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# Laparoscopic versus open pancreaticoduodenectomy for pancreatic cancer: study protocol for a multicentre randomised controlled trial

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## Abstract

**Introduction:** Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic cancer. Minimally invasive surgery, which initially emerged as hybrid-laparoscopy and recently developed into total laparoscopy surgery, has been widely used for various abdominal surgeries. However, controversy persists regarding whether laparoscopic PD (LPD) is inferior to open PD (OPD) for resectable pancreatic cancer treatment. Further studies, especially randomised clinical trials, are warranted to compare these two surgical techniques.

**Methods and analysis:** The TJDBPS07 study is designed as a prospective, randomised controlled, parallel-group, open-label, multicentre noninferiority study. All participating pancreatic surgical centres comprise specialists who have performed no less than 104 LPDs and OPDs, respectively. A total of 200 strictly selected PD candidates diagnosed with pancreatic cancer will be randomised to receive LPD or OPD. The primary outcome is the 5-year overall survival rate, whereas the secondary outcomes include overall survival, disease-free survival, 90-day mortality rate, incidence of severe perioperative complications, length of stay, estimated blood loss, and operation time. We hypothesize that LPD is not inferior to OPD for the treatment of resectable pancreatic cancer. The enrolment schedule is estimated to be 2 years and follow-up for each patient will be 5 years.

**Ethics and dissemination:** This study received approval from the Tongji Hospital Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology and monitor from an independent third-party organization. Results of this trial will be presented in international meetings and published in a peer-reviewed journal.

**Trial registration:** Clinical Trials Register, NCT03785743. Registered on 10 Mar. 2019.

## Strengths and limitations of this study

To the best of our knowledge, this will be the first randomised controlled trial to compare LPD and OPD for resectable pancreatic cancer treatment in a large multicentre setting and will provide convincing evidence on performance of pancreatic cancer resection.

All participating pancreatic surgical centres are qualified with experienced surgeons who have performed no less than 104 LPDs and OPDs, respectively.

Each patient will attend a follow-up of at least 5 years to determine the study primary outcome, the 5-year overall survival rate, which is the most used indicator for describing cancer survival.

This is an open-label trial; accordingly, participants and clinicians will not be blinded to interventions.

The primary outcome of this trial will be derived from data acquired during the long-term follow-up, requiring high levels of follow-up compliance and challenging coordination between surgeons, oncologists, visitors, and patients.

## INSTRODUCTION

Pancreatic cancer is a highly fatal malignancy having poor responses to therapy and is estimated to be the 4th leading cause of cancer mortality[1]. Pancreaticoduodenectomy (PD), the standard procedure for resectable pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures[2 3]. Compared with traditional open surgery, minimally invasive surgery has many advantages, such as small incision, minimal intraoperative bleeding, fast postoperative recovery, and so on.[4], which are essential factors in the development of modern surgery. However, the long-term survival benefits of minimally invasive surgery in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival (OS) and disease-free survival (DFS) than open surgery for patients with early-stage cervical cancer[5].

Since its inception by Gagner et al. in 1994, laparoscopic PD (LPD) has been increasingly performed owning to its potential technical advantages[6 7]. Recently, an increasing number of studies, including some large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for treatment of periampullary or pancreatic tumours[8]. Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) in highly experienced surgeons who have past the learning curve[9 10]. However, the application of LPD to pancreatic cancer treatment is concerning. Several studies have focused on the comparison of LPD and OPD in pancreatic cancer treatment and suggested that LPD generated equivalent oncologic outcomes and promising superior long-term survival outcomes compared with OPD[11]. However, retrospective studies are associated with inherent limitations, including patient selection biases, missing or incomplete data, and unaccounted-for variables, making results difficult to interpret definitively. No RCTs have investigated the effects of LPD and OPD on survival in patients with pancreatic cancer.

To explore the long-term safety and efficacy of LPD in patients with pancreatic cancer using high-level evidence, the Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM) designs and conducts this prospective large-scale multicentre RCT to analyse outcomes of interest, immediately after finishing the TJDBPS01 trial, which interpreted the safety and feasibility of LPD compared with those of OPD. Accordingly, this trial aims to compare the long-term oncological and short-term surgical outcomes of LPD and OPD performed by highly experienced surgeons that have surmounted the learning curve for pancreatic cancer treatment.

