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Hepatic venous pressure gradient guided laparoscopic versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030960
Article Type:	Protocol
Date Submitted by the Author:	09-Apr-2019
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Keywords:	Hepatology < INTERNAL MEDICINE, Hepatobiliary surgery < SURGERY, Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY

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TITLE PAGE**Title:**

Hepatic venous pressure gradient guided laparoscopic versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

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Keywords:

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4 31 Hepatic venous pressure gradient, variceal rebleeding, randomized controlled trial

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7 33 **Word count:**

8
9 34 2935 words
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For peer review only

35 **ABSTRACT**

36 **Introduction**

37 Gastroesophageal variceal bleeding is one of the most common and severe complications
38 with high mortality in cirrhotic patients who developed portal hypertension. Hepatic venous
39 pressure gradient (HVPG) is a globally recommended golden standard for portal pressure
40 assessment and an HVPG ≥ 16 mmHg indicates a higher risk of death and rebleeding. This
41 study aims to compare the effectiveness and safety of laparoscopic therapy plus propranolol
42 and endoscopic therapy plus propranolol for variceal rebleeding in cirrhotic patients with
43 HVPG between 16 and 20 mmHg.

45 **Methods and analysis**

46 This is a multicenter, randomized, controlled, clinical trial. Participants will be 1:1 assigned
47 randomly into either laparoscopic or endoscopic groups. 40 participants whose transjugular
48 HVPG lies between 16 and 20 mmHg with a history of gastroesophageal variceal bleeding
49 will be recruited from three sites in China. Participants will receive either endoscopic therapy
50 plus propranolol or laparoscopic therapy plus propranolol. The primary outcome measure will
51 be occurrence of gastroesophageal variceal rebleeding. Secondary outcome measures will
52 include: overall survival, occurrence of hepatocellular carcinoma, occurrence of venous
53 thrombosis, quality of life and tolerability of treatment. Outcome measures will be evaluated
54 at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks and 60 weeks. Multivariate COX
55 regression model will be introduced for analyses of occurrence data and Kaplan-Meier
56 analysis with Log-rank Test for inter-group comparison. Student's t test, Wilcoxon rank sum
57 test, chi-squared test or Fisher's exact test will be applied for analyses of other outcomes.

59 **Ethics and dissemination**

60 Ethical approval was obtained from all three participating sites. Primary and secondary
61 outcome data will be submitted for publication in peer-reviewed journals and widely
62 disseminated.

64 **Trial registration number**

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4 65 NCT03783065; Pre-results.
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8 67 **Trial status**

9 68 Recruitment for this study started on December 2018 while the first participant was
10
11 69 randomized on January 2019. Recruitment is estimated to stop on October 2019.
12
13 70

14
15 71 **Strengths and limitations of this study**

- 16
17 72 ■ This study is the first trial that concentrates on the best management on prevention of
18
19 73 rebleeding for cirrhotic patients with HVPG between 16 and 20 mmHg.
20
21 74 ■ This trial is the first one to compare the effectiveness of laparoscopic therapy plus
22
23 75 propranolol to endoscopic therapy plus propranolol recommended by international
24
25 76 guidelines.
26
27 77 ■ The surgical procedure involved in this study employs minimally invasive laparoscopy
28
29 78 instead of conventional operation, minimizing trauma and complications.
30
31 79 ■ Limitations of this trial include the lack of accessible data for sample size estimation,
32
33 80 potential influence in applicability in other countries due to etiological differences and
34
35 81 the relatively short follow-up period.
36
37 82

38
39 83 **INTRODUCTION**

40 84 Cirrhosis is the result of multiple liver diseases and is accounted as a dynamic process.¹
41
42 85 Portal hypertension is a vital event in the natural progression of cirrhosis that is responsible
43
44 86 for decompensating events like gastroesophageal variceal bleeding, ascites and hepatic
45
46 87 encephalopathy. Gastroesophageal varices could be seen in about 50% of cirrhotic patients
47
48 88 and those who developed variceal bleeding face a mortality of 5-20%.^{2,3} Thus, the
49
50 89 stratification and applicable secondary prevention for patients with high risk is of great
51
52 90 clinical significance.
53
54 91 Hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic
55
56 92 venous pressure and free hepatic venous pressure.⁴ Eliminating the influence of abdominal
57
58 93 pressure, HVPG is currently the most widely accepted reflection of portal pressure, and has
59
60 94 been demonstrated to have good performances in risk stratification^{3,5} and predicting the

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4 95 response to treatments.^{6 7} An HVPG over 12 mmHg suggests the occurrence of
5
6 96 gastroesophageal variceal bleeding.⁸ Patients with HVPG over 16mmHg face higher risk of
7
8 97 death⁸⁻¹¹ and rebleeding,⁶ while an HVPG over 20 mmHg predicts failure to control
9
10 98 bleeding, early rebleeding, and death due to acute variceal hemorrhage.^{12 13} Currently,
11
12 99 international guidelines recommend endoscopic therapy combined with non-selective
13
14 100 beta-blockers to be the first-line therapy of secondary prevention for cirrhotic patients with
15
16 101 gastroesophageal variceal bleeding.^{3 5} Nevertheless, patients with high HVPG still suffer
17
18 102 from risk of treatment failure. Recent years, early TIPS is recommended as a better choice for
19
20 103 patients with HVPG ≥ 20 mmHg,^{14 15} while there still lack a strong evidence to determine the
21
22 104 best method for patients with HVPG between 16 and 20 mmHg.

23 105 Splenectomy and pericardial devascularisation, first performed by Hassab,^{16 17} is a promising
24
25 106 surgical procedure for cirrhotic patients with gastroesophageal variceal bleeding, especially
26
27 107 for those with hypersplenism. With the rapid advance of laparoscopic techniques, since the
28
29 108 first laparoscopic splenectomy was reported in 1991,¹⁸ post-operational complications which
30
31 109 used to be a major concern of Hassab's operation have been cut down to a great extent due to
32
33 110 less invasive procedures.¹⁹ Laparoscopic therapy has been widely accepted for variceal
34
35 111 bleeding in Asia-pacific countries, where the predominant etiology of cirrhosis is hepatitis B
36
37 112 virus infection²⁰ combined with very high occurrence of hypersplenism.²¹ However, there
38
39 113 haven't been any prospective trials comparing the effectiveness of laparoscopic therapy plus
40
41 114 propranolol to the internationally recommended first-line therapy. Also, the precise indication
42
43 115 to perform laparoscopic therapy is still unclear.

44 116 In this study, the outcomes of recruited patients whose HVPG lies within 16 and 20 mmHg
45
46 117 will be compared to explore the optimized management. Taking into consideration the
47
48 118 preferred performance of HVPG in risk stratification and the lack of prospective study in
49
50 119 long-term performance of laparoscopic therapy, this trial will be meaningful for both the
51
52 120 extension of HVPG risk stratification and the clarification of laparoscopic therapy indication.

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54 121

55 122 **Objectives**

56 123 The aim of this trial is to assess the effectiveness and safety of laparoscopic therapy plus
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58 124 propranolol as first-line therapy of variceal rebleeding prevention for cirrhotic patients whose

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4 125 transjugular HVPG lies between 16 and 20 mmHg with gastroesophageal variceal bleeding
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6 126 compared with endoscopic therapy plus propranolol. The primary outcome will be variceal
7
8 127 rebleeding. Secondary outcomes include: death, hepatocellular carcinoma, venous
9
10 128 thrombosis, quality of life and tolerability of treatment. We hypothesise that:
11
12 129 1. Compared to endoscopic therapy plus propranolol, laparoscopic therapy plus propranolol is
13
14 130 more effective in reducing variceal rebleeding.
15
16 131 2. Participants receiving laparoscopic splenectomy and pericardial devascularisation plus
17
18 132 propranolol show non-inferior overall survival and lower occurrence of hepatocellular
19
20 133 carcinoma over those who receiving endoscopic therapy plus propranolol.
21
22 134 3. The occurrence of venous thrombosis, QOL and KPS scores are without significant
23
24 135 difference between two groups.
25
26 136

137 **METHODS AND ANALYSIS**

138 **Study design**

139 This study is a multicenter, prospective, randomized controlled clinical trial. The overview of
140 the study process is illustrated in Figure 1. After screened for eligibility, the participants will
141 be randomly allocated to laparoscopic group or endoscopic group. After the operative
142 intervention, there will be a 60-week follow-up period. All tests and interventions will be
143 performed at three involved centers in China: (1) Shunde Hospital, Southern Medical
144 University, (2) Xingtai People's Hospital and (3) The First Hospital of Lanzhou University.
145

146 **Eligibility criteria**

147 **Inclusion criteria**

148 Eligible participants should be (a) aged between 18 to 75 years, (b) clinically and/or
149 pathologically diagnosed cirrhosis with portal hypertension, (c) with a history of
150 gastroesophageal variceal bleeding (melena, hematemesis etc.), without receiving endoscopic
151 treatment, (d) screened with transjugular HVPG between 16 and 20 mmHg after
152 hospitalization, (e) with ECOG score ≤ 2 and KPS score ≥ 60 during screening, (f) assessed
153 to be Child-Pugh class A or B and (g) voluntarily participate in the study and able to provide
154 written informed consent and able to understand and willing to comply with the requirements

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8 157 Exclusion criteria

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10 158 Those who conforms to any of the following would be excluded: (a) pregnant or
11
12 159 breastfeeding women, (b) with prior known or suspected malignancy (hepatocellular
13
14 160 carcinoma, cholangiocarcinoma etc.), (c) with limited coagulation situation (Quick < 50%,
15
16 161 PTT > 50 sec, thrombocyte count < 50000 / μ l or disturbed thrombocyte function), (d) with
17
18 162 massive ascites, (e) assessed to be Child-Pugh class C, (f) refusing or inadequate for
19
20 163 transjugular HVPG measurement and (g) with other situations whose existence judged
21
22 164 inadequate for participation by the investigators.

23
24 165

25 166 **Recruitment**

26
27 167 Recruitment has started in December 2018 and will continue until the intent sample size has
28
29 168 been reached. Participants (n = 40) from China are recruited in three sites through (1) posters,
30
31 169 which show the condition of the trial, (2) social media (ie, websites, WeChat) and (3) the
32
33 170 advice of the doctors.

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35 171

36 172 **Patient and public involvement**

37
38 173 Patients and public were not involved in the design and development of the study.

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41 174

42 175 **Randomisation**

43
44 176 Eligible patients will be randomly allocated (1:1) to either the laparoscopic group or the
45
46 177 endoscopic group after signing on an informed consent, before which the patients will be
47
48 178 informed about the trial in detail. The groups will be stratified by Child-Pugh class, age (\leq 60
49
50 179 years or $>$ 60 years) and gender. For the randomization, the randPack package of R
51
52 180 software (R Project for Statistical Computing, Vienna, Austria) will be introduced. The
53
54 181 randomisation will be generated by a statistician independent of the study.

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56 182

57 183 **Operative interventions**

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59 184 All operative interventions will be performed by trained and experienced specialists affiliated
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4 185 to the university centers. Doppler ultrasonography, CT, electrocardiogram and
5 186 esophagogastroduodenoscopy will be performed routinely pre-operation.
6
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9 188 Participants assigned to the laparoscopic group will undergo laparoscopic therapy within 48h
10
11 189 after randomisation. Laparoscopic therapy will be performed as previously described.²⁰
12

13 190 General anesthesia will be applied for all participants. Major procedures of the operation
14
15 191 include splenectomy and the dissection and ligation of short gastric vessels, posterior gastric
16
17 192 vessels and all branches of proximal lesser curvature, cardia and lower 6 to 8 cm part of
18
19 193 abdominal esophagus from the stomach coronary vein. During the process of
20
21 194 devascularisation, the high esophageal branches and heterotopic high esophageal branches
22
23 195 will be carefully screened.
24

25 196
26
27 197 Participants assigned to the endoscopic group will undergo initial endoscopic therapy within
28
29 198 48h after randomisation. Candidate procedures for endoscopic therapy include endoscopic
30
31 199 variceal ligation (EVL), cyanoacrylate glue injection and sclerotherapy. Decision of which
32
33 200 procedure to adopt will be made by experienced specialist according to the condition of the
34
35 201 participant, while EVL will be considered the first option as recommended by guidelines.^{3 5}
36
37 202 Treatments will be performed again every 1-2 week until completely eradication of varices.
38
39 203

40 204 **Propranolol oral administration**

41
42 205 Participants assigned to both groups will begin to receive propranolol after the randomisation.
43
44 206 Propranolol shall be administrated orally while keeping monitoring the heart rate and blood
45
46 207 pressure daily, starting from 20-40 mg b.i.d and adjusting every 2 or 3 days (maximum dose:
47
48 208 320 mg/d for participants without ascites, 160 mg/d for participants with ascites) to achieve a
49
50 209 resting heart rate of 55-60 beats/min while the systolic blood pressure maintain > 90 mmHg.⁵
51
52 210 The dose can always be adjusted according to the response on participants.
53

54 211

55 212 **Outcomes and assessments**

56 213 **Primary outcome**

57
58 214 In order to compare the effectiveness of laparoscopic group with endoscopic group, the
59
60

215 primary outcome of the study is set to be variceal rebleeding. Endpoints will be 1-year
 216 rebleeding rate and rebleeding time.
 217
 218 Secondary outcomes
 219 Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, quality of
 220 life and tolerability of treatment. Following endpoints will be applied, respectively: (1)
 221 overall survival, (2) the occurrence of hepatocellular carcinoma, (3) the occurrence of venous
 222 thrombosis, (4) quality of life (QOL) score and (5) Karnofsky (KPS) score. QOL score and
 223 KPS score are treated as the reflection of safety and tolerability of treatment. The occurrence
 224 and exact kind of adverse events will be recorded to this end and treated as an outcome
 225 candidate. Also, serum markers will be introduced for monitor of change on liver functions
 226 and compared between two groups.

