trial Committee consists of the Coordinating Investigator, the
60

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3 531 Deputy Coordinating Investigator, and the Trial Organizer, originating from the
4
5 532 Division of Minimally Invasive and Robotic-assisted Surgery in the Department of
6
7 533 General, Visceral, and Transplantation Surgery at Heidelberg University Hospital. To
8
9
10 534 ensure objectivity, the third-party Institute of Medical Biometry (IMBI) is responsible
11
12 535 for data management, statistical planning, and analysis. Project management and
13
14 536 monitoring are handled by the SDGC (Study Center of the German Society of
15
16 537 Surgery), in Heidelberg. Additionally, a Data Safety and Monitoring Board (DSMB)
17
18 538 consisting of independent experts will advise on the continuation, modification, or
19
20 539 termination of the trial and a steering committee will supervise the conduction of the
21
22 540 trial and make decisions based on DSMB recommendations.
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26 541

27 28 542 **Data availability**

29
30 543 The full protocol, results and statistical code will be made available by the
31
32 544 corresponding authors upon reasonable request.
33
34

35 545

36 37 546 **Conflict of interest statements**

38
39 547 The authors declare that they have no conflicts of interest or relevant financial ties to
40
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42
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44
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46
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48

49 551

50 51 552 **References**

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3 727 **Figure 1 | Trial design flow chart.** * Intraoperative conversion from MIG to OG, e.g.,
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5 728 due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day
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7 729 (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).
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12 731 **Figure 2 | Schematic lymphadenectomy.** Stations for lymphadenectomy (LAD) as
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14 732 required for total gastrectomy according to the cited Japanese classification.
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16 733 Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.
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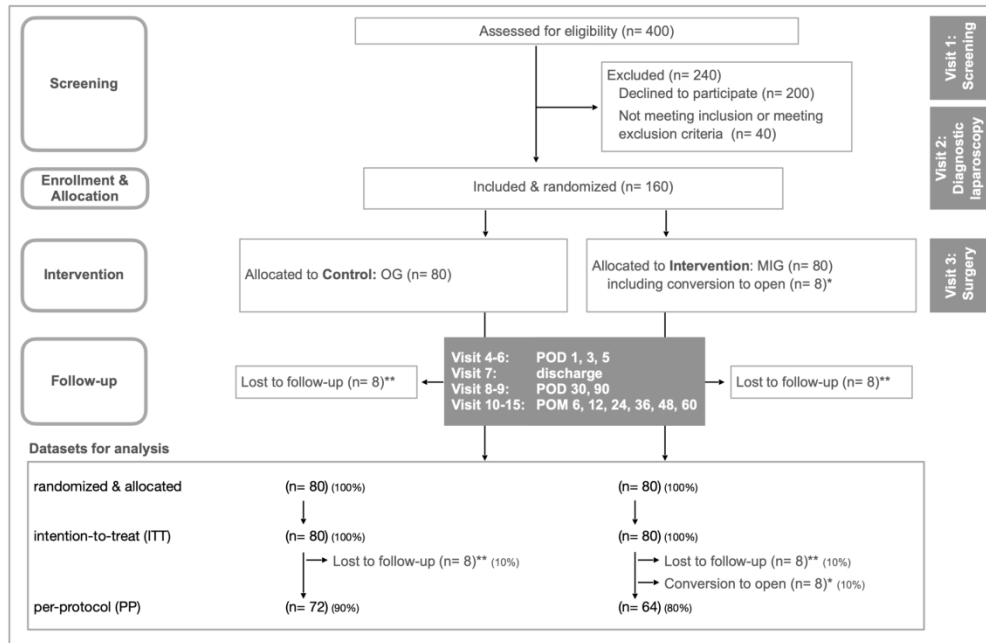


Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

200x129mm (300 x 300 DPI)

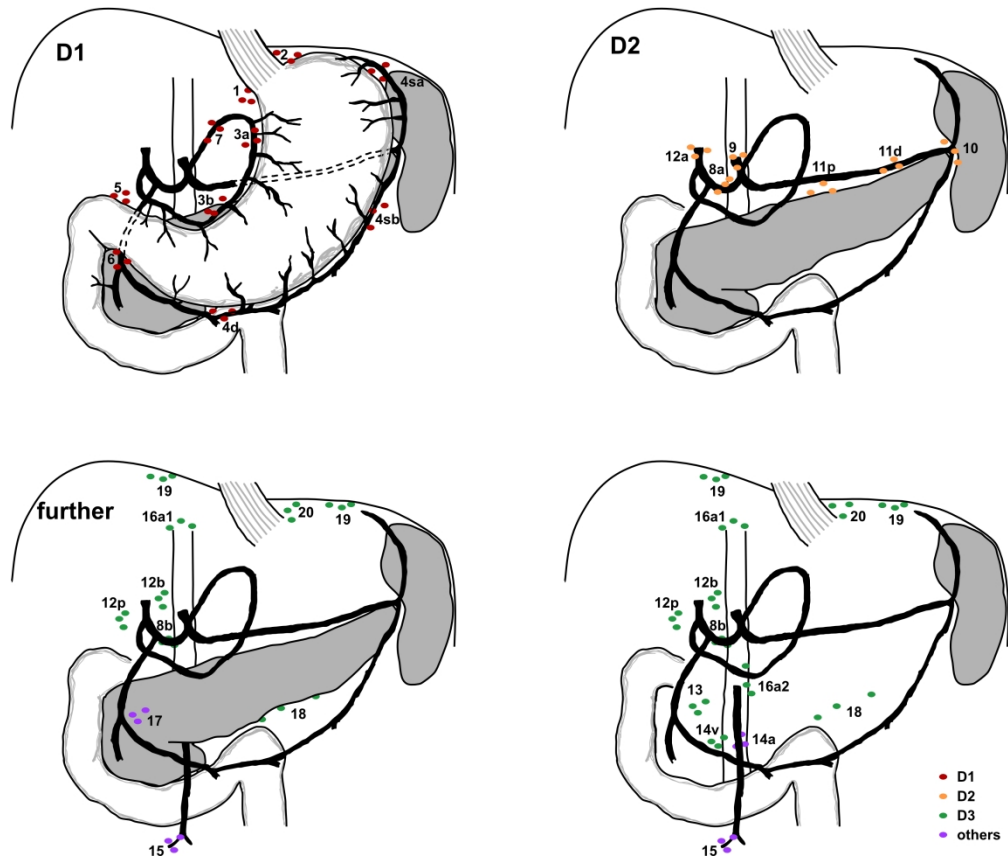


Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

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.