## METHODS AND ANALYSIS

## Trial design

This trial is characterized as a prospective, multicentre, randomised controlled, and open-label study comprising two parallel groups of OPD and LPD. Patients diagnosed with pancreatic malignant tumour requiring PD will be consecutively recruited. This study will be conducted at ten high-volume pancreatic surgery centres in China, with surgeries being conducted by experienced surgeons. After providing written informed consents, 200 patients will be preoperatively allocated in a 1:1 ratio to either the LPD or OPD arm. The recruiting time is estimated to be 2 years and the follow-up time will be 5 years. The primary endpoint of this trial is the 5-year OS rate. The study will be prepared, analysed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines[12], as presented in Figure 1.

## Qualifications of participating surgeons and centres

The responsible participating surgeons shall satisfy the following qualifications as previously described in the TJDBPS01 study[9]: (1) having completed no less than 104 cases of LPDs; (2) having completed no less than 104 cases of OPDs[10]; and (3) having completed trainings of the Tongji Hospital LPD training program. Moreover, the participating centres shall perform more than 50 PDs annually. Surgeons willing to participate shall offer one recently unedited LPD and OPD surgery video, respectively, to the TJDBPS07 research council for evaluation. If the research council approves the surgical techniques, the surgeon and the centre will be permitted to participate in this study as a collaborator. Eligible patients will be discussed at regularly scheduled multidisciplinary team (MDT) meetings. Randomisation and assignment of a study-specific ID will be performed by the study sponsor.

## Population and eligibility criteria

All adult patients indicated for elective PD because of a pancreatic mass will be screened for eligibility. Eligible patients will be assessed by the pancreatic MDTs of the participating centres. The MDTs should confirm that the pancreatic mass is highly suspected to be a pancreatic malignant tumour and of sufficient concern to require resection. Imaging data of contrast enhanced multi-thin sliced computed tomography (CT) scan (1mm) with or without endoluminal ultrasonography (EUS) will be regarded as the standard evaluation for each PD candidate. Histological diagnoses of malignancies are encouraged to be acquired but not a necessity[13]. All patients will sign the informed consent and be allowed to leave the trial at any time. The exact inclusion and exclusion criteria are below.

Inclusion criteria

1) Age between 18 years and 75 years.

2) Histologically confirmed pancreatic cancer or clinically diagnosed pancreatic cancer by an MDT without histopathologic evidence.

3) Patients feasible to undergo both LPD and OPD according to MDT evaluations.

4) Patients without vascular invasion and not requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.

5) Patients without distant metastases, including peritoneal, liver, distant lymph node metastases, or involvement of other organs.

6) Preoperative American Society of Anaesthesiologists (ASA) score ≤ 3.

7) Patients understanding and willing to comply with this trial.

8) Provision of written informed consent before patient registration.

9) Patients meeting the curative treatment intent in accordance with clinical guidelines.

Exclusion criteria

1) Pregnant or breast-feeding women.

2) Patients with serious mental disorders.

3) Patients treated with neoadjuvant therapy.

4) Patients requiring left, central or total pancreatectomy or other palliative surgery.

5) History of other malignant disease.

6) Body mass index > 35 kg/m$^2$.

7) Patients participating in any other clinical trials within 3 months.

**Endpoints**

The primary endpoint of this trial is the 5-year overall survival rate, which is defined as the percentage of patients in this trial who are alive 5 years postoperatively [time frame: 5 years postoperatively].

Other crucial indicators are included as secondary endpoints, including (1) overall survival (i.e., the interval between the day of surgery and the day of death for various reasons [time frame: 5 years postoperatively]); (2) disease-free survival (i.e., the interval between the day of surgery and the day of tumour recurrence [time frame: 5 years postoperatively]; (3) 90-day mortality (i.e., the percentage of patients who died within 90 days postoperatively). Mortality will be calculated by dividing the number of patients who died by the number of all patients undergoing surgical treatment; (4) incidence of severe perioperative complications (i.e., the proportion of patients demonstrating severe perioperative complications with Clavien-Dindo score ≥ III). Proportions will be calculated by dividing the number of patients with any severe intraoperative/postoperative complication by the number of all patients undergoing surgical treatment; (5) length of stay (i.e., the number of nights spent in the hospital from the end of the surgical procedure until discharge or death); and (6) intraoperative indicators, including estimated blood loss and operation time.