Table 1 Assessments and time points

Assessment	Time points						
	Pre-operation	Post-operation	12w	24w	36w	48w	60w
HVPG measurement	x						
Laboratory tests	x		x	x	x	x	x
Color Doppler ultrasound	x						
Liver stiffness	x						
CT	x						
Esophagogastroduodenoscopy	x	x					
Electrocardiogram	x						
Quality of life			x	x	x	x	x
Karnofsky			x	x	x	x	x

228
 229 Assessments
 230 Time points of involved assessments to be performed are outlined in Table 1. For participants
 231 allocated to either the groups, the following assessments will be performed and
 232 corresponding data will be collected:
 233 1. Demographic characteristics including gender, height, weight, date of birth and ethnic.
 234 2. Disease history with clear record about the number of occurrence of gastroesophageal
 235 variceal bleeding and other complexes including ascites, spontaneous bacterial peritonitis,

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4 236 hepatic encephalopathy, electrolyte imbalance, portal venous thrombosis, hepatorenal
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6 237 syndrome and hepatopulmonary syndrome, etc.
7
8 238 3. Clinical diagnosis and etiology for cirrhosis.
9
10 239 4. Laboratory test results including red blood cells, white blood cells, haemoglobin, blood
11
12 240 ammonia, platelet count, prothrombin time, activated partial thromboplastin time,
13
14 241 international normalized ratio, total bilirubin, direct and indirect bilirubin, glutamine
15
16 242 transferase, alanine aminotransferase, aspartate aminotransferase, albumin and serum
17
18 243 creatinine.
19
20 244 5. Color Doppler ultrasound results including general condition of spleen and liver, spleen
21
22 245 diameter, portal vein diameter, portal vein velocity, splenic vein velocity, splenic venous
23
24 246 reflux, cardiac output, left ventricular ejection fraction and heart output.
25
26 247 6. Liver stiffness and spleen stiffness assessed by FibroTouch or FibroScan.
27
28 248 7. Abdominal CT scans.
29
30 249 8. Esophagogastroduodenoscopy results including the location, classification, diameter of
31
32 250 varices and red signs.
33
34 251 9. Electrocardiogram results.
35
36 252 10. Child-Pugh score and classes.
37
38 253 11. QOL score.
39
40 254 12. KPS score.
41
42 255 13. Adjustment records of dosage of propranolol.
43
44 256 14. Adverse events and severe adverse events of any cause.
45
46 257 Upon occurrence of the first variceal rebleeding after the operative intervention, the
47
48 258 following data will be additionally collected:
49
50 259 1. Cause of rebleeding.
51
52 260 2. Time of rebleeding since enrollment.
53
54 261 3. Treatment and outcome of the rebleeding.
55
56 262 Upon death of a participant, the following data will be additionally collected:
57
58 263 1. Time of death since enrollment.
59
60 264 2. Cause of death.
265

266 **Sample size estimation**

267 No study has yet compared the outcome between cirrhotic patients with gastroesophageal
 268 variceal bleeding receiving either laparoscopic therapy or endoscopic therapy. Also, because
 269 of the lack of study restricting HVPG baseline level and studies about laparoscopic therapy
 270 plus propranolol oral administration, the sample size is determined based on pooled data of
 271 variceal rebleeding rate of several studies including endoscopic therapy plus propranolol oral
 272 administration or laparoscopic therapy. The variceal rebleeding rate of endoscopic therapy
 273 plus propranolol oral administration is estimated by 6 RCTs (Table 2).²²⁻²⁷ The variceal
 274 rebleeding rate of laparoscopic therapy is estimated by 6 retrospective studies (Table 2).²⁰
 275 ²⁸⁻³² Pooled rates of variceal rebleeding for endoscopic group and laparoscopic group are 44%
 276 and 6%, respectively. Considering a type I error rate (α) of 5% and a type II error rate ($1-\beta$) of
 277 20% and a dropout rate of 10%, the calculated sample size for this trial is 40.

Table 2 Variceal rebleeding rates in cirrhotic patients with portal hypertension bleeding treated by endoscopic therapy plus propranolol or laparoscopic therapy: a review of 12 studies.

Laparoscopic therapy			Endoscopic therapy plus propranolol		
First author, year	Number of patients	Number of rebleeding (%)	First author, year	Number of patients	Number of rebleeding (%)
Zheng, 2018	250	9 (3.6%)	Lv, 2018	25	13 (52%)
Bai, 2017	40	2 (5%)	Holster, 2016	35	10 (28.6%)
Bao, 2017	76	19 (25%)	Luo, 2015	36	21 (58.3%)
Cheng, 2014	204	7 (3.4%)	Hung, 2012	47	22 (46.8%)
Jiang, 2009	26	0 (0%)	Sauer, 2002	40	12 (30%)
Wang, 2008	22	0 (0%)	Rössle, 1997	62	29 (46.8%)

280 **Ethics and dissemination**

281 Ethical approval was obtained from all three participating centers. Any modifications in
 282 protocol will be done under the premise of adequate communication and approval. All
 283 interventions and assessments included in this trial will be in full compliance with Good
 284 Clinical Practice (GCP).

285 Before the allocation, all participant candidates will be fully informed about the purpose,
 286 process and possible consequences of the trial. Before any treatment, the participants will be

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4 287 informed about the interventions they will undergo and the interventions will not be applied
5 288 before a written informed consent signed by the participants themselves is provided.

6
7 289 The result of this trial (CHESS1803) will be presented at national and international
8
9 290 conferences and published in peer-reviewed journals.

10
11 291

12 13 292 **Safety**

14
15 293 Laparoscopic therapy is accepted and performed in Asia-pacific countries, while endoscopic
16
17 294 therapy is generally implemented worldwide. Both surgical interventions showed low risks of
18
19 295 severe adverse events. Nevertheless, the participants and whose relatives will be able to
20
21 296 contact the study team when any severe adverse event or disease complication occurs. The
22
23 297 participants will receive proper treatments as soon as feasible.

24
25 298 The following data will be recorded when an adverse event occurs:

- 26
27 299 1. The exact kind of adverse event.
28
29 300 2. The starting, ending and reporting time of the adverse event.
30
31 301 3. Severity of the adverse event.
32
33 302 4. Treatment and outcome of the adverse event.

34
35 303 Adverse events will be documented and reported to the investigators and ethics board of the
36
37 304 involved center in 48h. Severe adverse events will be documented and reported to the
38
39 305 investigators and ethics board of the involved center, principle investigator and supervision
40
41 306 departments required by GCP immediately.

42
43 307

44 45 308 **Data management**

46
47 309 For imaging data, the electronic form images will be collected. Other raw data will be
48
49 310 recorded in the written form case report form first and saved electronically afterwards. All
50
51 311 electronic data will be kept by a member of the study team without direct clinical contact
52
53 312 with any of the centers. All written form data will be stored in cabinets with lock permitting
54
55 313 access for only investigators. All data will be kept for 25 years after publication and
56
57 314 destroyed after then.

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60 316 **Statistical analyses**

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4 317 Statistical analyses will be performed in intention-to-treat cases. No interim analyses will be
5
6 318 conducted on the primary outcome. Multivariate COX regression model will be introduced
7
8 319 for analyses of variceal rebleeding and survival, while applying Kaplan-Meier analysis with
9
10 320 Log-rank test for inter-group comparison. Occurrence data including variceal rebleeding,
11
12 321 overall survival, hepatocellular carcinoma and portal venous thrombosis will be compared
13
14 322 using the chi square test. For data with repeated measurements including QOL score, KPS
15
16 323 score and laboratory tests results, repeated measures ANOVA will be applied. The
17
18 324 occurrence and severity of all adverse events will be collected and compared with descriptive
19
20 325 analyses and Wilcoxon rank sum test. Student's t test or Wilcoxon rank sum test (for
21
22 326 continuous data) and chi square test or Fisher's exact test (for discrete variable) will be
23
24 327 applied for analyses of other unmentioned outcomes. All results will be presented with 95%
25
26 328 CIs.

329 330 **DISCUSSION**

331 To the best of our knowledge, this study is the first to compare the effectiveness and safety of
332
333 laparoscopic therapy plus propranolol with endoscopic therapy plus propranolol, the first-line
334
335 therapy recommended by international guidelines,^{3 5} under an HVPG-guided manner. The
336
337 risk stratification performance of HVPG has been receiving more concentration and several
338
339 attempts have been made on HVPG-guided therapy.^{33 34} By introducing HVPG restriction as
340
341 an eligibility criterion, this study targets the population that faces high risk of variceal
342
343 rebleeding and death^{6 8-11} better, enabling exploration of better management for these patients
344
345 as well as extension of clinical performance of HVPG.

346
347 The first splenectomy and pericardial devascularisation was performed by Hassab in 1964³⁵
348
349 and modified by Qiu Fazu in 1981.³⁶ Benefitted from the rapid development of laparoscopic
350
351 equipment and techniques, surgical procedures for variceal bleeding are becoming
352
353 decreasingly invasive and also with much lower occurrence of adverse events.^{20 29 37-39} Such
354
355 laparoscopic therapy has been accepted as one of the most common used methods for variceal
356
357 bleeding in Asia-pacific countries. Pericardial devascularisation and splenectomy increase the
358
359 blood flow of portal vein and ameliorate leukopenia and thrombocytopenia. Thus,
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361 laparoscopic therapy is considered an effective method for variceal bleeding while only

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4 347 minimally affect liver function with satisfying performance on long-term survival and general
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6 348 condition of patients. However, it is also reported to be correlated with high occurrence of
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8 349 portal venous thrombosis⁴⁰ and exacerbation of portal hypertensive gastropathy.⁴¹ Therefore,
9
10 350 a multicenter prospective study about laparoscopic therapy will provide valuable information
11
12 351 for the clarification of its influence to the overall outcome.

13
14 352 Endoscopic therapy plus non-selective beta blockers is recommended as the first-line therapy
15
16 353 and widely served as control groups in many studies.^{22-27 42} On the contrary, studies about
17
18 354 laparoscopic therapy are mainly single-arm^{20 32 43} or compared with variants and other
19
20 355 surgeries.^{28-31 40 44 45} To the best of our knowledge, there haven't been any trials about
21
22 356 laparoscopic therapy using endoscopic therapy plus non-selective beta blockers as controls.
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24 357 Thus, this study will also provide data with better comparability to other commonly used
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26 358 therapies.

27
28 359 Still, this study has several limitations. First, this is the first prospective study investigating
29
30 360 the HVPg-guided therapeutic effect of laparoscopic therapy plus propranolol and endoscopic
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32 361 therapy plus propranolol. The lack of enough previous studies may lead to deviations in
33
34 362 sample size estimation. Second, the major cause of cirrhosis of the target population of this
35
36 363 study is hepatitis B virus infection while it is more complex in American and European
37
38 364 countries. Differences in etiology may bring problems in applicability. Third, the period of
39
40 365 follow-up in this study is set to be about one year, which may not be enough to thoroughly
41
42 366 unfold the long-term effect of laparoscopic therapy.

43 367

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7 378 **Contributors** Xiaolong Qi, Weidong Wang, Changzeng Zuo, Zhiwei Li and Xun Li conceived and

8
9 379 designed the study. Qingbo Liu, Weijie Zhang, Xiaorong Mao, Xiaojing Song, Jitao Wang and Chuan Liu

10
11 380 are responsible of the data collecting and management. Ruoyang Shao drafted this manuscript. Ruizhao Qi,

12
13 381 Xin Zhao and Xiaolong Qi critically revised the manuscript. The final version of the manuscript was

14
15 382 reviewed and approved by all authors.

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18
19 384 **Funding** This work is funded by the grants from National Natural Science Foundation of China

20
21 385 (81600510); Guangdong Science Fund for Distinguished Young Scholars (2018B030306019); Guangzhou

22
23 386 Industry-Academia-Research Collaborative Innovation Major Project (201704020015).

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27 388 **Disclaimer** The funders do not participate in the design, recruitment, intervention, data collection, data

28
29 389 management and analysis of the study and the preparation and revision of this protocol.