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

13 Appendix 2: Documentation of lymphadenectomy during total gastrectomy

Japanese classification of gastric carcinoma: 3rd English edition Gastric Cancer (2011) 14:101–112			D2 Lymphadenectomy completed lymphadenectomy = <input type="checkbox"/>
No.	Location		
1*	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.	<input type="checkbox"/>
2*	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	<input type="checkbox"/>
3a*	Left gastric vessel	Lesser curvature LNs along the branches of the left gastric artery	<input type="checkbox"/>
3b*	Right gastric vessel	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery	<input type="checkbox"/>
4sa*	Short gastric vessel	Left greater curvature LNs along the short gastric arteries (perigastric area)	<input type="checkbox"/>
4sb*	Left gastroepiploic	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	<input type="checkbox"/>
4d*	Right gastroepiploic	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	<input type="checkbox"/>
5*	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	<input type="checkbox"/>
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 pancreaticoduodenal vein	<input type="checkbox"/>
7*	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	<input type="checkbox"/>
8a**	Common hepatic artery	Anterosuperior LNs along the common hepatic artery	<input type="checkbox"/>
8b	Common hepatic artery	Posterior LNs along the common hepatic artery	<input type="checkbox"/>
9**	Celiac artery	Celiac artery LNs	<input type="checkbox"/>
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	(<input type="checkbox"/>)
11p**	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
13	Posterior surface of pancreatic head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla	<input type="checkbox"/>
14v	Superior mesenteric vein	LNs along the superior mesenteric vein	<input type="checkbox"/>
14a	Superior mesenteric artery	-	<input type="checkbox"/>
15	Middle colic vessels	LNs along the middle colic vessels	<input type="checkbox"/>
16a1	Aortic hiatus	Paraaortic LNs in the diaphragmatic aortic hiatus	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
17	Anterior surface of pancreatic head	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath	<input type="checkbox"/>
18	Inferior margin of pancreas	LNs along the inferior border of the pancreatic body	<input type="checkbox"/>
19	Infradiaphragmatic	Infradiaphragmatic LNs predominantly along the subphrenic artery	<input type="checkbox"/>
20	Esophageal hiatus of the diaphragm	Paraesophageal LNs in the diaphragmatic esophageal hiatus	<input type="checkbox"/>
110	Paraesophageal lower thorax	Paraesophageal LNs in the lower thorax	<input type="checkbox"/>
111	Supradiaphragmatic	Supradiaphragmatic LNs separate from the esophagus	<input type="checkbox"/>
112	Posterior mediastinal	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus	<input type="checkbox"/>

*required for D1 lymphadenectomy

**required for D2 lymphadenectomy

<input type="checkbox"/>	Not required for MEGA trial
<input type="checkbox"/>	Optional for MEGA trial
<input type="checkbox"/>	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 transfusions and total parenteral nutrition are 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 multiorgan dysfunction
V	Death of a patient

*brain hemorrhage, ischemic stroke, subarachnoidal bleeding, 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

1 **Introduction**

2

3 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

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6 6b Explanation for choice of comparators 5

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8 Objectives 7 Specific objectives or hypotheses 5, 11, 19

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10 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

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14 **Methods: Participants, interventions, and outcomes**

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16 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

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19 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

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 11, 12

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25 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

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) 4, 16

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 11, 12

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34 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

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40 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

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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
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
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6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence	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
11	generation			
12				
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15				
16	Allocation	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
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
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22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
28				
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31	Methods: Data collection, management, and analysis			
32				
33	Data collection	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
34	methods			
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39		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
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1	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
2				
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4				
5	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
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
9				
10		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
11				
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14	Methods: Monitoring			
15				
16	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
17				
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22		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
23				
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25	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
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
35				
36				
37	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
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
2				
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
5				
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7	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
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24, 25
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13	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
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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
18				
19				
20	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
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	24
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
32				
33				
34	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
35				
36				

37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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Minimally invasive versus open total GAstrectomy (MEGA): Study protocol for a multicenter randomized controlled trial (DRKS00025765)

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3 1 **Minimally invasivE versus open total GAstrectomy (MEGA): Study protocol for a**
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5 2 **multicenter randomized controlled trial (DRKS00025765)**
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40
41
42 44

43
44 45 **Abstract**

45
46 46 **Introduction:**

47
48 47 The only curative treatment for most gastric cancer is radical gastrectomy with D2
49
50 48 lymphadenectomy (LAD). Minimally invasive total gastrectomy (MIG) aims to reduce
51
52 49 postoperative morbidity, but its use has not yet been widely established in Western
53
54 50 countries. MEGA is the first Western multicenter randomized controlled trial (RCT) to
55
56 51 compare postoperative morbidity following MIG versus open total gastrectomy (OG).
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3 **53 Methods and analysis:**
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5
6 54 This superiority multicenter RCT compares MIG (intervention) to OG (control) for
7
8 55 oncological total gastrectomy with D2 or D2+ LAD. Recruitment is expected to last for
9
10 56 2 years. Inclusion criteria comprise age between 18 and 84 years and planned total
11
12 57 gastrectomy after initial diagnosis of gastric carcinoma. Exclusion criteria include
13
14 58 ECOG performance status > 2 (**Appendix 1**), tumors requiring extended gastrectomy
15
16 59 or less than total gastrectomy, previous abdominal surgery or extensive adhesions
17
18 60 seriously complicating MIG, other active oncologic disease, advanced stages (T4 or
19
20 61 M1), emergency setting, and pregnancy.
21
22

23
24 62 The sample size was calculated at 80 participants per group. The primary endpoint is
25
26 63 30-day postoperative morbidity as measured by the Comprehensive Complications
27
28 64 Index (CCI). Secondary endpoints include postoperative morbidity and mortality,
29
30 65 adherence to a fast-track protocol, and patient-reported quality of life (QoL) scores
31
32 66 (QoR-15, EUROQOL EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-STO22, ADLs, and
33
34 67 BIS). Oncologic endpoints include rate of R0 resection, lymph node yield, disease-free
35
36 68 survival, and overall survival at 60-month follow-up.
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41
42 **70 Ethics and dissemination:**
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44
45 71 Ethical approval has been received by the independent Ethics Committee of the
46
47 72 Medical Faculty, University of Heidelberg (S-816/2021) and will be received from each
48
49 73 responsible ethics committee for each individual participating center prior to
50
51 74 recruitment. Results will be published open access.
52
53

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55
56 76 **Trial registration:** German Clinical Trials Register DRKS00025765. Registered on
57
58 77 December 22nd, 2021.
59
60