## Sample size

The sample size calculation was performed according to the primary endpoint, the 5-year OS rate, and the non-inferiority design of this trial. Assumptions were made based on a previous study by Kuesters et al.[14], which compared LPD with OPD for pancreatic cancer treatment with the 5-year OS rate being 20% in the LPD group and 14% in the OPD group. Based on the 6% decrease in 5-year OS rate in the OPD group compared with the LPD group, the sample size required for each group was estimated to be 86 patients to achieve a non-inferiority limit of 10% at a one-tailed significance level of 2.5% with a power of 80% and a balanced design (1:1 ratio). Moreover, the primary analyses will be based on the modified intention to treat (mITT), per protocol (PP), and as treated (AT) sets. We aimed to reach a statistical power of 80% when analysing the smallest population, namely the PP set.

Patients converted from LPD to open surgery will not be included in the PP set. Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group and 91 patients in the OPD group will be needed to analyse using the one-sided *t* test at a one-sided significance level of 0.025. PASS version15.0.5 will be used to make calculations. An additional 10% of patients will be needed to be randomised considering the non-resectable patients, patients withdrawing from the study, and patients lost to follow-up. Accordingly, 91 patients in the LPD arm and 100 patients in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1, requiring 100 patients in each arm and 200 patients in total to be included for randomisation.

## Patient timeline and description of trial visits

The study duration is estimated to be 7 calendar years, with an enrolment schedule of 2 years and follow-up period of 5 years for each patient. The end of the trial was defined as 5 calendar years since the last enrolled patient received surgery. This protocol is reported in accordance with the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Table 1, supplemental file 1)[15].

Data collection and assessment are recommended to be conducted at the responsible surgical centre. Baseline data will be collected during the screening/baseline visit, and surgical data will be collected intra- and postoperatively.

Short-term follow-ups will be conducted 1 day, 1 week, 1 month, and 3 months postoperatively, and follow-up contents will include laboratory inspection indicators, Eastern Cooperative Oncology Group (ECOG) score, Karnofsky Performance Scale (KPS) score, postoperative wound recovery, wound pain level, drainage of each drainage tube postoperatively, postoperative recovery (i.e., time until getting out of

bed, imported food, and so on), weight, adverse events, combined medication, and postoperative complications.

Long-term follow-ups will be conducted every 3 months in the first postoperative year and every 6 months from the second postoperative year onwards. The following follow-up contents will be traced and recorded: clinical evaluations including internal inspections (such as weight, KPS score, and ECOG score), chemotherapy-related adverse events, imaging items to prove the existence of tumour recurrence or metastasis (record the date of recurrence, location and follow-up treatment), the date of death, and the cause of death (i.e., disease- or treatment-related mortality).

## Randomisation and blinding

Eligible patients signed the informed consent form will be screened within one week prior to randomisation. We will employ a 1:1 randomisation pattern for arms A and B, stratified by participating centres. Random numbers will be generated by SAS software version 9.40 (SAS Institute, Inc., Cary, NC) and randomisation will be performed through a centralized computer-generated system by providing random numbers using dynamic blocks. Within each block, randomisation is balanced, and every patient is assigned to a treatment using the randomisation scheme.

This is an open-label trial, and randomisation procedure and outcome will not be blinded to patients and surgeons. However, data collectors, outcome assessors, and data analysts will be blinded during statistical analysis. Surgeons will not participate in the data collection process which will be conducted by an independent team. Analysis processes will be blinded, and the statistician will be provided with only group codes instead of group names.

## Intervention

Surgical procedures need to comply with PD technique standards as previously described[16]. Any appropriate changes in surgical procedures according to the surgeon's own experience and preference are permitted, including changes in procedure order, surgical approach, and anastomosis method. All Changes will be recorded in the case report form.

## Experimental intervention-LPD techniques

Patients will take a supine position and undergo the general anaesthesia. Five trocars in total will be used. Routine and standard lymph node dissections will be maintained as recommended by guidelines. The pancreatic stump will be sent for quick frozen pathological examination intraoperatively; moreover, it is necessary to confirm that the pancreatic margin specimen is pathologically negative before digestive tract reconstruction. Surgeons will determine reconstruction type according to their

experiences and preferences. After reconstruction, two drainage tubes are routinely placed, with one near the anastomosis of the pancreaticojejunostomy and the other near the anastomosis of the bile jejunum.