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33 391 **Competing interests** None declared.

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37 393 **Patient consent for publication** Obtained.

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41 395 **Ethics approval** This study has been approved by the ethics committee of Shunde Hospital, Southern

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43 396 Medical University (20190104); Xingtai People's Hospital ([2019]001); The First Hospital of Lanzhou

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45 397 University (LDYYLL2019-179).

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49 399 **Provenance and peer review** Not commissioned; internally peer reviewed.

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53 401 **Data availability statement** All data from this study will be made available upon reasonable request. To

54
55 402 request for data, please contact the corresponding author.

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59 404 **Open access** This is an open access article distributed in accordance with the Creative Commons

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4 406 build upon this work non-commercially, and license their derivative works on different terms, provided the
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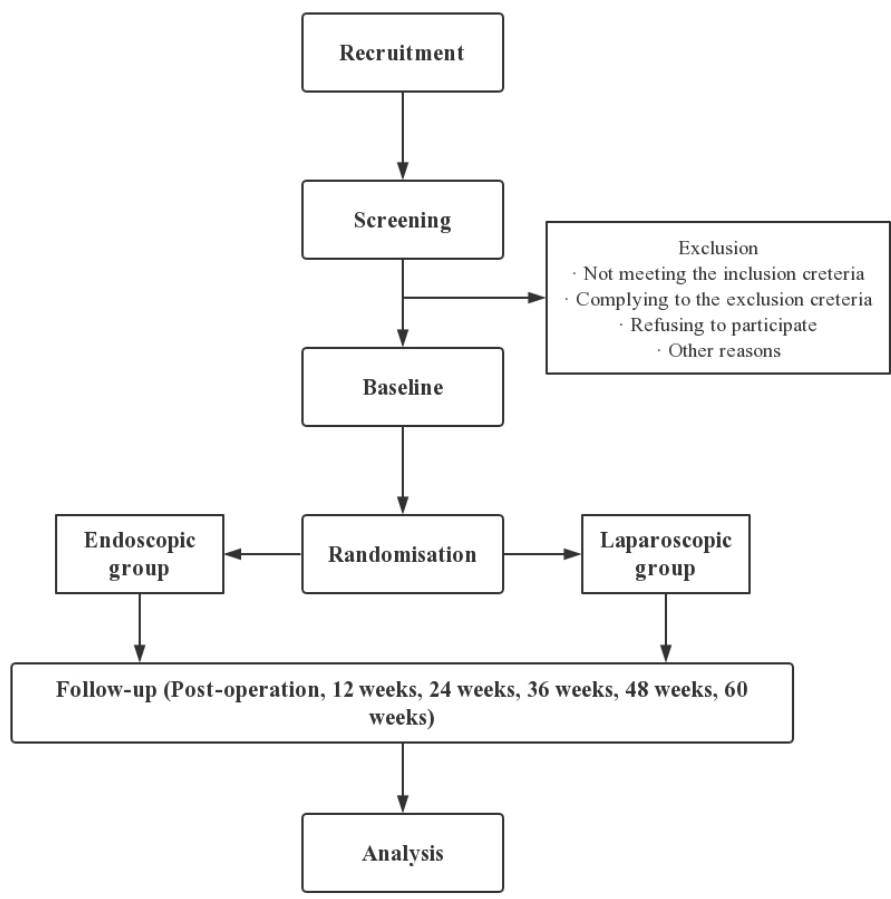
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Flow chart for study design.

Informed Consent Form

Dear madam/sir,

You are invited to participate in a multicenter randomized controlled trial assessing the effectiveness and safety of laparoscopic therapy plus propranolol as first-line therapy of secondary prevention for cirrhotic patients with gastroesophageal varices. The following items contain important information including the background, aim, method, possible merits and risks for participants about this trial. We would like to request you to read them carefully before you make your decision for they may assist you to decide whether to participate in this trial or not. If you have any questions, please contact the investigator in charge for this trial directly to ensure your fully understanding. Your participation is of completely voluntary. Please sign in the statements section of this form if you agree to participate.

Aim of study

Laparoscopic therapy is one of the most commonly used interventions for gastroesophageal variceal bleeding. Current experience in clinical practice has proved it to be a promising procedure to control rebleeding bringing only minimal trauma and bleeding. In this trial, we intend to compare laparoscopic therapy plus propranolol to endoscopic therapy plus propranolol, the first-line therapy currently recommended by international guidelines, to evaluate the effectiveness and safety of laparoscopic therapy for secondary prevention of cirrhotic patients with history of gastroesophageal variceal bleeding.

Design and interventions

This is a prospective, multicenter randomized controlled trial. 40 participants will be recruited in this trial.

Appropriate participants will be invited by the investigators according to the inclusion

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4 and exclusion criteria and randomly assigned to the endoscopic group or the
5
6 laparoscopic group. Participants in the endoscopic group will receive endoscopic
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8 therapy plus propranolol and those in the laparoscopic group will receive laparoscopic
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10 therapy plus propranolol. For participants assigned to the endoscopic group, either of
11
12 the procedures including endoscopic variceal ligation, cyanoacrylate glue injection
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14 and sclerotherapy. Decision of which procedure to be adopt for each participant will
15
16 be individually made by experienced specialist according to the condition of the
17
18 varices. Nevertheless, EVL will be considered the first option when there are multiple
19
20 appropriate procedures as recommended by international guidelines.
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22

23 **Term and procedure**

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25 During the trial, the staff will perform corresponding procedure for the participants
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27 according to the assignation after necessary tests and data collection been performed.
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29 Propranolol administration will start since assignation. The term of the trial for each
30
31 participant will be 60 weeks. Follow-up will take place on week 12, 24, 36,48 and 60
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33 since enrollment. The following data will be collected during the procedure:

- 34 ■ General information: gender, date of birth, height, weight, ethnic.
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36 ■ Clinical data: type of portal hypertension, etiology for cirrhosis, co-morbidity,
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38 combined medication, time of bleeding.
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40 ■ Test results: blood routine, blood coagulation, liver function,
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42 esophagogastroduodenoscopy, renal function, Color Doppler ultrasound,
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44 abdominal CT, electrocardiogram, transient elastography, QOL score, KPS score,
45
46 etc.
- 47
48 ■ Adjustment records of dosage of propranolol, adverse events and severe adverse
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50 events.
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53 **Possible conflict of interest**

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55 The trial has no possible conflict of interest with participants.
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60 **Possible merits**

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4 All participants will receive either endoscopic therapy or laparoscopic therapy, plus
5 propranolol oral administration. Either therapy is widely performed and accepted and
6 may lower rebleeding rate and improve survival and life of quality. Furthermore, all
7 clinical events the participants will be carefully monitored and managed by the staff.
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13 **Possible risks**

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15 Possible risks include complications of endoscopic therapy (including but not limited
16 to nausea, vomit, ferverescence, esophagostenosis, esophageal ulcer, dysphagia and
17 early rebleeding), laparoscopic therapy (including but not limited to intraoperative
18 hemorrhage, portal vein thrombosis, subphrenic infection, pancreatic fistula and early
19 rebleeding) and side-effects of propranolol. All clinical events will be carefully
20 monitored and managed by the staff in order to minimize possible risks.
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29 Upon occurrence of safety issues during the process, the trial will be terminated, and
30 necessary medical procedures will be performed for participants suffering from
31 research related adverse effect. If the reason is confirmed to be non-human factors,
32 the trial will be announced failure.
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39 **Confidentiality**

40 The individual privacy of participants will be carefully preserved during the trial. The
41 Food and Drug Administration and Ethics Committee have the right to censor the
42 materials related to the participants when necessary. Any private information of
43 participants will not be disclosed upon publication of the result of this study.
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50 **Voluntarity**

51 The participation and exit of this study is of completely voluntary. Participants have
52 the right to exit the study at any time without getting penalized, discriminated or
53 retaliated of any form. Nevertheless, the research group strongly recommend all
54 participants to cooperate and complete the process.
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4 The process of a participant may be terminated by the investigator if the participant
5 requests other diagnosis or treatment, failed to comply to the plan or for any other
6 reasonable cause.
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10 11 **Ethics approval**

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13 This study has been reported to the ethics committee of XXX hospital and been
14 approved after thorough investigation on ethical issues. Please contact the ethics
15 committee upon any ethical concerns.
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21 **If you have read and fully understood the above items and agree to participate,**
22 **please sign the statements below.**
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Statements

Statement of participant

I have carefully read and understood the contents of this informed consent form. I have the chance to question to the investigators and all questions have been answered. I understand that my participation is of completely voluntary. I agree that related medical data to be used for research and publication. I understand that I have the right to exit the study at any time without getting penalized, discriminated or retaliated, in which case my subsequent medical treatment will not be affected.

If I request other diagnosis or treatment, failed to comply to the plan or for any other reasonable cause, the investigators have the right to terminate my participation. I volunteer to participate in this trial and I will receive a copy of signed informed consent form.

Participant: _____

Data: _____ Time: _____ : _____

The legal guardian of the participant or an impartial witness should sign in the case of incapability of the participant to sign for any reason.

Legal guardian/impartial witness: _____

Relationship with the participant: _____

Data: _____ Time: _____ : _____

Statement of investigator

I have accurately informed the participant about this informed consent form and responded to all questions asked. The participant volunteer to participate in this trial.

Investigator: _____

Data: _____ Time: _____ : _____



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title (P 1/line 3)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration (P 3/line 65)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding (P 15/line 386)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P 14/line 369) (P 15/line 390)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale (P 4/line 84)	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
	6b	Explanation for choice of comparators
Objectives (P 5/line 123)	7	Specific objectives or hypotheses

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Trial design (P 6/line 139)	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)
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Methods: Participants, interventions, and outcomes

Study setting (P 6/line 139)	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
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Eligibility criteria (P 6/line 147)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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Interventions (P 7/line 184)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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	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)
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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Outcomes (P 8/line 213)	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
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Participant timeline (P 9/line 228)	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)
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Sample size (P 11/line 267)	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
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Recruitment (P 7/line 167)	15	Strategies for achieving adequate participant enrolment to reach target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation: (P 7/line 176)		
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

Methods: Data collection, management, and analysis

28			
29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods (P 9/line		trial data, including any related processes to promote data quality (eg,
32	230)		duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management (P		related processes to promote data quality (eg, double data entry;
44	12/ line 310)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods (P		Reference to where other details of the statistical analysis plan can be
50	13/line 318)		found, if not in the protocol
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses)
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation)
58			
59			
60			

1 2 3 4 5 6 7 8 9 10 11 12 13	Dissemination policy (P 11/line 281)	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
		31b	Authorship eligibility guidelines and any intended use of professional writers
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

14 15 16 17 18 19 20 21 22 23 24 25	Informed consent materials (supplementary file)	32	Model consent form and other related documentation given to participants and authorised surrogates
22 23 24 25	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

*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.

BMJ Open

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030960.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Jul-2019
Complete List of Authors:	<p>Shao, Ruoyang; Southern Medical University Nanfang Hospital, Department of Hepatology Unit and Infectious Diseases Zuo, Changzeng; Department of Hepatobiliary Surgery, Xingtai Institute of Cancer Control Li, Zhiwei; Department of Hepatobiliary Surgery, Xingtai Institute of Cancer Control Qi, Ruizhao; Department of General Surgery, The Fifth Medical Center of PLA General Hospital Liu, Qingbo; CHESS, Department of Hepatobiliary Surgery, Shunde Hospital, Southern Medical University Zhang, Weijie; CHESS, Department of Hepatobiliary Surgery, Shunde Hospital, Southern Medical University Mao, Xiaorong; CHESS Frontier Center Working Party, The First Hospital of Lanzhou University, Lanzhou University Song, Xiaojing; CHESS Frontier Center Working Party, The First Hospital of Lanzhou University, Lanzhou University Li, Lei; CHESS Frontier Center Working Party, The First Hospital of Lanzhou University, Lanzhou University Wang, Jitao; Xingtai People's Hospital, Xingtai, China, Department of Hepatobiliary Surgery Liu, Yanna; Southern Medical University Nanfang Hospital, Department of Hepatology Unit and Infectious Diseases Zhao, Xin; Department of Hepatobiliary Surgery, The Third People's Hospital of Shenzhen Liu, Chuan; Nanfang Hospital, Southern Medical University, Department of General Surgery Li, Xun; The First Hospital of Lanzhou University Wang, Weidong; Shunde Hospital, Southern Medical University, Department of Hepatobiliary Surgery Qi, Xiaolong; The First Hospital of Lanzhou University, CHESS Frontier Center</p>
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology, Surgery, Research methods

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Keywords:	Hepatology < INTERNAL MEDICINE, Hepatobiliary surgery < SURGERY, Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY

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TITLE PAGE**Title:**

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

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11 35 **Keywords:**

12
13 36 Hepatic venous pressure gradient, variceal rebleeding, randomized controlled trial
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16
17 38 **Word count:**

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19 39 3205 words
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For peer review only

40 ABSTRACT**41 Introduction**

42 Gastroesophageal variceal bleeding is one of the most common and severe complications
43 with high mortality in cirrhotic patients who developed portal hypertension. Hepatic venous
44 pressure gradient (HVPG) is a globally recommended golden standard for portal pressure
45 assessment and an HVPG ≥ 16 mmHg indicates a higher risk of death and rebleeding. This
46 study aims to compare the effectiveness and safety of splenectomy and pericardial
47 devascularization (laparoscopic therapy) plus propranolol and endoscopic therapy plus
48 propranolol for variceal rebleeding in cirrhotic patients with HVPG between 16 and 20
49 mmHg.