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2
3 79 **Keywords:** Minimally invasive gastrectomy, total gastrectomy, gastric cancer, Roux-Y
4
5 80 reconstruction, linear stapled anastomosis, circular stapled anastomosis, randomized
6
7 81 controlled trial, comprehensive complication index, fast-track, enhanced recovery after
8
9 82 surgery
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13
14 84 **Strengths and limitations of this study**

- 15
16
17 85 - MEGA is the first Western multicenter RCT to specifically compare OG with MIG
18
19 86 in terms of postoperative morbidity using the comprehensive complication index
20
21 87 (CCI).
22
23
24 88 - Usage of the CCI as a comprehensive outcome measure allows for objective
25
26 89 comparisons with other trials.
27
28 90 - Differentiation between robotic and laparoscopic total gastrectomy will be made
29
30 91 in the explorative subgroup analysis only.
31
32
33 92 - High levels of standardization, intraoperative photo documentation, well-
34
35 93 powered group sizes, and risk-based monitoring by the Study Center of the
36
37 94 German Society of Surgery (SDGC) will guarantee objective data acquisition,
38
39 95 increase patients' adherence to the protocol, and ultimately lead to exceptional
40
41 96 data quality.
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98 Introduction

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

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

112 The current gold standard is open gastrectomy (OG) with D2 lymphadenectomy (LAD)
113 (**Appendix 2**), but its highly invasive nature leads to potentially high complication rates,
114 especially in elderly and obese patients. These frequent postoperative complications
115 result in higher mortality, lower QoL, a longer hospital stay, and thus a higher burden
116 on the health care system [6, 19]. In other fields of visceral surgery, such as
117 appendectomy, cholecystectomy, obesity surgery, and esophagectomy, minimally
118 invasive surgery has already replaced the open approach as the standard of care [7,
119 20-22]. Several randomized controlled trials (RCT) have demonstrated reduced
120 postoperative complications following minimally invasive surgery compared to the
121 open approach. This finding is due to the procedure's resulting smaller wounds,
122 reduced operative trauma, lower blood loss, shorter hospital stay, and faster
123 rehabilitation time [22-24].

1
2
3 124 Postoperative complications, however, are not only important for the immediate
4
5 125 postoperative course, which is usually secondary in relevance, but can also affect long-
6
7 126 term oncologic outcome [25-27]. In a study of 432 patients with curative gastrectomy
8
9 127 and D2 LAD for treatment of gastric cancer, the occurrence of postoperative in-hospital
10
11 128 complications was an independent predictor of worse 5-year survival (22% vs. 40%).
12
13
14 129 This can be perceived as an indication that postoperative complications may lead to
15
16
17 130 higher mortality in the long term [28]. Therefore, the trend towards favoring minimally
18
19 131 invasive gastrectomy (MIG) for gastric cancer is increasing.
20
21
22 132

23 133 **Methods and analysis**

24 134 **Setting**

25
26 135 The MEGA trial is a prospective randomized, controlled, non-blinded, two-armed
27
28 136 multicenter surgical superiority trial with a confirmatory character. It includes 14
29
30
31 137 surgical centers in Germany and Switzerland and is coordinated by the Department of
32
33
34 138 General, Visceral and Transplantation Surgery at Heidelberg University Hospital, in
35
36
37 139 Germany. Recruitment is planned for 2 consecutive years. The study protocol was
38
39
40 140 accepted by the Independent Ethics Committee of the Medical Faculty, University of
41
42 141 Heidelberg (registration number S-816/2021) prior to recruitment. The trial was
43
44 142 registered at DRKS under the registration number DRKS00025765 on December 22nd,
45
46
47 143 2021 [29]. No secondary identifying numbers such as a Universal Trial Number have
48
49 144 been assigned. Recommendations of the SPIRIT (Standard Protocol Items:
50
51 145 Recommendations for Interventional Trials) checklist were followed [30].
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53
54 146

55 147 **Patient recruitment**

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57
58 148 Recruitment is planned to take place at 14 surgical centers in Germany and
59
60 149 Switzerland. Certain eligibility criteria have to be met by the participating centers and

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2
3 150 surgeons in order to eliminate bias from inexperience or learning curves. Therefore,
4
5 151 hospitals need to have a case load of ≥ 20 gastrectomies per year, and every trial
6
7 152 surgeon has to provide evidence of at least 20 previously performed surgeries of the
8
9 153 respective surgical procedure/s he or she wants to contribute [OG, laparoscopic
10 154 gastrectomy (LAG) or robotic-assisted gastrectomy (RAG)]. Eligible patients will be
11
12 155 screened consecutively to eliminate selection bias and will receive diagnostic staging
13
14 156 laparoscopy prior to randomization.

15 157 Inclusion criteria:

- 16 158 - Age between 18 and 84 years
17
18 159 - Planned total gastrectomy after first diagnosis of gastric carcinoma
19
20 160 - Ability of patient to understand character and consequences of the trial
21
22 161 - Written informed consent

23 162 Exclusion criteria:

- 24 163 - ECOG performance status > 2
25
26 164 - Planned extended gastrectomy or less than total gastrectomy (e.g.,
27
28 165 adenocarcinoma of the esophagogastric junction (AEG) I and AEG II, or distal
29
30 166 gastric tumors of an intestinal subtype)
31
32 167 - Previous gastric surgery or extensive adhesions seriously complicating MIG
33
34 168 - Other active oncologic disease or history of cancer limiting prognosis in
35
36 169 comparison to the gastric cancer
37
38 170 - Emergency setting
39
40 171 - Language barriers rendering the patient unable to fill out patient-reported
41
42 172 outcome questionnaires
43
44 173 - Participation in another intervention trial that might interfere with the
45
46 174 intervention and/or outcome of this trial
47
48 175 - Pregnancy

1
2
3 176 Exclusion criteria previously or during staging laparoscopy:
4

5 177 - T4
6

7 178 - M1
8
9

10 179 Neoadjuvant chemotherapy does explicitly not contribute to inclusion or exclusion
11
12 180 criteria, but will of course be monitored. Inclusion takes place after the staging
13
14 181 laparoscopy, and patients will be randomized to the intervention arm (MIG) or the
15
16 182 control arm (OG) (**Figure 1**).
17
18

19 183
20

21 184 **Trial duration and schedule**

22
23 185 Recruitment is planned to take 24 months. The duration of the trial for each patient is
24
25 186 expected to be 1 month for the primary endpoint and 60 months for the secondary
26
27 187 endpoints with long-term follow-up. Consequently, the duration of data collection is
28
29 188 expected to be 25 months for the primary endpoint and 84 months for the secondary
30
31 189 endpoints [first-patient-in (FPI) to last-patient-out (LPO)]. FPI is planned for September
32
33 190 2022 and Last-patient-in (LPI) is planned for September 2024. LPO is consequently
34
35 191 planned for September 2029. Trial analysis will take an additional 6 months. The actual
36
37 192 overall duration or recruitment time may differ. Recruitment is planned to be active until
38
39 193 both arms contain at least 80 patients in the intention-to-treat (ITT) dataset.
40
41
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45 194