Conversion to open surgery is defined as the use of any skin incision during LPD for other than trocar placement or surgical specimen removal. In cases of conversion, data will be analysed in the LPD group in an intention-to-treat manner. However, reasons for conversion shall be realistically registered and carefully recorded.

**Control intervention-OPD techniques**

Open surgery shall be performed by the same group of surgeons as LPD. Key steps are performed essentially as described in the LPD group. Methods used for reconstruction during OPD must be consistent with those during LPD in the same single centre.

**Concomitant treatment**

The TJDBPS07 trial follows TJDBPS01 which compared LPD and OPD; accordingly, the principles of perioperative management are similar to those previously described[16]. Whatever medical devices and materials that are most used in daily practice of each participant centre can be used if recorded carefully in surgical records. Antibiotics are given to patients 30 min before skin incision and 2 h after incision. Patient-controlled analgesia will be used to control postoperative pain. Time to remove the nasogastric tube depends on each patients' situation evaluated by doctors of each participating centre; early removal is encouraged. Patients can be discharged if they do not need any intravenous infusion or intravenous analgesics, do not have incision infections or any major organ dysfunction, can tolerate oral semi-liquid food, can get off bed and walk at least 250 m in a plain road without assistance, and have normal haematological parameters.

After surgical resection, patients pathologically diagnosed with pancreatic cancer will receive adjuvant chemotherapy according to the National Comprehensive Cancer Network (NCCN) guideline[17]. Written consent for adjuvant chemotherapy should be obtained. Different regimens recommended in the aforementioned guideline are permitted, and the treatment duration is at the discretion of the responsible treating oncologist. Detailed information on adjuvant chemotherapy will be recorded. Relapse cases will be treated according to the recommendations of NCCN guideline at the corresponding participating centres.

**Data collection and management**

All data will be collected using an electronic case report form. The datasets generated during the study will be stored in a local database, which is managed by the data

collection group of Tongji Hospital. Investigators from each participating institution will have access to the data of their respective patients. All data are pseudonymized, and patient details are encoded.

Data collection will include variables related to patient demographics, intraoperative information, histopathological information, postoperative clinical findings, adjuvant chemotherapy, and follow-up.

Patient demographics: age, gender, height (cm), weight (kg), smoking, drinking, main complaint, clinical diagnosis, comorbidities, surgical history, underlying malignant disease, ECOG score, ASA score, imaging results, preoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA), preoperative biliary drainage, and date of admission.

Intraoperative information: operation date, surgical approach (laparoscopic or open), conversion to open surgery, intraoperative death, texture of pancreas, diameter of the main pancreatic duct, placement of intra-abdominal drain, type of reconstruction, anastomosis approach (intracorporeal or extracorporeal), anastomosis performance (linear stapler, circular stapler, hand-sewn, or combinations), total operative time, each anastomosis time (pancreaticojejunostomy, cholangiohepaticojejunostomy, and gastroenterostomy), intraoperative complications, estimated blood loss, and intraoperative blood transfusion.

Histopathological information: tumour location, tumour size, histological type, surgical margin status (R0 resection rates), number of lymph nodes, number of positive lymph nodes, depth of invasion (T classification), lymph node status (N classification), and American Joint Committee on Cancer staging.

Postoperative clinical findings: length of postoperative stay, postoperative blood transfusion, length of intravenous analgesic use, drain production and amylase, postoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA), date of patient mobilization, date of liquid diet, date of drain removal, postoperative complication, reoperation, Clavien-Dindo grade, adverse event, cost of surgery, and cost of hospitalization.

Adjuvant chemotherapy: date of adjuvant chemotherapy, chemotherapy regimens, side effects, imaging results, haemoglobin level, white blood cell count, and related tumour markers (i.e., CA19–9, CA125, and CEA).

Follow-up: date of follow-up visit, patient status (alive, dead or lost to follow-up), ECOG score, KPS score, imaging results, related tumour markers (i.e., CA19–9, CA125, and CEA), DFS, and OS.

**Risk of bias**

All adult patients with pancreatic masses suitable for PD will be screened in all participating centres. The recruited patients will be expected to be generalizable and representative to the wider population. Standard randomisation will be conducted to ensure comparable baseline characteristics between each group. To minimize confounding, allocations will be stratified by centre.