51 Methods and analysis

52 This is a multicenter, randomized, controlled, clinical trial. Participants will be 1:1 assigned
53 randomly into either laparoscopic or endoscopic groups. 40 participants whose transjugular
54 HVPG lies between 16 and 20 mmHg with a history of gastroesophageal variceal bleeding
55 will be recruited from three sites in China. Participants will receive either endoscopic therapy
56 plus propranolol or laparoscopic therapy plus propranolol. The primary outcome measure will
57 be occurrence of gastroesophageal variceal rebleeding. Secondary outcome measures will
58 include: overall survival, occurrence of hepatocellular carcinoma, occurrence of venous
59 thrombosis, occurrence of adverse events, quality of life and tolerability of treatment.
60 Outcome measures will be evaluated at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks
61 and 60 weeks. Multivariate COX regression model will be introduced for analyses of
62 occurrence data and Kaplan-Meier analysis with Log-rank test for inter-group comparison.

64 Ethics and dissemination

65 Ethical approval was obtained from all three participating sites. Primary and secondary
66 outcome data will be submitted for publication in peer-reviewed journals and widely
67 disseminated.

69 Trial registration number

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4 70 NCT03783065; Pre-results.
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8 72 **Trial status**

9 73 Recruitment for this study started on December 2018 while the first participant was
10 74 randomized on January 2019. Recruitment is estimated to stop on October 2019.
11
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13 75

14
15 76 **Strengths and limitations of this study**

- 16
17 77 ■ This study is the first trial that concentrates on the best management on prevention of
18 78 rebleeding for cirrhotic patients with HVPG between 16 and 20 mmHg.
19
20 79 ■ This trial is the first one to compare the effectiveness of laparoscopic therapy plus
21 80 propranolol to endoscopic therapy plus propranolol recommended by international
22 81 guidelines.
23
24 82 ■ The surgical procedure involved in this study employs minimally invasive laparoscopy
25 83 instead of conventional operation, minimizing trauma and complications.
26
27 84 ■ Limitations of this trial include the lack of accessible data for sample size estimation,
28 85 potential influence in applicability in other countries due to etiological differences and
29 86 the relatively short follow-up period.
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40 88 **INTRODUCTION**

41 89 Cirrhosis is the result of multiple liver diseases and is accounted as a dynamic process.¹
42 90 Portal hypertension is a vital event in the natural progression of cirrhosis that is responsible
43 91 for decompensating events like gastroesophageal variceal bleeding, ascites and hepatic
44 92 encephalopathy. Gastroesophageal varices could be seen in about 50% of cirrhotic patients
45 93 and those who developed variceal bleeding face a mortality of 5-20%.^{2,3} Thus, the
46 94 stratification and applicable secondary prevention for patients with high risk is of great
47 95 clinical significance.
48
49 96 Hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic
50 97 venous pressure and free hepatic venous pressure.⁴ Eliminating the influence of abdominal
51 98 pressure, HVPG is currently the most widely accepted reflection of portal pressure, and has
52 99 been demonstrated to have good performances in risk stratification^{3,5} and predicting the

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4 100 response to treatments.^{6 7} An HVPG over 12 mmHg suggests the occurrence of
5
6 101 gastroesophageal variceal bleeding.⁸ Patients with HVPG over 16mmHg face higher risk of
7
8 102 death⁸⁻¹¹ and rebleeding,⁶ while an HVPG over 20 mmHg predicts failure to control
9
10 103 bleeding, early rebleeding, and death due to acute variceal hemorrhage.^{12 13} Currently,
11
12 104 international guidelines recommend endoscopic therapy combined with non-selective beta-
13
14 105 blockers to be the first-line therapy of secondary prevention for cirrhotic patients with
15
16 106 gastroesophageal variceal bleeding.^{3 5} Nevertheless, patients with high HVPG still suffer
17
18 107 from risk of treatment failure. Recent years, early transjugular intrahepatic portal-systemic
19
20 108 shunts is recommended as a better choice for patients with HVPG \geq 20 mmHg,^{14 15} while
21
22 109 there still lack a strong evidence to determine the best method for patients with HVPG
23
24 110 between 16 and 20 mmHg.
25
26 111 Splenectomy and pericardial devascularization, first performed by Hassab,^{16 17} is a promising
27
28 112 surgical procedure for cirrhotic patients with gastroesophageal variceal bleeding, especially
29
30 113 for those with hypersplenism. With the rapid advance of laparoscopic techniques, since the
31
32 114 first laparoscopic splenectomy was reported in 1991,¹⁸ post-operational complications which
33
34 115 used to be a major concern of Hassab's operation have been cut down to a great extent due to
35
36 116 less invasive procedures.¹⁹ Laparoscopic splenectomy and pericardial devascularization
37
38 117 (laparoscopic therapy) has been widely accepted for variceal bleeding in Asia-pacific
39
40 118 countries, where the predominant etiology of cirrhosis is hepatitis B virus infection²⁰
41
42 119 combined with very high occurrence of hypersplenism.²¹ However, there haven't been any
43
44 120 prospective trials comparing the effectiveness of laparoscopic therapy plus propranolol to the
45
46 121 internationally recommended first-line therapy. Also, the precise indication to perform
47
48 122 laparoscopic therapy is still unclear.
49
50 123 In this study, the outcomes of recruited patients whose HVPG lies within 16 and 20 mmHg
51
52 124 will be compared to explore the optimized management. Taking into consideration the
53
54 125 preferred performance of HVPG in risk stratification and the lack of prospective study in
55
56 126 long-term performance of laparoscopic therapy, this trial will be meaningful for both the
57
58 127 extension of HVPG risk stratification and the clarification of laparoscopic therapy indication.
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60

129 **Objectives**

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4 130 The aim of this trial is to assess the effectiveness and safety of laparoscopic therapy plus
5
6 131 propranolol as first-line therapy of variceal rebleeding prevention for cirrhotic patients whose
7
8 132 transjugular HVPG lies between 16 and 20 mmHg with gastroesophageal variceal bleeding
9
10 133 compared with endoscopic therapy plus propranolol. The primary outcome will be variceal
11
12 134 rebleeding. Secondary outcomes include: death, hepatocellular carcinoma, venous
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14 135 thrombosis, adverse events, quality of life and tolerability of treatment. We hypothesise that:
15
16 136 1. Compared to endoscopic therapy plus propranolol, laparoscopic therapy plus propranolol is
17
18 137 more effective in reducing variceal rebleeding.
19
20 138 2. Participants receiving laparoscopic therapy plus propranolol show non-inferior overall
21
22 139 survival and lower occurrence of hepatocellular carcinoma over those who receiving
23
24 140 endoscopic therapy plus propranolol.
25
26 141 3. The occurrence of venous thrombosis and adverse events and QOL and KPS scores are
27
28 142 without significant difference between two groups.
29
30 143

31 144 **METHODS AND ANALYSIS**

32 145 **Study design**

33
34 146 This study is a multicenter, prospective, randomized controlled clinical trial. The overview of
35
36 147 the study process is illustrated in Figure 1. After screened for eligibility and measurement of
37
38 148 HVPG, the participants will be randomly allocated to laparoscopic group or endoscopic
39
40 149 group. After the operative intervention, there will be a 60-week follow-up period. All tests
41
42 150 and interventions will be performed at three involved centers in China: (1) Shunde Hospital,
43
44 151 Southern Medical University, (2) Xingtai People's Hospital and (3) The First Hospital of
45
46 152 Lanzhou University.
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49 154 **Eligibility criteria**

50 155 **Inclusion criteria**

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52 156 Eligible participants should be (a) aged between 18 to 75 years, (b) clinically and/or
53
54 157 pathologically diagnosed cirrhosis with portal hypertension, (c) with a history of
55
56 158 gastroesophageal variceal bleeding (melena, hematemesis etc.), without receiving
57
58 159 splenectomy or any secondary prevention, (d) screened with transjugular HVPG between 16

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4 160 and 20 mmHg after hospitalization, (e) with Eastern Cooperative Oncology Group (ECOG)
5 161 score ≤ 2 and Karnofsky performance status (KPS) score ≥ 60 during screening, (f) assessed
6 162 to be Child-Pugh class A or B, and (g) voluntarily participate in the study and able to provide
7
8 163 written informed consent and able to understand and willing to comply with the requirements
9
10 164 of the study.
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15 166 Exclusion criteria

16 167 Those who conforms to any of the following would be excluded: (a) pregnant or
17 168 breastfeeding women, (b) with prior known or suspected malignancy (hepatocellular
18 169 carcinoma, cholangiocarcinoma etc.), (c) with limited coagulation situation (Quick $< 50\%$,
19 170 partial thromboplastin time (PTT) > 50 sec, platelet count $< 50000 / \mu\text{l}$ or qualitative platelet
20 171 dysfunction that affects conglutination function of congenital (Bernard-Soulier syndrome,
21 172 Glanzmann thrombasthenia, storagepool disease, aspirin-like defects, platelet-type Von
22 173 Willebrand disease, etc) or acquired (medication or other systemic diseases) causes), (d) with
23 174 massive ascites, (e) assessed to be Child-Pugh class C, (f) refusing or inadequate for
24 175 transjugular HVPG measurement, (g) with active bleeding upon screening and (h) with other
25 176 situations whose existence judged inadequate for participation by the investigators.
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39 178 **Recruitment**

40 179 Recruitment has started in December 2018 and will continue until the intent sample size has
41 180 been reached. Participants ($n = 40$) from China are recruited in three sites through (1) posters,
42 181 which show the condition of the trial, (2) social media (ie, websites, WeChat) and (3) the
43 182 advice of the doctors.
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50 184 **Patient and public involvement**

51 185 Patients and public were not involved in the design and development of the study.
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56 187 **Randomization**

57 188 Eligible patients will be randomly allocated (1:1) to either the laparoscopic group or the
58 189 endoscopic group after signing on an informed consent, before which the patients will be
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4 190 informed about the trial in detail. The groups will be stratified by Child-Pugh class, age (≤ 60
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6 191 years or > 60 years) and gender. For the randomization, the randPack package of R
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8 192 software (R Project for Statistical Computing, Vienna, Austria) will be introduced. The
9
10 193 randomization will be generated by a statistician independent of the study.

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12 194

13 195 **HVPG measurement**

15 196 Transjugular HVPG measurement will be performed for all participants when screening for
16
17 197 eligibility by experienced interventional radiologists. The procedure will be performed using
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19 198 a balloon catheter with a pressure transducer at the tip (Edwards Lifesciences, Irvine,
20
21 199 California). At first, a zero measurement will be made with the transducer open to air. After
22
23 200 transjugular catheterization, free hepatic venous pressure will be measured in the right
24
25 201 hepatic vein at about 1-3 cm from the inferior vena cava. Then, the right hepatic vein will be
26
27 202 occluded completely by the inflated balloon, after which will the wedged hepatic venous
28
29 203 pressure be measured. The measurement will be continued until the pressure reach a plateau.
30
31 204 Measurements will be performed in at least triplicate, and the average value will be used.
32
33 205 HVPG is the difference between wedged hepatic venous pressure and free hepatic venous
34
35 206 pressure.

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37 207

38 208 **Operative interventions**

40 209 All operative interventions will be performed by trained and experienced specialists affiliated
41
42 210 to the university centers. Doppler ultrasonography, computed tomography (CT),
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44 211 electrocardiogram and esophagogastroduodenoscopy will be performed routinely pre-
45
46 212 operation.

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50 214 Participants assigned to the laparoscopic group will undergo laparoscopic therapy within 48h
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52 215 after randomization. Laparoscopic therapy will be performed as previously described.²⁰
53
54 216 General anesthesia will be applied for all participants. Major procedures of the operation
55
56 217 include splenectomy and the dissection and ligation of short gastric vessels, posterior gastric
57
58 218 vessels and all branches of proximal lesser curvature, cardia and lower 6 to 8 cm part of
59
60 219 abdominal esophagus from the stomach coronary vein. During the process of

220 devascularization, the high esophageal branches and heterotopic high esophageal branches
221 will be carefully screened.

222
223 Participants assigned to the endoscopic group will undergo initial endoscopic therapy within
224 48h after randomization. Candidate procedures for endoscopic therapy include endoscopic
225 variceal ligation (EVL), cyanoacrylate glue injection and sclerotherapy. Decision of which
226 procedure to adopt will be made by experienced specialist according to the condition of the
227 participant, while EVL will be considered the first option as recommended by guidelines.^{3 5}
228 Treatments will be performed again every 1-2 week until completely eradication of varices.