46 195 **Trial visits**

47
48 196 Patients will be monitored intraoperatively, on postoperative days (POD) 1, 3, and 5,
49
50 197 and on the day of discharge. Follow-up will be conducted on POD 30, 90, and after
51
52 198 postoperative months (POM) 6, 12, 24, 36, 48, and 60 (**Table 1**). Demographic and
53
54 199 baseline clinical data, intraoperative findings, and postoperative results will be
55
56 200 recorded. During follow-up, patients will complete established and validated
57
58 201 questionnaires. To enhance participant retention and to avoid loss to follow-up,
59
60

	Tumor histopathology****			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

207

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

224

225

226 **Primary endpoint**

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

237 **Secondary endpoints**

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

244 **Standardized therapy and trial interventions**

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

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

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

1
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3 252 invasive approach, the remaining treatment is identical in both groups. Any other form
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5 253 of gastrectomy, explicitly conventional subtotal gastrectomy (preserved short gastric
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7 254 vessels and limited LAD of station 2 and 4sa), extended gastrectomy, and distal
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9
10 255 gastrectomy with Billroth I or II reconstruction are not allowed. Reconstruction can be
11
12 256 of any form including Roux-Y reconstruction, interposition, or pouch reconstruction.
13
14 257 Any other step of the procedure such as antibiotic prophylaxis, placement of abdominal
15
16
17 258 drains, and closure of the abdominal wall can be performed according to in-house
18
19 259 standards. D2 LAD is defined according to the Japanese classification [35], with
20
21 260 stations 1, 2, 3a, 3b, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a obligatory for the
22
23
24 261 MEGA trial (**Figure 2**). Station 10 is optional. Incomplete LAD is not allowed and has
25
26 262 to be documented as a protocol deviation.

27
28 263 Removal of further stations (8b, 12b, 12p, 13, 14v, 14a, 15, 16a1, 16a2, 16b1, 16b2,
29
30 264 17, 18, 19, 20, 110, 111, and 112) is allowed when deemed appropriate, e.g., in case
31
32
33 265 of assumed tumor invasion, and has to be documented as D2+.

34
35 266

36 37 267 **Postoperative management**

38
39 268 Postoperative management should be performed in a fast-track approach with short
40
41
42 269 durations until patient mobilization, drainage removal, and first oralization of food. The
43
44
45 270 patient should be extubated immediately after surgery and transferred to a normal
46
47 271 ward, if possible. Further specifications for the postoperative course will be outlined in
48
49 272 the provided standard operating procedure (SOP) for fast-track gastrectomy. The last
50
51 273 in-hospital trial visit takes place on the day of discharge. Subsequent trial visits will be
52
53
54 274 conducted via telephone. These will be questionnaire-based and focus on CCI (until
55
56 275 POD 90), quality of life, and oncologic outcome.

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278 **Randomization and blinding**

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

286 **Quality assurance and quality management**

287 **Clinical data monitoring**

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

296 **Surgical quality control**

297 Several steps are necessary to ensure and evaluate surgical quality:

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

- 1
2
3 302 3) Each trial surgeon has to provide photographic or video documentation of the
4
5 303 trial procedures, which will be assessed by an expert. This photographic or
6
7 304 video documentation is defined as follows:
8
9
10 305 a. lymph node station 7 (left gastric artery) after dissection
11
12 306 b. lymph node station 8a (common hepatic artery) after dissection
13
14 307 c. lymph node station 9 (celiac artery) after dissection
15
16 308 d. lymph node station 10 (splenic hilum) after dissection
17
18 309 e. lymph node station 11p (proximal splenic artery) after dissection
19
20 310 f. lymph node station 11d (distal splenic artery) after dissection
21
22 311 g. lymph node station 12a (hepatoduodenal ligament along the hepatic
23
24 312 artery) after dissection
25
26 313 h. duodenal stump
27
28 314 i. all anastomoses
29
30 315 j. incision for specimen retrieval in MIG
31
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317 **Assessment of safety**

40 318 Since the primary endpoint is postoperative complications as measured by the CCI,
41
42 319 adverse (AE) and serious adverse events (SAE) are already captured and no
43
44 320 additional safety analysis will be performed (**Table 2**).
45
46
47
48

49 322 **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				
Grade IV complication		SAE		Major complication
Grade V complication				

323

324

325 **Data management**

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

341

342

343

344

345 **Statistical methods**

346 **Sample size**

347 The sample size calculation is based on the primary endpoint “postoperative morbidity
348 as measured with the CCI until POD 30.” A decrease of the CCI by 10 points between
349 OG and MIG is considered relevant by patients and clinicians, and a conservative
350 standard deviation of 20 is assumed based on existing literature for upper GI surgery
351 [36], leading to an effect size of $d=0.5$. Based on a t-test with a two-sided significance
352 level of $\alpha=0.05$, a sample size of $n=128$ patients (64 per group) has to be recruited to
353 achieve a power of 80%. The primary endpoint will be analyzed with a linear mixed
354 regression model, which leads to equal or even increased power when compared to a
355 two-sided t-test. To compensate for drop-outs and patients lost to follow-up, a further
356 20% of patients will be randomized, leading to a total sample size of $n=160$ (80 per
357 group; $80 \times 0,8 = 64.8$). The number of patients to be screened ($n=400$ to be assessed
358 for eligibility; $400 \times 0.5 \times 0.8 = 160$) was calculated with an assumed 50% participation
359 rate and an exclusion rate of 20%.

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

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

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

363

364 **Statistical analysis**

365 For the examination of the primary endpoint “postoperative morbidity measured with
366 the CCI until POD 30,” the hypotheses to be assessed in the primary analysis are as
367 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
368 and intervention groups, respectively. The significance level is set to a two-sided
369 $\alpha=0.05$. Therefore, the primary endpoint will be examined using a linear mixed model
370 adjusting for the variables age and treatment group, as well as the surgical center as

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2
3 371 a random effect (due to the stratified randomization and relatively large number of
4
5 372 centers in relation to the sample size, inclusion of center as a random effect is
6
7 373 recommended). Details of the primary model (e.g., handling of missing values,
8
9 374 sensitivity analyses) will be fully described in the statistical analysis plan.