The primary outcome of this trial is the 5-year OS rate, which is objective and will be obtained from the planned follow-up data. The participants, surgeons, and nursing staff will not be blinded to interventions due to the characteristics of this trial, which compares minimally invasive and conventional open surgery. The responsible surgeons will not be involved in the postoperative management of patients and determination of patients' discharge. Data collectors, outcome assessors, and data analysts will all be blinded to surgical techniques.

To minimize missing data bias, data for the primary outcome will be routinely collected and regularly reviewed.

Results of this trial will be reported in accordance with the CONSORT statement[12] to minimize reporting bias. In addition, the trial protocol is reported according to the SPIRIT statement[15] to assure full transparency throughout this trial and subsequent reporting.

**Assessment of cross-over patients**

Conversion from LPD to OPD is closely associated with intraoperative situations, including technical infeasibility and significant bleeding, which is unavoidable even in experienced surgeons who have past the learning curves, making it impossible to completely vanish conversion by modifying inclusion and exclusion criteria. The conversion rate in our previous trial comparing LPD and OPD for pancreatic or periampullary tumours was 4%[9]. Considering the techniques complexity in LPD for pancreatic cancer, the maximum conversion rate within this trial is cautiously estimated to be 10%. Reasons for conversion will be recorded in detail and will be further evaluated in the subgroup analysis.

**Statistical analysis**

A statistical analysis plan will be developed and agreed upon by the data collection group. All main statistical analyses will be performed by an intention-to-treat principle, and the primary analysis will be based on the mITT, PP, and AT set. Patients deemed unresectable intraoperatively or who did not receive surgery resection will not be considered in any of the analysis sets. The mITT set will comprise all patients in the group to which they were randomised regardless of the actual received surgery. The PP set will include patients without major protocol violations. Patients converted from LPD to OPD will not be included in the PP set. The AT set will be analysed with considering the actual treatment of patients, rather

than their randomisation. For robust interpretation, the results of the three primary analysis sets should lead to similar conclusions; otherwise, possible reasons behind discrepancies must be discussed. OS and DFS will be analysed from the date of pancreatic resection to the date of death (for OS) or date of regional recurrence or systemic spread (for DFS). The OS and DFS curves for the entire follow-up period will be estimated according to Kaplan-Meier method and compared using a log-rank test. Time-specific OS and DFS probabilities at appropriate time points will be derived from the survival curves and the Greenwood estimate was used to construct corresponding a 95% confidence interval (CI). Hazard ratios (HRs) and two-sided 95% CIs were estimated using a Cox regression model after confirming the proportional hazards assumptions.

In summary, continuous data will be presented as mean ± standard deviation and will be compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables will be compared using the $\chi^2$ test or Fisher's exact test, as appropriate. Statistical analysis will be conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). $P < 0.05$ will be considered as statistically significant.

This trial is registered at ClinicalTrials.gov (registration number: NCT03785743).

### Monitoring

Throughout the trial, a trained, qualified, and independent monitor will periodically visit each participating centre to randomly check protocol compliance, compliance with the inclusion and exclusion criteria, proper implementation, obtainment of informed consent forms, source data verification, and reporting of serious adverse events. Adverse events are graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[18]. The Hospital Ethical Committee and Chinese Clinical Trial Registry are responsible for collection and management of these data. Moreover, an independent agency will handle the auditing every month.

## DISCUSSION

The TJDBPS07 trial is designed as a prospective, multicentre, randomised controlled, and open-label trial to assess the long-term oncological and short-term surgical outcomes of LPD and OPD for pancreatic cancer treatment. The results of our TJDBPS01 trial suggested that LPD is a safe and feasible procedure for treating pancreatic or periampullary tumours, with comparable short-term outcomes to OPD in highly experienced hands[9 16]. The TJDBPS07 trial follows TJDBPS01 and focuses on the comparison of LPD and OPD for treatment of resectable pancreatic cancer. In consideration of the complexity and difficulty of PD, surgeons participating in this trial are required to complete a structured training program for LPD and pass the learning curve by finishing a minimum of 104 LPDs, as suggested by the results of a retrospective study on the learning curve for LPD in China[10].