230 **Propranolol oral administration**

231 Participants assigned to both groups will begin to receive propranolol after the
232 randomization. Propranolol shall be administrated orally while keeping monitoring the heart
233 rate and blood pressure daily, starting from 20-40 mg b.i.d and adjusting every 2 or 3 days
234 (maximum dose: 320 mg/d for participants without ascites, 160 mg/d for participants with
235 ascites) to achieve a resting heart rate of 55-60 beats/min while the systolic blood pressure
236 maintain > 90 mmHg.⁵ The dose can always be adjusted according to the response on
237 participants.

239 **Outcomes and assessments**

240 **Primary outcome**

241 In order to compare the effectiveness of laparoscopic group with endoscopic group, the
242 primary outcome of the study is set to be variceal rebleeding. Endpoints will be 1-year
243 rebleeding rate and rebleeding time.

245 **Secondary outcomes**

246 Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, adverse
247 events, quality of life and tolerability of treatment. Following endpoints will be applied,
248 respectively: (1) overall survival, (2) the occurrence of hepatocellular carcinoma, (3) the
249 occurrence of venous thrombosis, (4) the occurrence of adverse events, (5) quality of life

(QOL) score and (6) KPS score. Occurrence of adverse events, QOL score and KPS score are treated as the reflection of safety and tolerability of treatment. Length stay and intra-hospital mortality will be recorded also to this end and treated as outcome candidates. Also, serum markers will be introduced for monitor of change on liver functions and compared between two groups.

Table 1 Assessments and time points

Assessment	Time points						
	Pre-operation	Post-operation	12w	24w	36w	48w	60w
HVPG measurement	x						
Laboratory tests	x		x	x	x	x	x
Color Doppler ultrasound	x						
Liver stiffness	x						
CT	x						
Esophagogastroduodenoscopy	x	x					
Electrocardiogram	x						
QOL			x	x	x	x	x
KPS			x	x	x	x	x

Assessments
Time points of involved assessments to be performed are outlined in Table 1. For participants allocated to either the groups, the following assessments will be performed and corresponding data will be collected:

1. Demographic characteristics including gender, height, weight, date of birth and ethnic.
2. Transjugular measurement of HVPG.
3. Disease history with clear record about the number of occurrence of gastroesophageal variceal bleeding and other complexes including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, electrolyte imbalance, portal venous thrombosis, hepatorenal syndrome and hepatopulmonary syndrome, etc.
4. Clinical diagnosis and etiology for cirrhosis.
5. Laboratory test results including red blood cells, white blood cells, hemoglobin, blood ammonia, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, total bilirubin, direct and indirect bilirubin, glutamine transferase, alanine aminotransferase, aspartate aminotransferase, albumin and serum

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4 271 creatinine.
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6 272 6. Color Doppler ultrasound results including general condition of spleen and liver, spleen
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8 273 diameter, portal vein diameter, portal vein velocity, splenic vein velocity, splenic venous
9
10 274 reflux, cardiac output, left ventricular ejection fraction and heart output.
- 11
12 275 7. Liver stiffness and spleen stiffness assessed by FibroTouch or FibroScan.
- 13
14 276 8. Abdominal CT scans.
- 15
16 277 9. Esophagogastroduodenoscopy results including the location, classification, diameter of
17
18 278 varices and red signs.
- 19
20 279 10. Electrocardiogram results.
- 21
22 280 11. Child-Pugh score and classes.
- 23
24 281 12. Model for end-stage liver disease (MELD) score.
- 25
26 282 13. QOL score.
- 27
28 283 14. KPS score.
- 29
30 284 15. Adjustment records of dosage of propranolol.
- 31
32 285 16. Adverse events and severe adverse events of any cause.
- 33
34 286 17. Length stay.

35 287 Upon occurrence of the first variceal rebleeding after the operative intervention, the
36
37 288 following data will be additionally collected:

- 38
39 289 1. Cause of rebleeding.
- 40
41 290 2. Time of rebleeding since enrollment.
- 42
43 291 3. Treatment and outcome of the rebleeding.

44
45 292 Upon death of a participant, the following data will be additionally collected:

- 46
47 293 1. Time of death since enrollment.
- 48
49 294 2. Cause of death.

50
51 295

52 296 **Sample size estimation**

53
54 297 No study has yet compared the outcome between cirrhotic patients with gastroesophageal
55
56 298 variceal bleeding receiving either laparoscopic therapy or endoscopic therapy. Also, because
57
58 299 of the lack of study restricting HVPG baseline level and studies about laparoscopic therapy
59
60 300 plus propranolol oral administration, the sample size is determined based on pooled data of

variceal rebleeding rate of several studies including endoscopic therapy plus propranolol oral administration or laparoscopic therapy. The variceal rebleeding rate of endoscopic therapy plus propranolol oral administration is estimated by 6 randomized controlled trials (Table 2).²²⁻²⁷ The variceal rebleeding rate of laparoscopic therapy is estimated by 6 retrospective studies (Table 2).^{20 28-32} Pooled rates of variceal rebleeding for endoscopic group and laparoscopic group are 44% and 6%, respectively. Considering a type I error rate (α) of 5% and a type II error rate ($1-\beta$) of 20% and a dropout rate of 10%, the calculated sample size for this trial is 40.

Table 2 Variceal rebleeding rates in cirrhotic patients with portal hypertension bleeding treated by endoscopic therapy plus propranolol or laparoscopic therapy: a review of 12 studies.

Laparoscopic therapy			Endoscopic therapy plus propranolol		
First author, year	Number of patients	Number of rebleeding (%)	First author, year	Number of patients	Number of rebleeding (%)
Zheng, 2018	250	9 (3.6%)	Lv, 2018	25	13 (52%)
Bai, 2017	40	2 (5%)	Holster, 2016	35	10 (28.6%)
Bao, 2017	76	19 (25%)	Luo, 2015	36	21 (58.3%)
Cheng, 2014	204	7 (3.4%)	Hung, 2012	47	22 (46.8%)
Jiang, 2009	26	0 (0%)	Sauer, 2002	40	12 (30%)
Wang, 2008	22	0 (0%)	Rössle, 1997	62	29 (46.8%)

Ethics and dissemination

Ethical approval was obtained from all three participating centers. Any modifications in protocol will be done under the premise of adequate communication and approval. All interventions and assessments included in this trial will be in full compliance with Good Clinical Practice (GCP).

Before the allocation, all participant candidates will be fully informed about the purpose, process and possible consequences of the trial. Before any treatment, the participants will be informed about the interventions they will undergo and the interventions will not be applied before a written informed consent signed by the participants themselves is provided.

The result of this trial (CHESS1803) will be presented at national and international conferences and published in peer-reviewed journals.

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Safety

Laparoscopic therapy is accepted and performed in Asia-pacific countries, while endoscopic therapy is generally implemented worldwide. Both surgical interventions showed low risks of severe adverse events. Nevertheless, the participants and whose relatives will be able to contact the study team when any severe adverse event or disease complication occurs. The participants will receive proper treatments as soon as feasible.

The following data will be recorded when an adverse event occurs:

1. The exact kind of adverse event.
2. The starting, ending and reporting time of the adverse event.
3. Severity of the adverse event.
4. Treatment and outcome of the adverse event.

Adverse events will be documented and reported to the investigators and ethics board of the involved center in 48h. Severe adverse events will be documented and reported to the investigators and ethics board of the involved center, principle investigator and supervision departments required by GCP immediately.

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Data management

For imaging data, the electronic form images will be collected. Other raw data will be recorded in the written form case report form first and saved electronically afterwards. All electronic data will be kept by a member of the study team without direct clinical contact with any of the centers. All written form data will be stored in cabinets with lock permitting access for only investigators. All data will be kept for 25 years after publication and destroyed after then.

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Statistical analyses

Statistical analyses will be performed in intention-to-treat cases. A case will be censored when the participant received liver transplantation. Subgroup analysis will be performed for Child-Pugh class A and class B patients respectively. Continuous variables will be shown as mean (\pm SE) or median (range). No interim analyses will be conducted on the primary

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4 352 outcome. Multivariate COX regression model including age, sex, platelet, HVPG, aspartate
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6 353 aminotransferase, alanine aminotransferase, albumin, total bilirubin, MELD score and Child-
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8 354 Pugh score as confounders will be introduced for analyses of variceal rebleeding and
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10 355 survival, while applying Kaplan-Meier analysis with Log-rank test for inter-group
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12 356 comparison. Occurrence data including variceal rebleeding, overall survival, hepatocellular
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14 357 carcinoma and portal venous thrombosis will be compared using the chi square test. The
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16 358 occurrence of all adverse events will also be collected, described and compared using chi
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18 359 square test overall and specifically. For data with repeated measurements including QOL
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20 360 score, KPS score and laboratory tests results, repeated measures ANOVA will be applied.
21
22 361 Student's t test or Wilcoxon rank sum test (for continuous data) and chi square test or
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24 362 Fisher's exact test (for discrete variable) will be applied for analyses of other unmentioned
25
26 363 outcomes. All results will be presented with 95% CIs.

364 365 **DISCUSSION**

366 To the best of our knowledge, this study is the first to compare the effectiveness and safety of
367 laparoscopic therapy plus propranolol with endoscopic therapy plus propranolol, the first-line
368 therapy recommended by international guidelines,^{3 5} under an HVPG-guided manner. The
369 risk stratification performance of HVPG has been receiving more concentration and several
370 attempts have been made on HVPG-guided therapy.^{33 34} By introducing HVPG restriction as
371 an eligibility criterion, this study targets the population that faces high risk of variceal
372 rebleeding and death^{6 8-11} better, enabling exploration of better management for these patients
373 as well as extension of clinical performance of HVPG.

374 The first splenectomy and pericardial devascularization was performed by Hassab in 1964³⁵
375 and modified by Qiu Fazu in 1981.³⁶ Benefitted from the rapid development of laparoscopic
376 equipment and techniques, surgical procedures for variceal bleeding are becoming
377 decreasingly invasive and also with much lower occurrence of adverse events.^{20 29 37-39} Such
378 laparoscopic therapy has been accepted as one of the most common used methods for variceal
379 bleeding in Asia-pacific countries. Pericardial devascularization and splenectomy increase the
380 blood flow of hepatic artery while lower portal pressure and ameliorate leukopenia and
381 thrombocytopenia. Thus, laparoscopic therapy is considered an effective method for variceal

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4 382 bleeding while benefitting liver function with satisfying performance on long-term survival
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6 383 and general condition of patients. However, it is also reported to be correlated with high
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8 384 occurrence of portal venous thrombosis⁴⁰ and exacerbation of portal hypertensive
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10 385 gastropathy.⁴¹ Therefore, a multicenter prospective study about laparoscopic therapy will
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12 386 provide valuable information for the clarification of its influence to the overall outcome.
13
14 387 Endoscopic therapy plus non-selective beta blockers is recommended as the first-line therapy
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16 388 and widely served as control groups in many studies.^{22-27 42} On the contrary, studies about
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18 389 laparoscopic therapy are mainly single-arm^{20 32 43} or compared with variants and other
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20 390 surgeries.^{28-31 40 44 45} To the best of our knowledge, there haven't been any trials about
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22 391 laparoscopic therapy using endoscopic therapy plus non-selective beta blockers as controls.
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24 392 Thus, this study will also provide data with better comparability to other commonly used
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26 393 therapies.
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28 394 Still, this study has several limitations. First, this is the first prospective study investigating
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30 395 the HVPg-guided therapeutic effect of laparoscopic therapy plus propranolol and endoscopic
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32 396 therapy plus propranolol. The lack of enough previous studies may lead to deviations in
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34 397 sample size estimation. Second, the major cause of cirrhosis of the target population of this
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36 398 study is hepatitis B virus infection while it is more complex in American and European
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38 399 countries. Differences in etiology may bring problems in applicability. Third, the period of
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40 400 follow-up in this study is set to be about one year, which may not be enough to thoroughly
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42 401 unfold the long-term effect of laparoscopic therapy.

43 402

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5 412 **Contributors** Xiaolong Qi, Weidong Wang, Changzeng Zuo, Zhiwei Li and Xun Li conceived and
6 413 designed the study. Qingbo Liu, Weijie Zhang, Xiaorong Mao, Xiaojing Song, Jitao Wang, Lei Li and
7 414 Chuan Liu are responsible of the data collecting and management. Ruoyang Shao and Yanna Liu drafted
8 415 this manuscript. Ruizhao Qi, Xin Zhao and Xiaolong Qi critically revised the manuscript. The final version
9 416 of the manuscript was reviewed and approved by all authors.

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16 418 **Funding** This work is funded by the grants from National Natural Science Foundation of China
17 419 (81600510); Guangdong Science Fund for Distinguished Young Scholars (2018B030306019); Guangzhou
18 420 Industry-Academia-Research Collaborative Innovation Major Project (201704020015).