10 375 The number of patients included in the primary analysis is determined as the full
11
12 376 analysis set. Patients will be analyzed in the group they were randomized to (converted
13
14 377 patients remain in their group). This reflects an analysis according to the intention to
15
16 378 treat (ITT) principle. Specific events (e.g., death) that can occur after randomization
17
18 379 will be handled within the primary endpoint definition, reflecting a composite strategy
19
20 380 [according to the ICH E9 (R1) addendum]. Other post randomization events will not be
21
22 381 considered. This choice reflects our treatment policy approach.

23
24 382 In general, for the full analysis set, all baseline values and secondary outcomes will be
25
26 383 evaluated descriptively, with p-values reported alongside 95% confidence intervals for
27
28 384 the corresponding effects. Furthermore, secondary endpoints will be evaluated
29
30 385 descriptively, using appropriate regression models. Time-to-event endpoints will be
31
32 386 evaluated by methods of survival analysis including Kaplan-Meier methods and Cox
33
34 387 proportional hazards models. In addition, subgroup analyses (including age, gender,
35
36 388 tumor stage, tumor grade, histological tumor type, linear vs. circular stapler for proximal
37
38 389 anastomosis, linear vs. hand-sewn for distal anastomosis, type of retrieval incision,
39
40 390 and intraoperative conversion) will be carried out. A detailed and comprehensive
41
42 391 statistical analysis plan will be written shortly after the first patient is recruited. All
43
44 392 analyses will be performed using SAS version 9.4 or higher.

45
46 393

47 394 **Discussion**

48 395 We performed a systematic literature search prior to planning this trial and identified
49
50 396 974 publications. Of those, 17 RCTs comparing LAG with OG [7, 37-55] and two RCTs

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2
3 397 comparing RAG with OG [56, 57] were found to be relevant. The studies showed
4
5 398 comparable oncologic and short-term postoperative outcomes for MIG and OG.
6
7 399 However, 16 of the 19 studies were conducted in China, Korea, and Japan [7, 38-50,
8
9 400 56, 57]. These countries have a significantly higher incidence of gastric cancer, which
10
11 401 consequently leads to significantly higher surgical volume and expertise among the
12
13 402 participating centers [58]. In addition, the body constitution of Asian patients is often
14
15 403 different from that of Western patients, which limits the direct transferability of study
16
17 404 results. Also, the incidence of gastric cancer is lower in Western populations and
18
19 405 advanced disease stages are more frequently detected, because screening is less
20
21 406 common. Therefore, it is unclear whether these results would be reproducible in a
22
23 407 Western population.

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27
28 408 Currently, there have only been three non-Asian RCTs directly comparing LAG and
29
30 409 OG. The first RCT, by Huscher et al., focused exclusively on distal gastrectomy, did
31
32 410 not define any specific primary or secondary endpoints, and included a total of 59
33
34 411 patients [37]. Due to the missing differentiation between primary and secondary
35
36 412 endpoints, the trial can be perceived as methodically limited and was most likely
37
38 413 underpowered. However, no significant difference was found in perioperative outcome,
39
40 414 oncologic outcome, or mortality [morbidity rates: 26.7% (LAG) and 27.6% (OG), lymph
41
42 415 nodes harvested: 30.0 ± 14.9 (LAG) and 33.4 ± 17.4 (OG), operative mortality rates:
43
44 416 3.3% (LG) and 6.7% (OG), 5-year survival rate: 54.8% (LAG) and 55.7% (OG)].

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48
49 417 The only two currently existing relevant Western multicenter RCTs comparing open
50
51 418 versus minimally invasive oncologic total gastrectomy are the LOGICA trial [52, 53]
52
53 419 and the STOMACH trial [51, 54, 55], which were both published in 2021.

54
55
56 420 The LOGICA trial is a non-blinded, multicenter superiority trial with 227 patients with
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58 421 postoperative hospital stay as the primary endpoint. The study identified significant
59
60 422 differences regarding blood loss [150 ml (LAG) and 300 ml (OG), $p < 0.001$] and

1
2
3 423 operating time [216 min (LAG) and 182 min (OG), $p < 0.001$], but no significant
4
5 424 differences in hospital stay ($p = 0.34$), postoperative complications [44% (LAG) and 42%
6
7 425 (OG), $p = 0.91$], in-hospital mortality [4% (LAG) and 7% (OG), $p = 0.40$], R0 resections
8
9 426 [95% (LAG) and 95% (OG), $p = 1.00$], median lymph node yield [29 (LAG) and 29 (OG),
10
11 427 $p = 0.49$], 1-year overall survival [76% (LAG) and 78% (OG), $p = 0.74$], and health-related
12
13 428 quality of life [+1.5 (LAG) and +3.6 (OG) on a 1-100 scale].

14
15
16
17 429 The STOMACH trial is an observer-blinded, multicenter, non-inferiority trial with 96
18
19 430 patients following neoadjuvant chemotherapy with quality of oncological resection
20
21 431 (radicality of surgery and number of retrieved lymph nodes) as the primary endpoint.
22
23 432 Mean number of resected lymph nodes [41.7±16.1 (LAG) and 43.4±17.3 (OG),
24
25 433 $p = 0.612$], number of R0 resections (44/47 (LAG) and 48/49 (OG), $p = 0.617$], 1-year
26
27 434 survival (85.5% (LAG) and 90.4% (OG), $p = 0.701$], postoperative complications [16/47
28
29 435 (LAG) and 21/49 (OG), $p = 0.408$], and postoperative QoL [measured with EQ5D,
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31 436 EORTC-QLQ-C30, and EORTC-QLQ-STO22] were not significantly different.

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35 437 In a regular setting with a diagnosed carcinoma, patients should usually be advised to
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37 438 make their decision for or against a certain treatment option with regards to a
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39 439 combination of highest expected overall survival and simultaneous conservation of
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41 440 long-term QoL. Short-term postoperative complications should only be treated as
42
43 441 secondary deciding factors. However, if postoperative complications might impair long-
44
45 442 term QoL or even overall survival, they become equally relevant. In general,
46
47 443 postoperative complications can have negative effects on QoL or overall survival;
48
49 444 however, this is much more the case for gastric cancer, as time to continuation of
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51 445 peroperative chemotherapy can be prolonged and the prognosis therefore worsened.
52
53 446 The STOMACH trial provides evidence that MIG is non-inferior to OG in terms of
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55 447 oncologic quality of resection, which is a necessary requirement for the MEGA trial, as
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3 448 postoperative morbidity and complications can only be decisive factors in the case of
4
5 449 oncological non-inferiority for an oncological resection with curative intent.