With rapid advances in minimally invasive technology, minimally invasive surgery is favoured by surgeons in more and more fields due to its minimal invasiveness and enhanced patient recovery[19]. Few RCTs focusing on the impact of minimally invasive surgery on the long-term survival of cancer patients have been conducted, and different conclusions have emerged from existing studies. A study by Yu et al. found that laparoscopic distal gastrectomy and open surgery had comparable DFS and OS in patients with locally advanced gastric cancer[20]. Moreover, a study by Kitano et al. concluded that laparoscopic D3 surgery was not non-inferior to open surgery in terms of OS in patients with stage II and III colon cancer[21]. However, research by Pedro et al. suggested that for patients with early cervical cancer, minimally invasive radical hysterectomy resulted in lower rates of DFS and OS than open radical hysterectomy[5]. The current guidelines of NCCN suggest that minimally invasive surgery and open surgery are both suitable for surgical treatment of several tumours[17 22-26], resulting in the widespread use of minimally invasive surgery. However, more high-quality RCTs are needed to verify whether minimally invasive surgeries can bring the same long-term benefits for patients with tumours as open surgeries do.

With a 5-year survival rate of approximately 10%, the highly fatal pancreatic cancer is becoming an increasingly common cause of cancer related mortality. Surgical resection represents the only chance of cure for patients with resectable pancreatic cancer[27]. Moreover, application of adjuvant chemotherapy significantly improves long-term survival in these patients[28]. Although an increasing number of researchers are concerned about therapeutic effects of LPD on patients with pancreatic cancer, current evidence is still based on a few observational studies with limited quality[29]. The data of 322 patients with pancreatic cancer (108 undergoing LPD and 214 undergoing OPD) demonstrated that LPD was technically feasible for pancreatic cancer treatment and had better length of stay, postoperative recovery, and pursuing adjuvant treatment than OPD. This study simultaneously showed comparable OS but longer DFS in LPD than OPD[30], while other studies have indicated that the long-term survival and perioperative outcomes were comparable between LPD and OPD for treatment of selected pancreatic cancer patients[31-33]. Considering the controversies among existing publications and limitations of observational studies, doctors and researchers in the field of pancreatic cancer emphasize the necessity and importance of large-scale multicentre RCTs.

In conclusion, the TJDBPS07 trial is a multicentre randomised controlled, non-inferiority trial investigating the long-term survival and the preoperative safety of LPD and OPD for resectable pancreatic cancer. This trial aims to evaluate differences in the 5-year OS rate between LPD and OPD for pancreatic cancer treatment. The results of this trial will provide high-level evidence for guiding the daily practice of pancreatic cancer management.

## Trial status

The TJDBPS07 trial was registered on 10 March 2019 on the ClinicalTrials Registry

(registration number: NCT03785743). The protocol of this trial was proposed by the investigator from Tongji Hospital, and the final version was approved by Tongji Institutional Review Board. The first enrolled patient has been given the randomised number in September 2019. All ten centres are actively recruiting patients by the time this protocol is submitted. Recruitment will approximately be completed by December 2021.

## Patient and public involvement

This trial will not involve either patients or the public in the design, recruitment, conduct of the study, or measurement of outcomes. The trial results will not be notified to every single patient, while instead, the results will be presented in academic conferences, and disseminated via open-access and peer-reviewed journals. This trial will investigate patient-reported outcomes, such as questionnaires about quality of life.

## Ethics and dissemination

Each subject will sign an informed consent document before inclusion; this form is provided by a qualified team member and subsequently sent to and preserved by the data collection team. All participations are voluntary and have the right to withdraw from the study for any reason whenever they want to. If they do withdraw, they will still receive standard treatment according to local hospital procedures. The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and its later amendments[34]. This trial was registered under the Tongji Hospital (trail ID: NCT03785743) and approved by Tongji Hospital Ethics Committee (approval number: TJ-IRB20190318) in March 2019. Local ethical approval was confirmed from each participating centre before recruiting at other centres. All authors have access to study data and reviewed and approved the final manuscript. The results of this trial will be presented in international meetings, and final trial results will be published in an open access, peer-reviewed journal.



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## Authors' contributions

RYQ, MW and FZ obtained funding for the study. RYQ, HZ and MW designed the study. XJY, JiL, JuL, WXZ, XMC, DWL, JHL, JDL, YHL and RYQ performed the

operations. STP TTQ and TYY drafted the manuscript. RYQ, HZ and MW contributed to critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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**Disclaimer**

The funder had no role in the design of the study, data collection, or writing this manuscript.