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24 422 **Disclaimer** The funders do not participate in the design, recruitment, intervention, data collection, data
25 423 management and analysis of the study and the preparation and revision of this protocol.

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30 425 **Competing interests** None declared.

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34 427 **Patient consent for publication** Obtained.

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38 429 **Ethics approval** This study has been approved by the ethics committee of Shunde Hospital, Southern
39 430 Medical University (20190104); Xingtai People's Hospital ([2019]001); The First Hospital of Lanzhou
40 431 University (LDYYLL2019-179).

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45 433 **Provenance and peer review** Not commissioned; internally peer reviewed.

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50 435 **Data availability statement** All data from this study will be made available upon reasonable request. To
51 436 request for data, please contact the corresponding author.

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4 441 original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-
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6 442 commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

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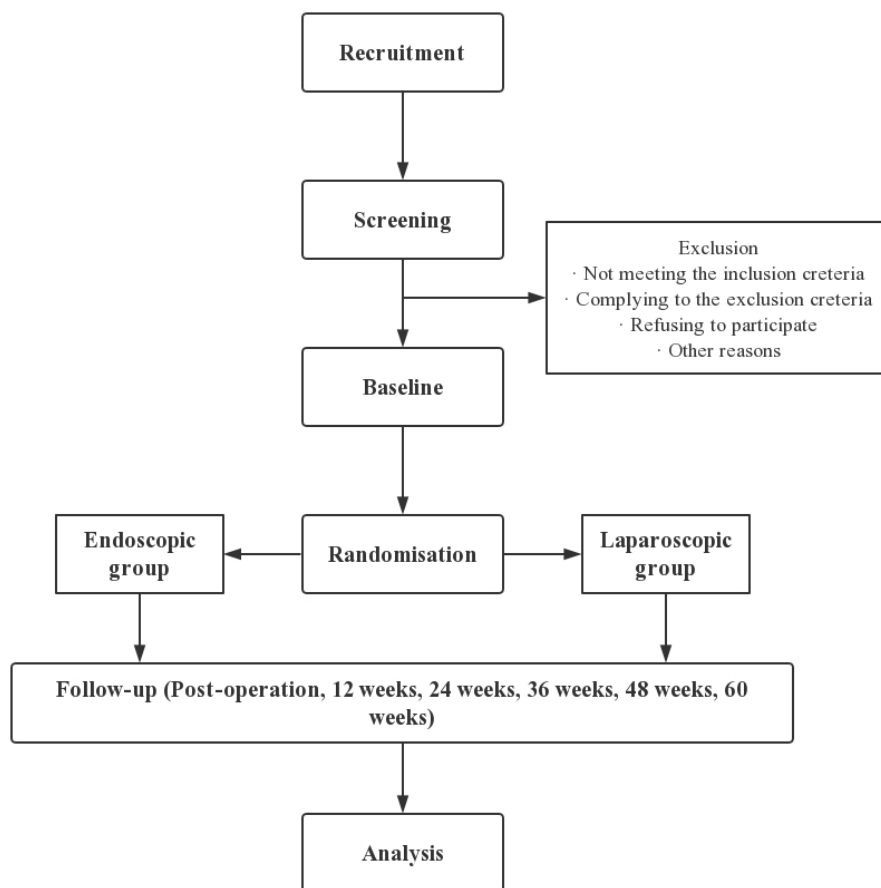
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36 551 **Figure 1** Flow chart for study design.

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Flow chart for study design.



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title (P 1/line 3)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration (P 3/line 65)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding (P 15/line 386)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P 14/line 369) (P 15/line 390)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale (P 4/line 84)	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
	6b	Explanation for choice of comparators
Objectives (P 5/line 123)	7	Specific objectives or hypotheses

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Trial design (P 6/line 139)	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)
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Methods: Participants, interventions, and outcomes

Study setting (P 6/line 139)	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
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Eligibility criteria (P 6/line 147)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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Interventions (P 7/line 184)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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	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)
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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Outcomes (P 8/line 213)	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
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Participant timeline (P 9/line 228)	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)
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Sample size (P 11/line 267)	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
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Recruitment (P 7/line 167)	15	Strategies for achieving adequate participant enrolment to reach target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation: (P 7/line 176)		
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
18	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how
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23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods (P 9/line		trial data, including any related processes to promote data quality (eg,
32	230)		duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
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37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management (P		related processes to promote data quality (eg, double data entry;
44	12/ line 310)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
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47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods (P		Reference to where other details of the statistical analysis plan can be
50	13/line 318)		found, if not in the protocol
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53		20b	Methods for any additional analyses (eg, subgroup and adjusted
54			analyses)
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56		20c	Definition of analysis population relating to protocol non-adherence
57			(eg, as randomised analysis), and any statistical methods to handle
58			missing data (eg, multiple imputation)
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1 2 3 4 5 6 7 8 9 10 11 12 13	Dissemination policy (P 11/line 281)	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
		31b	Authorship eligibility guidelines and any intended use of professional writers
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

14 15 16 17 18 19 20 21 22 23 24 25	Informed consent materials (supplementary file)	32	Model consent form and other related documentation given to participants and authorised surrogates
22 23 24 25	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

*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.

BMJ Open

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for secondary prophylaxis for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial in China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030960.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Feb-2020
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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology, Surgery, Research methods

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Keywords:	Hepatology < INTERNAL MEDICINE, Hepatobiliary surgery < SURGERY, Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY

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4 **TITLE PAGE**

5
6 **Title:**

7 Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial
8 devascularization versus endoscopic therapy for secondary prophylaxis for variceal rebleeding
9 in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled
10 trial in China
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18 38 **Keywords:**

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20 39 Hepatic venous pressure gradient, variceal rebleeding, randomized controlled trial

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24 41 **Word count:**

25
26 42 3205 words

43 ABSTRACT**44 Introduction**

45 Gastroesophageal variceal bleeding is one of the most common and severe complications
46 with high mortality in cirrhotic patients who developed portal hypertension. Hepatic venous
47 pressure gradient (HVPG) is a globally recommended golden standard for portal pressure
48 assessment and an HVPG ≥ 16 mmHg indicates a higher risk of death and rebleeding. This
49 study aims to compare the effectiveness and safety of splenectomy and pericardial
50 devascularization (laparoscopic therapy) plus propranolol and endoscopic therapy plus
51 propranolol for variceal rebleeding in cirrhotic patients with HVPG between 16 and 20
52 mmHg.

54 Methods and analysis

55 This is a multicenter, randomized, controlled, clinical trial. Participants will be 1:1 assigned
56 randomly into either laparoscopic or endoscopic groups. 40 participants whose transjugular
57 HVPG lies between 16 and 20 mmHg with a history of gastroesophageal variceal bleeding
58 will be recruited from three sites in China. Participants will receive either endoscopic therapy
59 plus propranolol or laparoscopic therapy plus propranolol. The primary outcome measure will
60 be occurrence of gastroesophageal variceal rebleeding. Secondary outcome measures will
61 include: overall survival, occurrence of hepatocellular carcinoma, occurrence of venous
62 thrombosis, occurrence of adverse events, quality of life and tolerability of treatment.
63 Outcome measures will be evaluated at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks
64 and 60 weeks. Multivariate COX regression model will be introduced for analyses of
65 occurrence data and Kaplan-Meier analysis with Log-rank test for inter-group comparison.

67 Ethics and dissemination

68 Ethical approval was obtained from all three participating sites. Primary and secondary
69 outcome data will be submitted for publication in peer-reviewed journals and widely
70 disseminated.

72 Trial registration number

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4 73 NCT03783065; Pre-results.

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8 75 **Trial status**

9
10 76 Recruitment for this study started on December 2018 while the first participant was
11 77 randomized on January 2019. Recruitment is estimated to stop on October 2019.

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15 79 **Strengths and limitations of this study**

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17 80 ■ This study is the first trial that concentrates on the best management on prevention of
18 81 rebleeding for cirrhotic patients with HVPG between 16 and 20 mmHg.

19
20 82 ■ This trial is the first one to compare the effectiveness of laparoscopic therapy plus
21 83 propranolol to endoscopic therapy plus propranolol recommended by international
22 84 guidelines.

23
24 85 ■ The surgical procedure involved in this study employs minimally invasive laparoscopy
25 86 instead of conventional operation, minimizing trauma and complications.

26
27 87 ■ Limitations of this trial include the lack of accessible data for sample size estimation,
28 88 potential influence in applicability in other countries due to etiological differences and
29 89 the relatively short follow-up period.

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33 91 **INTRODUCTION**

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35 92 Cirrhosis is the result of multiple liver diseases and is accounted as a dynamic process.¹

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37 93 Portal hypertension is a vital event in the natural progression of cirrhosis that is responsible
38 94 for decompensating events like gastroesophageal variceal bleeding, ascites and hepatic
39 95 encephalopathy. Gastroesophageal varices could be seen in about 50% of cirrhotic patients
40 96 and those who developed variceal bleeding face a mortality of 5-20%.^{2,3} Thus, the
41 97 stratification and applicable secondary prevention for patients with high risk is of great
42 98 clinical significance.

43
44 99 Hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic
45 100 venous pressure and free hepatic venous pressure.⁴ Eliminating the influence of abdominal
46 101 pressure, HVPG is currently the most widely accepted reflection of portal pressure, and has
47 102 been demonstrated to have good performances in risk stratification^{3,5} and predicting the

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4 103 response to treatments.^{6,7} An HVPG over 12 mmHg suggests the occurrence of
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6 104 gastroesophageal variceal bleeding.⁸ Patients with HVPG over 16mmHg face higher risk of
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8 105 death ^{8,9,10,11} and rebleeding,⁶ while an HVPG over 20 mmHg predicts failure to control
9
10 106 bleeding, early rebleeding, and death due to acute variceal hemorrhage.^{12,13} Currently,
11
12 107 international guidelines recommend endoscopic therapy combined with non-selective beta-
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14 108 blockers to be the first-line therapy of secondary prevention for cirrhotic patients with
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16 109 gastroesophageal variceal bleeding.^{3,5} Nevertheless, patients with high HVPG still suffer
17
18 110 from risk of treatment failure. Recent years, early transjugular intrahepatic portal-systemic
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20 111 shunts is recommended as a better choice for patients with HVPG ≥ 20 mmHg,^{14,15} while
21
22 112 there still lack a strong evidence to determine the best method for patients with HVPG
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24 113 between 16 and 20 mmHg.

25 114 Splenectomy and pericardial devascularization, first performed by Hassab,^{16,17} is a promising
26
27 115 surgical procedure for cirrhotic patients with gastroesophageal variceal bleeding, especially
28
29 116 for those with hypersplenism. With the rapid advance of laparoscopic techniques, since the
30
31 117 first laparoscopic splenectomy was reported in 1991,¹⁸ post-operational complications which
32
33 118 used to be a major concern of Hassab's operation have been cut down to a great extent due to
34
35 119 less invasive procedures.¹⁹ Laparoscopic splenectomy and pericardial devascularization
36
37 120 (laparoscopic therapy) has been widely accepted for variceal bleeding in Asia-pacific
38
39 121 countries, where the predominant etiology of cirrhosis is hepatitis B virus infection²⁰
40
41 122 combined with very high occurrence of hypersplenism.²¹ However, there haven't been any
42
43 123 prospective trials comparing the effectiveness of laparoscopic therapy plus propranolol to the
44
45 124 internationally recommended first-line therapy. Also, the precise indication to perform
46
47 125 laparoscopic therapy is still unclear.

48 126 In this study, the outcomes of recruited patients whose HVPG lies within 16 and 20 mmHg
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50 127 will be compared to explore the optimized management. Taking into consideration the
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52 128 preferred performance of HVPG in risk stratification and the lack of prospective study in
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54 129 long-term performance of laparoscopic therapy, this trial will be meaningful for both the
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56 130 extension of HVPG risk stratification and the clarification of laparoscopic therapy indication.

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132 **Objectives**

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4 133 The aim of this trial is to assess the effectiveness and safety of laparoscopic therapy plus
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6 134 propranolol as first-line therapy of variceal rebleeding prevention for cirrhotic patients whose
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8 135 transjugular HVPG lies between 16 and 20 mmHg with gastroesophageal variceal bleeding
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10 136 compared with endoscopic therapy plus propranolol. The primary outcome will be variceal
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12 137 rebleeding. Secondary outcomes include: death, hepatocellular carcinoma, venous
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14 138 thrombosis, adverse events, quality of life and tolerability of treatment. We hypothesise that:
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16 139 1. Compared to endoscopic therapy plus propranolol, laparoscopic therapy plus propranolol is
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18 140 more effective in reducing variceal rebleeding.
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20 141 2. Participants receiving laparoscopic therapy plus propranolol show non-inferior overall
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22 142 survival over those receiving endoscopic therapy plus propranolol.
23
24 143 3. Participants receiving laparoscopic therapy plus propranolol show lower occurrence of
25
26 144 hepatocellular carcinoma over those receiving endoscopic therapy plus propranolol.
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146 **METHODS AND ANALYSIS**

147 **Study design**

148 This study is a multicenter, prospective, randomized controlled clinical trial. The overview of
149 the study process is illustrated in Figure 1. After screened for eligibility and measurement of
150 HVPG, the participants will be randomly allocated to laparoscopic group or endoscopic
151 group. After the operative intervention, there will be a 60-week follow-up period. All tests
152 and interventions will be performed at three involved centers in China: (1) Shunde Hospital,
153 Southern Medical University, (2) Xingtai People's Hospital and (3) The First Hospital of
154 Lanzhou University.