6
7 450 While both the STOMACH and LOGICA trials suggest that postoperative complications
8
9 451 might not be significantly different between both groups, a premature confirmative
10
11 452 statement must be avoided as complications have only been investigated as
12
13 453 secondary endpoints so far. Consequently, a multicenter RCT comparing total MIG
14
15 454 and OG for gastric cancer in terms of postoperative complications is needed to decide
16
17 455 whether MIG should be established as the new standard treatment for resectable
18
19 456 gastric cancer in Europe.

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23 457 The MEGA trial has strict quality control measures and will be conducted in line with
24
25 458 all relevant guidelines. Therefore, it will provide the highest level of evidence on this
26
27 459 very relevant clinical research question.

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31 460

32 33 461 **Ethics and dissemination**

34
35 462 The MEGA trial conforms to the Declaration of Helsinki [59]. The Independent Ethics
36
37 463 Committee of the Medical Faculty, University of Heidelberg, approved the MEGA trial
38
39 464 protocol (registration number S-816/2021). For other trial centers, recruitment will only
40
41 465 be initiated after receiving approval from their respective local ethics committees.

42
43 466 **Additional file 1** provides the SPIRIT checklist for interventional trials [60].

44
45
46 467 Study objectives and procedures will be communicated clearly to all qualifying patients
47
48 468 and written informed consent will be obtained from those who agree to participate.

49
50 469 Results will be presented at scientific meetings and published in international peer-
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52 470 reviewed journals. Summaries will be provided to the funders of the study and results
53
54 471 will be published in open-access journals.

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3 474 **Patient and Public Involvement**
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5 475 Patients are involved in the design and conduction of this trial. Priority of the research
6
7 476 question, outcome measures, and recruitment methods were discussed with patients
8
9 477 during the initial planning stage. Patients have stated an uneventful postoperative
10
11 478 course as a very notable feature, and every possible intervention contributing to lower
12
13 479 postoperative morbidity was rated to be of great importance.
14

15
16 480 The chairman of one of Germany's largest patient self-aid groups concerning minimally
17
18 481 invasive surgery (SHG Frankfurt Sachsenhausen) will be a member of the data safety
19
20 482 and monitoring board as a patient representative. Therefore, this study will continue to
21
22 483 take the patient's perspective into account.
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28 485 **Modification of the protocol**
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30 486 The current protocol version (1.2) will be utilized during trial initiation. In case of
31
32 487 protocol amendments, these will be submitted to the relevant ethics committees for
33
34 488 approval.
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40 490 **Additional file**

41
42 491 **Additional file 1:** SPIRIT checklist.
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45 492

46
47 493 **Abbreviations**
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49 494	ADLs	Activities of daily living
50 51 495	AE	Adverse event
52 53 496	AEG	Adenocarcinoma of esophagogastric junction
54 55 497	ASA	American Society of Anesthesiologists Classification
56 57 498	BIS	Body Image Scale
58 59 499	BMBF	Federal Ministry of Education and Research
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2			
3	500	CA	Carbohydrate antigen
4			
5	501	CEA	Carcinoembryonic antigen
6			
7	502	CCI	Comprehensive Complication Index according to Clavien-
8			
9			
10	503		Dindo classification
11			
12	504	eCRF	Electronic Case Report Forms
13			
14	505	CRP	C-reactive protein
15			
16			
17	506	DALY	Disability-adjusted life years
18			
19	507	DRKS	Deutsches Register Klinischer Studien (German Clinical
20			
21			
22	508		Trials Register)
23			
24	509	DSMB	Data Safety and Monitoring Board
25			
26	510	EORTC QLQ-C30	European Organisation for Research and Treatment of
27			
28	511		Cancer Quality of Life Questionnaire Core 30
29			
30	512	EORTC QLQ-STO22	European Organisation for Research and Treatment of
31			
32			
33	513		Cancer Quality of Life Questionnaire for Gastric Cancer
34			
35	514	EUROQOL EQ-5D-5L	EuroQol Group Questionnaire for Quality of Life with 5
36			
37			
38	515		dimensions and 5 levels
39			
40	516	FPI	First-patient-in
41			
42	517	FU	Follow-up
43			
44	518	GCP	Good Clinical Practice
45			
46			
47	519	ICH	International Council for Harmonisation of Technical
48			
49	520		Requirements for Pharmaceuticals for Human Use
50			
51	521	ICU	Intermediate / intensive care unit
52			
53			
54	522	IMBI	Institute of Medical Biometry
55			
56	523	ITT	Intention-to-treat
57			
58	524	LAG	Laparoscopic gastrectomy
59			
60	525	LPI	Last-patient-in

1			
2			
3	526	LPO	Last-patient-out
4			
5	527	MIG	Minimally invasive gastrectomy
6			
7	528	OG	Open gastrectomy
8			
9			
10	529	POD	Postoperative day
11			
12	530	POM	Postoperative month
13			
14	531	PRO	Patient-reported outcome
15			
16	532	QoL	Quality of life
17			
18	533	QoR-15	Quality of Recovery 15 questionnaire
19			
20	534	RAG	Robotic-assisted gastrectomy
21			
22	535	RCT	Randomized controlled trial
23			
24	536	SAE	Serious adverse event
25			
26	537	SDGC	Study Center of the German Society of Surgery
27			
28	538	SDV	Source data verification
29			
30	539	SOP	Standard operating procedure
31			
32	540	V	Visit
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40	541		
41			
42	542	Acknowledgements	
43			
44	543	The authors gratefully acknowledge the Study Center of the German Society of	
45	544	Surgery (SDGC) in the Department of General, Visceral, and Transplantation Surgery	
46	545	at Heidelberg University Hospital for its assistance in coordinating this RCT. We would	
47	546	also like to thank the other centers that have committed to participating in the trial.	
48			
49	547		
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52			
53	548	Funding statement	
54			
55	549	The MEGA trial is funded by the Federal Ministry of Education and Research (BMBF),	
56	550	funding number 01KG2029. All trial aspects will be performed independently from the	
57			
58	551	funding source, including trial design and conduction, analysis, and interpretation of	
59			
60			

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3 552 data, as well as submission of the report for publication. The funder does not have any
4
5 553 influence in study design or collection, management, analysis, and interpretation of
6
7 554 data.
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9