**Competing interests**

The authors and each study site declare no conflicts of interest.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

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Table 1: Schedule of study enrolment, interventions, and assessments

| | Study Period | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Enrollment | Allocation | Treatment | Discharge | Post-allocation | | | | | | | | | | | | Close-out |
| **Time point** | Outpatient clinic /Admission | Before Surgery | Surgery | After Surgery | Month 1 (T1) | Month 3 (T2) | Month 6 (T3) | Month 9 (T4) | Month 12 (T5) | Month 18 (T6) | Month 24 (T7) | Month 30 (T8) | Month 36 (T9) | Month 42 (T10) | Month 48 (T11) | Month 54 (T12) | Month 60 (T13) |
| **Enrollment** | | | | | | | | | | | | | | | | | |
| Eligibility screen | × | | | | | | | | | | | | | | | | |
| Informed consent | × | | | | | | | | | | | | | | | | |
| Allocation | | × | | | | | | | | | | | | | | | |
| **Interventions** | | | | | | | | | | | | | | | | | |
| LPD | | | × | | | | | | | | | | | | | | |
| OPD | | | × | | | | | | | | | | | | | | |
| **Assessments** | | | | | | | | | | | | | | | | | |
| Baseline characteristics | × | | | | | | | | | | | | | | | | |
| Blood routine | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Blood biochemistry | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Tumor marker | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Abdominal CT scan | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Surgical record | | | × | | | | | | | | | | | | | | |
| Postoperative record | | | | × | | | | | | | | | | | | | |
| Pathological findings | | | | × | | | | | | | | | | | | | |
| Adjuvant therapy | | | | | × | × | × | × | × | × | × | × | × | × | × | × | × |
| Survival status | | | | | | × | × | × | × | × | × | × | × | × | × | × | × |

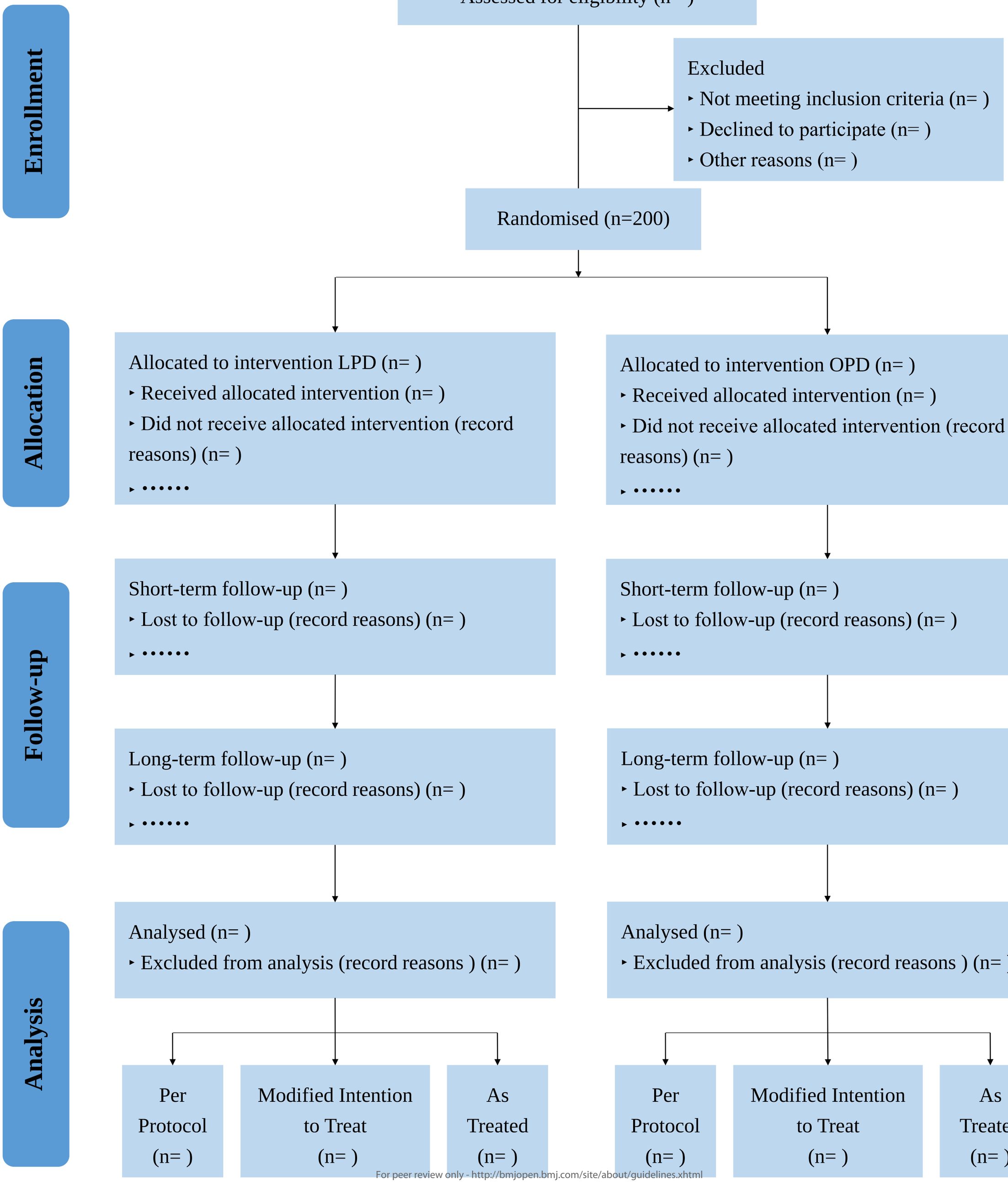
LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