156 **Eligibility criteria**

157 **Inclusion criteria**

158 Eligible participants should be (a) aged between 18 to 75 years, (b) clinically and/or
159 pathologically diagnosed cirrhosis with portal hypertension, (c) with a history of
160 gastroesophageal variceal bleeding (melena, hematemesis etc.), without receiving
161 splenectomy or any secondary prevention, (d) screened with transjugular HVPG between 16
162 and 20 mmHg after hospitalization, (e) with Eastern Cooperative Oncology Group (ECOG)

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4 163 score ≤ 2 and Karnofsky performance status (KPS) score ≥ 60 during screening, (f) assessed
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6 164 to be Child-Pugh class A or B, and (g) voluntarily participate in the study and able to provide
7
8 165 written informed consent and able to understand and willing to comply with the requirements
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10 166 of the study.

11 167 12 13 168 Exclusion criteria

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15 169 Those who conforms to any of the following would be excluded: (a) pregnant or
16
17 170 breastfeeding women, (b) with prior known or suspected malignancy (hepatocellular
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19 171 carcinoma, cholangiocarcinoma etc.), (c) with limited coagulation situation (Quick $< 50\%$,
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21 172 partial thromboplastin time (PTT) > 50 sec, platelet count $< 50000 / \mu\text{l}$ or qualitative platelet
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23 173 dysfunction that affects conglutination function of congenital (Bernard-Soulier syndrome,
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25 174 Glanzmann thrombasthenia, storagepool disease, aspirin-like defects, platelet-type Von
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27 175 Willebrand disease, etc) or acquired (medication or other systemic diseases) causes), (d) with
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29 176 massive ascites, (e) assessed to be Child-Pugh class C, (f) refusing or inadequate for
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31 177 transjugular HVPG measurement, (g) with active bleeding upon screening, (h) patients with
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33 178 recurrent bleeding and (i) with other situations whose existence judged inadequate for
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35 179 participation by the investigators.

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38 39 181 **Recruitment**

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41 182 Recruitment has started in December 2018 and will continue until the intent sample size has
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43 183 been reached. Participants ($n = 40$) from China are recruited in three sites through (1) posters,
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45 184 which show the condition of the trial, (2) social media (ie, websites, WeChat) and (3) the
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47 185 advice of the doctors.

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50 51 187 **Patient and public involvement**

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53 188 Patients and public were not involved in the design and development of the study.

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56 57 190 **Randomization**

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59 191 Eligible patients will be randomly allocated (1:1) to either the laparoscopic group or the
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192 endoscopic group after signing on an informed consent, before which the patients will be

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4 193 informed about the trial in detail. The groups will be stratified by Child-Pugh class, age (≤ 60
5 194 years or > 60 years) and gender. For the randomization, the randPack package of R
6 195 software (R Project for Statistical Computing, Vienna, Austria) will be introduced. The
7 196 randomization will be generated by a statistician independent of the study.
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13 198 **HVPG measurement**

15 199 Transjugular HVPG measurement will be performed for all participants when screening for
16 200 eligibility by experienced interventional radiologists. The procedure will be performed using
17 201 a balloon catheter with a pressure transducer at the tip (Edwards Lifesciences, Irvine,
18 202 California). At first, a zero measurement will be made with the transducer open to air. After
19 203 transjugular catheterization, free hepatic venous pressure will be measured in the right
20 204 hepatic vein at about 1-3 cm from the inferior vena cava. Then, the right hepatic vein will be
21 205 occluded completely by the inflated balloon, after which will the wedged hepatic venous
22 206 pressure be measured. The measurement will be continued until the pressure reach a plateau.
23 207 Measurements will be performed in at least triplicate, and the average value will be used.
24 208 HVPG is the difference between wedged hepatic venous pressure and free hepatic venous
25 209 pressure.
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40 211 **Operative interventions**

41 212 All operative interventions will be performed by trained and experienced specialists affiliated
42 213 to the university centers. Doppler ultrasonography, computed tomography (CT),
43 214 electrocardiogram and esophagogastroduodenoscopy will be performed routinely pre-
44 215 operation.
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50 217 Participants assigned to the laparoscopic group will undergo laparoscopic therapy within 48h
51 218 after randomization. Laparoscopic therapy will be performed as previously described.²⁰
52 219 General anesthesia will be applied for all participants. Major procedures of the operation
53 220 include splenectomy and the dissection and ligation of short gastric vessels, posterior gastric
54 221 vessels and all branches of proximal lesser curvature, cardia and lower 6 to 8 cm part of
55 222 abdominal esophagus from the stomach coronary vein. During the process of

223 devascularization, the high esophageal branches and heterotopic high esophageal branches
224 will be carefully screened.

225
226 Participants assigned to the endoscopic group will undergo initial endoscopic therapy within
227 48h after randomization. Candidate procedures for endoscopic therapy include endoscopic
228 variceal ligation (EVL), cyanoacrylate glue injection and sclerotherapy. Decision of which
229 procedure to adopt will be made by experienced specialist according to the condition of the
230 participant, while EVL will be considered the first option as recommended by guidelines.^{3,5}
231 Treatments will be performed again every 1-2 week until completely eradication of varices.

232 233 **Propranolol oral administration**

234 Participants assigned to both groups will begin to receive propranolol after the
235 randomization. Propranolol shall be administrated orally while keeping monitoring the heart
236 rate and blood pressure daily, starting from 20-40 mg b.i.d and adjusting every 2 or 3 days
237 (maximum dose: 320 mg/d for participants without ascites, 160 mg/d for participants with
238 ascites) to achieve a resting heart rate of 55-60 beats/min while the systolic blood pressure
239 maintain > 90 mmHg.⁵ The dose can always be adjusted according to the response on
240 participants.

241 242 **Outcomes and assessments**

243 **Primary outcome**

244 In order to compare the effectiveness of laparoscopic group with endoscopic group, the
245 primary outcome of the study is set to be variceal rebleeding. Endpoints will be 1-year
246 rebleeding rate and rebleeding time.

247 248 **Secondary outcomes**

249 Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, adverse
250 events, quality of life and tolerability of treatment. Following endpoints will be applied,
251 respectively: (1) overall survival, (2) the occurrence of hepatocellular carcinoma, (3) the
252 occurrence of venous thrombosis, (4) the occurrence of adverse events, (5) quality of life

(QOL) score and (6) KPS score. Occurrence of adverse events, QOL score and KPS score are treated as the reflection of safety and tolerability of treatment. Length stay and intra-hospital mortality will be recorded also to this end and treated as outcome candidates. Also, serum markers will be introduced for monitor of change on liver functions and compared between two groups.

Table 1 Assessments and time points

Assessment	Time points						
	Pre-operation	Post-operation	12w	24w	36w	48w	60w
HVPG measurement	x						
Laboratory tests	x		x	x	x	x	x
Color Doppler ultrasound	x						
Liver stiffness	x						
CT	x						
Esophagogastroduodenoscopy	x	x					
Electrocardiogram	x						
QOL			x	x	x	x	x
KPS			x	x	x	x	x

Assessments
Time points of involved assessments to be performed are outlined in Table 1. For participants allocated to either the groups, the following assessments will be performed and corresponding data will be collected:

1. Demographic characteristics including gender, height, weight, date of birth and ethnic.
2. Transjugular measurement of HVPG.
3. Disease history with clear record about the number of occurrence of gastroesophageal variceal bleeding and other complexes including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, electrolyte imbalance, portal venous thrombosis, hepatorenal syndrome and hepatopulmonary syndrome, etc.
4. Clinical diagnosis and etiology for cirrhosis.
5. Laboratory test results including red blood cells, white blood cells, hemoglobin, blood ammonia, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, total bilirubin, direct and indirect bilirubin, glutamine transferase, alanine aminotransferase, aspartate aminotransferase, albumin and serum

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4 274 creatinine.

5 275 6. Color Doppler ultrasound results including general condition of spleen and liver, spleen

6 276 diameter, portal vein diameter, portal vein velocity, splenic vein velocity, splenic venous

7 277 reflux, cardiac output, left ventricular ejection fraction and heart output.

8 278 7. Liver stiffness and spleen stiffness assessed by FibroTouch or FibroScan.

9 279 8. Abdominal CT scans.

10 280 9. Esophagogastroduodenoscopy results including the location, classification, diameter of

11 281 varices and red signs.

12 282 10. Electrocardiogram results.

13 283 11. Child-Pugh score and classes.

14 284 12. Model for end-stage liver disease (MELD) score.

15 285 13. QOL score.

16 286 14. KPS score.

17 287 15. Adjustment records of dosage of propranolol.

18 288 16. Adverse events and severe adverse events of any cause.

19 289 17. Length stay.

20 290 Upon occurrence of the first variceal rebleeding after the operative intervention, the

21 291 following data will be additionally collected:

22 292 1. Cause of rebleeding.

23 293 2. Time of rebleeding since enrollment.

24 294 3. Treatment and outcome of the rebleeding.

25 295 Upon death of a participant, the following data will be additionally collected:

26 296 1. Time of death since enrollment.

27 297 2. Cause of death.

28 298

29 299 **Sample size estimation**

30 300 No study has yet compared the outcome between cirrhotic patients with gastroesophageal

31 301 variceal bleeding receiving either laparoscopic therapy or endoscopic therapy. Also, because

32 302 of the lack of study restricting HVPG baseline level and studies about laparoscopic therapy

33 303 plus propranolol oral administration, the sample size is determined based on pooled data of

variceal rebleeding rate of several studies including endoscopic therapy plus propranolol oral administration or laparoscopic therapy. The variceal rebleeding rate of endoscopic therapy plus propranolol oral administration is estimated by 6 randomized controlled trials (Table 2).^{22,23,24,25,26,27} The variceal rebleeding rate of laparoscopic therapy is estimated by 6 retrospective studies (Table 2).^{20,28,29,30,31,32} Pooled rates of variceal rebleeding for endoscopic group and laparoscopic group are 44% and 6%, respectively. Considering a type I error rate (α) of 5% and a type II error rate ($1-\beta$) of 20% and a dropout rate of 10%, the calculated sample size for this trial is 40.

Table 2 Variceal rebleeding rates in cirrhotic patients with portal hypertension bleeding treated by endoscopic therapy plus propranolol or laparoscopic therapy: a review of 12 studies.

Laparoscopic therapy			Endoscopic therapy plus propranolol		
First author, year	Number of patients	Number of rebleeding (%)	First author, year	Number of patients	Number of rebleeding (%)
Zheng, 2018	250	9 (3.6%)	Lv, 2018	25	13 (52%)
Bai, 2017	40	2 (5%)	Holster, 2016	35	10 (28.6%)
Bao, 2017	76	19 (25%)	Luo, 2015	36	21 (58.3%)
Cheng, 2014	204	7 (3.4%)	Hung, 2012	47	22 (46.8%)
Jiang, 2009	26	0 (0%)	Sauer, 2002	40	12 (30%)
Wang, 2008	22	0 (0%)	Rössle, 1997	62	29 (46.8%)

Safety

Laparoscopic therapy is accepted and performed in Asia-pacific countries, while endoscopic therapy is generally implemented worldwide. Both surgical interventions showed low risks of severe adverse events. Possible risks related to interventions include: adverse events related to HVPG measurement (including but not limited to arrhythmia, allergy, intraoperative hemorrhage and ecchymoma) endoscopic therapy (including but not limited to nausea, vomit, fervescence, esophagostenosis, esophageal ulcer, dysphagia and early rebleeding), laparoscopic therapy (including but not limited to intraoperative hemorrhage, portal vein thrombosis, subphrenic infection, pancreatic fistula and early rebleeding) and side-effects of propranolol. Participants and whose relatives will be able to contact the study team when any severe adverse event or disease complication occurs. The participants who rebled will receive

325 proper treatments according to the recommendations of the Baveno VI guideline³ as soon as
326 feasible. Liver transplantation will be performed in an expedite manner in cases it is needed.

327 The following data will be recorded when an adverse event occurs:

- 328 1. The exact kind of adverse event.
- 329 2. The starting, ending and reporting time of the adverse event.
- 330 3. Severity of the adverse event.
- 331 4. Treatment and outcome of the adverse event.