10 555

11 556 **Authors' contributions**

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13
14 557 FN and ASF have contributed equally as first authors. BPMS, FN and ASF developed
15
16 558 the original concept of the trial and applied for funding. FN, ASF, DH, CK, MF, SZ and
17
18 559 BPMS developed the design and methodology. BPMS and FN recruited all
19
20 560 participating trial centers. FN, ASF, CK, MF, SZ and BPMS performed initial statistical
21
22 561 steps to develop the analysis plan. FN, ASF, RK, SVA, ST, PP, AB and HN contributed
23
24 562 to drafting the protocol. DH, CK, MF, SZ, BB, FB, CB, IG, SG, PG, CG, JH, KL, LM,
25
26 563 SM, DR, FS, DS, PP, TS and BPMS contributed to the revision of the final protocol. All
27
28 564 authors have read and approved of the final manuscript.
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33 565

34 566 **Responsibilities**

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36
37 567 Prof. Dr. Müller-Stich, Coordinating Investigator, is involved in every aspect of the trial
38
39 568 and has ultimate authority over study design, data collection, interpretation of data,
40
41 569 and oversight of the intermittent and final written reports. PD Dr. Nickel, MME, is
42
43 570 Deputy Coordinating Investigator. Alexander Studier-Fischer, MD, is Trial Organizer.
44
45 571 The Clinical Trial Committee consists of the Coordinating Investigator, the Deputy
46
47 572 Coordinating Investigator, and the Trial Organizer, originating from the Division of
48
49 573 Minimally Invasive and Robotic-assisted Surgery in the Department of General,
50
51 574 Visceral, and Transplantation Surgery at Heidelberg University Hospital. To ensure
52
53 575 objectivity, the third-party Institute of Medical Biometry (IMBI) is responsible for data
54
55 576 management, statistical planning, and analysis. Project management and monitoring
56
57 577 are handled by the SDGC (Study Center of the German Society of Surgery), in
58
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3 578 Heidelberg. Additionally, a Data Safety and Monitoring Board (DSMB) consisting of
4
5 579 independent experts will advise on the continuation, modification, or termination of the
6
7 580 trial and a steering committee will supervise the conduction of the trial and make
8
9 581 decisions based on DSMB recommendations.
10
11

12 582

14 583 **Data availability**

16 584 The full protocol, results and statistical code will be made available by the
17
18 585 corresponding authors upon reasonable request.
19
20

21 586

23 587 **Conflict of interest statements**

25 588 The authors declare that they have no conflicts of interest or relevant financial ties to
26
27 589 disclose. Felix Nickel reports support for courses and travel from Johnson and
28
29 590 Johnson, Medtronic, Intuitive Surgical, Cambridge Medical Robotics, and KARL
30
31 591 STORZ as well as consultancy fees from KARL STORZ.
32
33

34 592

36 593 **References**

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33 768 **Figure 1 | Trial design flow chart.** * Intraoperative conversion from MIG to OG, e.g.,
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35 769 due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day
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37 770 (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).
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42 772 **Figure 2 | Schematic lymphadenectomy.** Stations for lymphadenectomy (LAD) as
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44 773 required for total gastrectomy according to the cited Japanese classification. Schemes
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46 774 are separated into D1 LAD, D2 LAD, and further lymph node stations.
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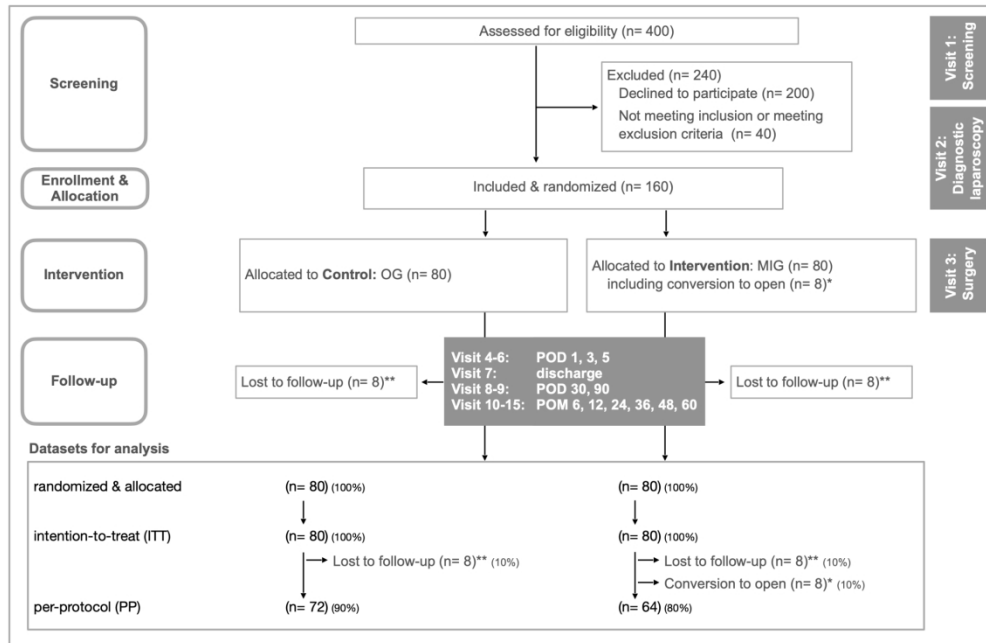


Figure 1 | Trial design flow chart. * Intraoperative conversion from MIG to OG, e.g., due to bleeding. ** Lost to follow-up over 30 postoperative days. Postoperative day (POD), postoperative month (POM), intention-to-treat (ITT), per-protocol (PP).

200x129mm (300 x 300 DPI)