332 Adverse events will be documented and reported to the investigators and ethics board of the
333 involved center in 48h. Severe adverse events will be documented and reported to the
334 investigators and ethics board of the involved center, principle investigator and supervision
335 departments required by GCP immediately.

337 **Data management**

338 For imaging data, the electronic form images will be collected. Other raw data will be
339 recorded in the written form case report form first and saved electronically afterwards. All
340 electronic data will be kept by a member of the study team without direct clinical contact
341 with any of the centers. All written form data will be stored in cabinets with lock permitting
342 access for only investigators. All data will be kept for 25 years after publication and
343 destroyed after then.

345 **Statistical analyses**

346 Statistical analyses will be performed in intention-to-treat cases. A case will be censored
347 when the participant received liver transplantation. Subgroup analysis will be performed for
348 Child-Pugh class A and class B patients respectively. Continuous variables will be shown as
349 mean (\pm SE) or median (range). No interim analyses will be conducted on the primary
350 outcome. Multivariate COX regression model including age, sex, platelet, HVP, aspartate
351 aminotransferase, alanine aminotransferase, albumin, total bilirubin, MELD score and Child-
352 Pugh score as confounders will be introduced for analyses of variceal rebleeding and
353 survival, while applying Kaplan-Meier analysis with Log-rank test for inter-group
354 comparison. Occurrence data including variceal rebleeding, overall survival, hepatocellular

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4 355 carcinoma and portal venous thrombosis will be compared using the chi square test. The
5
6 356 occurrence of all adverse events will also be collected, described and compared using chi
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8 357 square test overall and specifically. For data with repeated measurements including QOL
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10 358 score, KPS score and laboratory tests results, repeated measures ANOVA will be applied.
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12 359 Student's t test or Wilcoxon rank sum test (for continuous data) and chi square test or
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14 360 Fisher's exact test (for discrete variable) will be applied for analyses of other unmentioned
15
16 361 outcomes. All results will be presented with 95% CIs.

17 362 18 363 **DISCUSSION**

19
20 364 To the best of our knowledge, this study is the first to compare the effectiveness and safety of
21
22 365 laparoscopic therapy plus propranolol with endoscopic therapy plus propranolol, the first-line
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24 366 therapy recommended by international guidelines,^{3,5} under an HVPG-guided manner. The
25
26 367 risk stratification performance of HVPG has been receiving more concentration and several
27
28 368 attempts have been made on HVPG-guided therapy.^{33,34} By introducing HVPG restriction as
29
30 369 an eligibility criterion, this study targets the population that faces high risk of variceal
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32 370 rebleeding and death^{6,8,9,10,11} better, enabling exploration of better management for these
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34 371 patients as well as extension of clinical performance of HVPG.

35
36 372 The first splenectomy and pericardial devascularization was performed by Hassab in 1964³⁵
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38 373 and modified by Qiu Fazu in 1981.³⁶ Benefitted from the rapid development of laparoscopic
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40 374 equipment and techniques, surgical procedures for variceal bleeding are becoming
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42 375 decreasingly invasive and also with much lower occurrence of adverse events.^{20,29,37,38,39} Such
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44 376 laparoscopic therapy has been accepted as one of the most common used methods for variceal
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46 377 bleeding in Asia-pacific countries. Pericardial devascularization and splenectomy increase the
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48 378 blood flow of hepatic artery while lower portal pressure and ameliorate leukopenia and
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50 379 thrombocytopenia. Thus, laparoscopic therapy is considered an effective method for variceal
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52 380 bleeding while benefitting liver function with satisfying performance on long-term survival
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54 381 and general condition of patients. However, it is also reported to be correlated with high
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56 382 occurrence of portal venous thrombosis⁴⁰ and exacerbation of portal hypertensive
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58 383 gastropathy.⁴¹ Therefore, a multicenter prospective study about laparoscopic therapy will
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60 384 provide valuable information for the clarification of its influence to the overall outcome.

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4 385 Endoscopic therapy plus non-selective beta blockers is recommended as the first-line therapy
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6 386 and widely served as control groups in many studies.^{22,23,24,25,26,27,42} On the contrary, studies
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8 387 about laparoscopic therapy are mainly single-arm^{20,32,43} or compared with variants and other
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10 388 surgeries.^{28,29,30,31,40,44,45} To the best of our knowledge, there haven't been any trials about
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12 389 laparoscopic therapy using endoscopic therapy plus non-selective beta blockers as controls.
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14 390 Thus, this study will also provide data with better comparability to other commonly used
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16 391 therapies.
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18 392 Still, this study has several limitations. First, this is the first prospective study investigating
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20 393 the HVPG-guided therapeutic effect of laparoscopic therapy plus propranolol and endoscopic
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22 394 therapy plus propranolol. The lack of enough previous studies may lead to deviations in
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24 395 sample size estimation. Second, the major cause of cirrhosis of the target population of this
25
26 396 study is hepatitis B virus infection while it is more complex in American and European
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28 397 countries. Differences in etiology may bring problems in applicability. Third, the period of
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30 398 follow-up in this study is set to be about one year, which may not be enough to thoroughly
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32 399 unfold the long-term effect of laparoscopic therapy, the occurrence of hepatocellular
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34 400 carcinoma, especially. Patients with HVPG higher than 10 mmHg suffer from a 6-fold-
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36 401 increased incidence of hepatocellular carcinoma.⁴⁶ Due to the effect of lower portal pressure
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38 402 of laparoscopic therapy, we expect a decrease in the incidence of hepatocellular carcinoma.
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40 403 We may not be likely to observe this difference owing to the short designed follow-up
41
42 404 duration. However, follow-up will still be continued for the participants after the end of this
43
44 405 study, somehow making up for this drawback.
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407 **ETHICS AND DISSEMINATION**

408 Ethical approval was obtained from the ethics committee of Shunde Hospital, Southern
409 Medical University, the ethics committee of Xingtai People's Hospital, and the ethics
410 committee of The First Hospital of Lanzhou University. Any modifications in protocol will
411 be done under the premise of adequate communication and approval. All interventions and
412 assessments included in this trial will be in full compliance with Good Clinical Practice
413 (GCP).
414 Before the allocation, all participant candidates will be fully informed about the purpose,

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4 415 process and possible consequences of the trial. Before any treatment, the participants will be
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6 416 informed about the interventions they will undergo and the interventions will not be applied
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8 417 before a written informed consent signed by the participants themselves is provided.
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10 418 The result of this trial (CHESS1803) will be presented at national and international
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12 419 conferences and published in peer-reviewed journals.

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14 420

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31 429 **Contributors** Xiaolong Qi, Weidong Wang, Changzeng Zuo, Zhiwei Li and Xun Li conceived and
32
33 430 designed the study. Qingbo Liu, Weijie Zhang, Xiaorong Mao, Xiaojing Song, Jitao Wang, Lei Li and
34
35 431 Chuan Liu are responsible of the data collecting and management. Ruoyang Shao and Yanna Liu drafted
36
37 432 this manuscript. Ruizhao Qi, Xin Zhao and Xiaolong Qi critically revised the manuscript. The final version
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39 433 of the manuscript was reviewed and approved by all authors.

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42
43 435 **Funding** This work is funded by the grants from National Natural Science Foundation of China
44
45 436 (81600510); Guangdong Science Fund for Distinguished Young Scholars (2018B030306019); Guangzhou
46
47 437 Industry-Academia-Research Collaborative Innovation Major Project (201704020015).

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51 439 **Disclaimer** The funders do not participate in the design, recruitment, intervention, data collection, data
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53 440 management and analysis of the study and the preparation and revision of this protocol.

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57 442 **Competing interests** None declared.

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4 444 **Patient consent for publication** Obtained.

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7 446 **Ethics approval** This study has been approved by the ethics committee of Shunde Hospital, Southern
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9 447 Medical University (20190104); Xingtai People's Hospital ([2019]001); The First Hospital of Lanzhou
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11 448 University (LDYYLL2019-179).

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15 450 **Provenance and peer review** Not commissioned; internally peer reviewed.

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19 452 **Data availability statement** All data from this study will be made available upon reasonable request. To
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21 453 request for data, please contact the corresponding author.

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29 457 build upon this work non-commercially, and license their derivative works on different terms, provided the
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31 458 original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-
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33 459 commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

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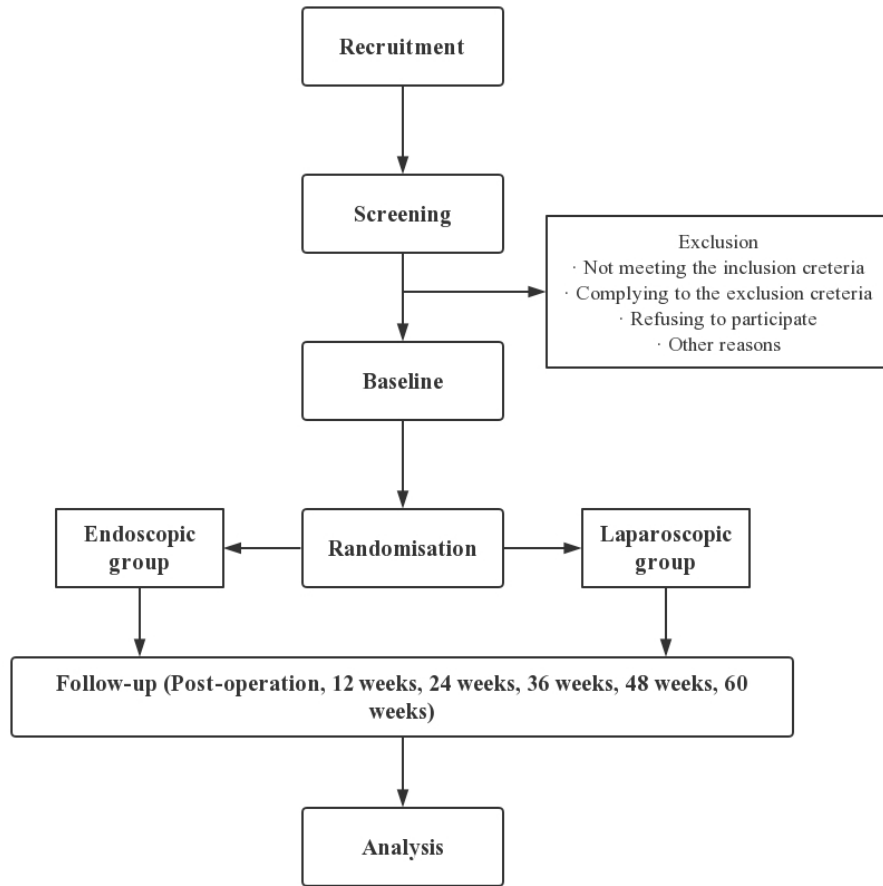
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9 570 **Figure 1** Flow chart for study design.

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Flow chart for study design.



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

Section/item	Item No	Description
Administrative information		
Title (P 1/line 3)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration (P 3/line 72)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding (P 16/line 433)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P 16/line 419) (P 16/line 437)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	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)
Introduction		
Background and rationale (P 4/line 91)	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
	6b	Explanation for choice of comparators
Objectives (P 5/line 132)	7	Specific objectives or hypotheses

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2 Trial design (P 8 Description of trial design including type of trial (eg, parallel group,
3 6/line 147) crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory)
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8 **Methods: Participants, interventions, and outcomes**
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10 Study setting (P 9 Description of study settings (eg, community clinic, academic hospital)
11 6/line 147) and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 (P 6/line 156) criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists)
17

18 Interventions (P 11a Interventions for each group with sufficient detail to allow replication,
19 8/line 211) including how and when they will be administered
20
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22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease)
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests)
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial
32
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34 Outcomes (P 12 Primary, secondary, and other outcomes, including the specific
35 9/line 242) measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended
40
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42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline (P 10/line washouts), assessments, and visits for participants. A schematic
44 257) diagram is highly recommended (see Figure)
45
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47 Sample size (P 14 Estimated number of participants needed to achieve study objectives
48 11/line 299) and how it was determined, including clinical and statistical
49 assumptions supporting any sample size calculations
50

51 Recruitment (P 15 Strategies for achieving adequate participant enrolment to reach
52 7/line 181) target sample size
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55 **Methods: Assignment of interventions (for controlled trials)**
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57 Allocation: (P
58 7/line 190)
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
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15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
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19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods (P		trial data, including any related processes to promote data quality (eg,
32	10/line 259)		duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
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38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management (P		related processes to promote data quality (eg, double data entry;
44	13/ line 349)		range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods (P		Reference to where other details of the statistical analysis plan can be
50	14/line 357)		found, if not in the protocol
51			
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53		20b	Methods for any additional analyses (eg, subgroup and adjusted
54			analyses)
55			
56		20c	Definition of analysis population relating to protocol non-adherence
57			(eg, as randomised analysis), and any statistical methods to handle
58			missing data (eg, multiple imputation)
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| Dissemination
policy (P 12/line
323) | 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 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

14 Appendices

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| Informed consent
materials
(supplementary
file) | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| 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 |

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