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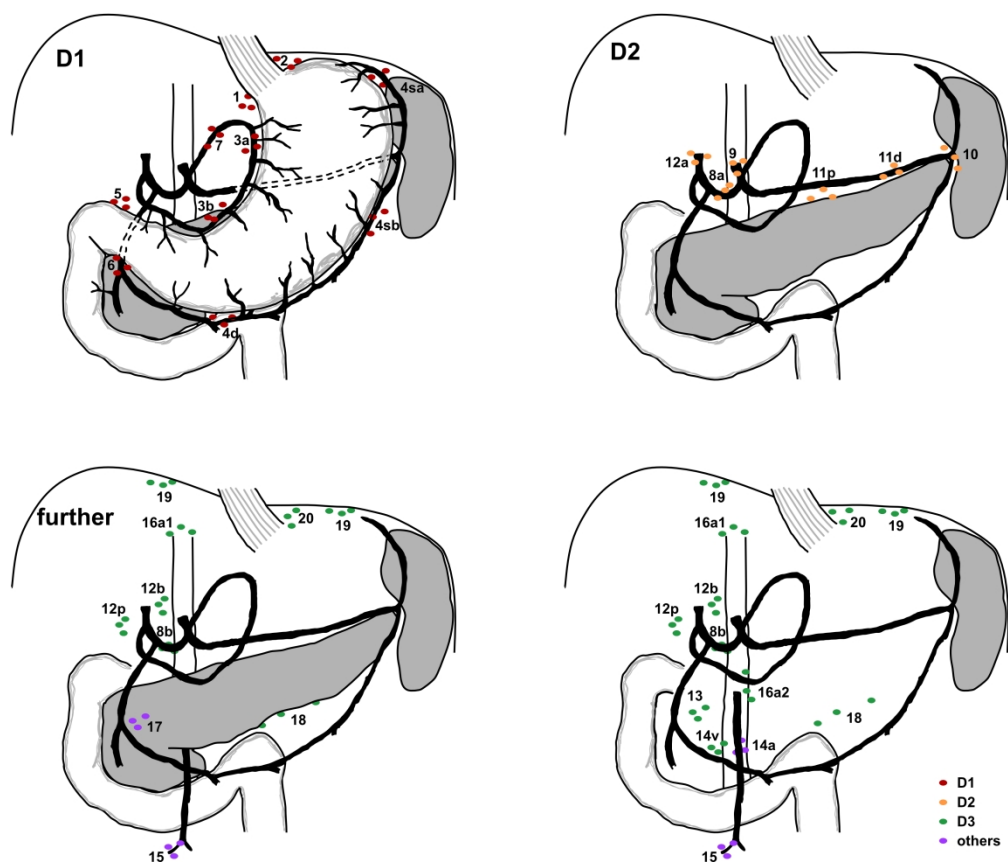


Figure 2 | Schematic lymphadenectomy. Stations for lymphadenectomy (LAD) as required for total gastrectomy according to the cited Japanese classification. Schemes are separated into D1 LAD, D2 LAD, and further lymph node stations.

295x250mm (300 x 300 DPI)

1 Appendices

2 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]

No.	Location		D2 Lymphadenectomy completed lymphadenectomy = <input type="checkbox"/>
1*	Right paracardial	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery.	<input type="checkbox"/>
2*	Left paracardial	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery	<input type="checkbox"/>
3a*	Left gastric vessel	Lesser curvature LNs along the branches of the left gastric artery	<input type="checkbox"/>
3b*	Right gastric vessel	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery	<input type="checkbox"/>
4sa*	Short gastric vessel	Left greater curvature LNs along the short gastric arteries (perigastric area)	<input type="checkbox"/>
4sb*	Left gastroepiploic	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)	<input type="checkbox"/>
4d*	Right gastroepiploic	Right greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery	<input type="checkbox"/>
5*	Suprapyloric	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery	<input type="checkbox"/>
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 pancreaticoduodenal vein	<input type="checkbox"/>
7*	Left gastric artery	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch	<input type="checkbox"/>
8a**	Common hepatic artery	Anterosuperior LNs along the common hepatic artery	<input type="checkbox"/>
8b	Common hepatic artery	Posterior LNs along the common hepatic artery	<input type="checkbox"/>
9**	Celiac artery	Celiac artery LNs	<input type="checkbox"/>
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	<input type="checkbox"/>
11p**	Proximal splenic artery	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
13	Posterior surface of pancreatic head	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla	<input type="checkbox"/>
14v	Superior mesenteric vein	LNs along the superior mesenteric vein	<input type="checkbox"/>
14a	Superior mesenteric artery	-	<input type="checkbox"/>
15	Middle colic vessels	LNs along the middle colic vessels	<input type="checkbox"/>
16a1	Aortic hiatus	Paraaortic LNs in the diaphragmatic aortic hiatus	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
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	<input type="checkbox"/>
17	Anterior surface of pancreatic head	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath	<input type="checkbox"/>
18	Inferior margin of pancreas	LNs along the inferior border of the pancreatic body	<input type="checkbox"/>
19	Infradiaphragmatic	Infradiaphragmatic LNs predominantly along the subphrenic artery	<input type="checkbox"/>
20	Esophageal hiatus of the diaphragm	Paraesophageal LNs in the diaphragmatic esophageal hiatus	<input type="checkbox"/>
110	Paraesophageal lower thorax	Paraesophageal LNs in the lower thorax	<input type="checkbox"/>
111	Supradiaphragmatic	Supradiaphragmatic LNs separate from the esophagus	<input type="checkbox"/>
112	Posterior mediastinal	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus	<input type="checkbox"/>

*required for D1 lymphadenectomy

**required for D2 lymphadenectomy

<input type="checkbox"/>	Not required for MEGA trial
<input type="checkbox"/>	Optional for MEGA trial
<input type="checkbox"/>	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 transfusions and total parenteral nutrition are 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 multiorgan dysfunction
V	Death of a patient

*brain hemorrhage, ischemic stroke, subarachnoidal 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 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

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	5
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	5, 11, 19
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	
17			will be collected. Reference to where list of study sites can be obtained	6
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	
23			administered	11 - 12
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	
26			change in response to harms, participant request, or improving/worsening disease)	15
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	
29			(eg, drug tablet return, laboratory tests)	4, 16
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
32				11 - 12
33				
34	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	
35			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation	
36			(eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
37			efficacy and harm outcomes is strongly recommended	11
38				
39				
40	Participant	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits	
41	timeline		for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
42				

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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16
5				

7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

10	Sequence	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
11	generation			
12				
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16	Allocation	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
17	concealment			
18	mechanism			
19				
20				
21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
22				
23				
24	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
25	(masking)			
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6, 13
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

33	Data collection	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
34	methods			
35				
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39		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
40				
41				
42				

1	Data	19	Plans for data entry, coding, security, and storage, including any related processes to promote data	
2	management		quality (eg, double data entry; range checks for data values). Reference to where details of data	16 - 17
3			management procedures can be found, if not in the protocol	
4				
5	Statistical	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of	
6	methods		the statistical analysis plan can be found, if not in the protocol	16 - 17
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and	
11			any statistical methods to handle missing data (eg, multiple imputation)	17
12				
13				
14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement	
17			of whether it is independent from the sponsor and competing interests; and reference to where further	
18			details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is	24 - 25
19			not needed	
20				
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these	
23			interim results and make the final decision to terminate the trial	16, 17
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	
26			events and other unintended effects of trial interventions or trial conduct	14 - 15
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	
29			from investigators and the sponsor	24 - 25
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	
35	approval			20
36				
37	Protocol	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,	
38	amendments		analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,	
39			regulators)	21 - 22
40				
41				
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1	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
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8 - 9
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23 - 25
11				
12				
13	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
14				
15				
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
17				
18				
19				
20	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
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	24
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached
32				
33				
34	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
35				
36				

*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”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.