**Figure legend.**

Figure 1: Flow diagram for TJDBPS07. CONSORT, Consolidated Standards of Reporting Trials; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

# CONSORT

## TRANSPARENT REPORTING of TRIALS



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3;14 |
| Protocol version | 3 | Date and version identifier | 14-15 |
| Funding | 4 | Sources and types of financial, material, and other support | 15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | 2 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16 |
| | 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) | 13 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 5 |

| | | | |
|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6-7 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 9-10 |
| | 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) | 10 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8-9 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |

| | | | |
|---|---|---|---|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 9 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10-11 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 10-11 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 10-11 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 12-13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 12-13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 12-13 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 6 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6;15 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | - |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 15 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 |
| | 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** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | annex |
| 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" license.

BMJ Open

# Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial



| | |
|---|---|
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| Secondary Subject Heading: | Oncology, Surgery |
| Keywords: | Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < ONCOLOGY |
| | |

# Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

*BMJ Open* will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

# Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial

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## Abstract

**Introduction:** Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic head cancer. Minimally invasive surgery, which initially emerged as hybrid-laparoscopy and recently developed into total laparoscopy surgery, has been widely used for various abdominal surgeries. However, controversy persists regarding whether laparoscopic PD (LPD) is inferior to open PD (OPD) for resectable pancreatic ductal adenocarcinoma (PDAC) treatment. Further studies, especially randomised clinical trials, are warranted to compare these two surgical techniques.

**Methods and analysis:** The TJDBPS07 study is designed as a prospective, randomised controlled, parallel-group, open-label, multicentre noninferiority study. All participating pancreatic surgical centres comprise specialists who have performed no less than 104 LPDs and OPDs, respectively. A total of 200 strictly selected PD candidates diagnosed with PDAC will be randomised to receive LPD or OPD. The primary outcome is the 5-year overall survival rate, whereas the secondary outcomes include overall survival, disease-free survival, 90-day mortality, complication rate, comprehensive complication index, length of stay, and intraoperative indicators. We hypothesize that LPD is not inferior to OPD for the treatment of resectable PDAC. The enrolment schedule is estimated to be 2 years and follow-up for each patient will be 5 years.

**Ethics and dissemination:** This study received approval from the Tongji Hospital Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, and monitor from an independent third-party organization. Results of this trial will be presented in international meetings and published in a peer-reviewed journal.

**Trial registration:** Clinical Trials Register, NCT03785743. Registered on 10 Mar. 2019.

## Strengths and limitations of this study

This trial aims to compare long-term safety of LPD and OPD for resectable PDAC treatment in a large multicentre setting and will provide evidence on performance of PDAC resection.

All participating pancreatic surgical centres are qualified with experienced surgeons who have performed no less than 104 LPDs and OPDs, respectively.

Each patient will attend a follow-up of at least 5 years to determine the study primary outcome, the 5-year overall survival rate, which is the most used indicator for describing cancer survival.

This is an open-label trial; accordingly, participants and clinicians will not be blinded to interventions.

The primary outcome of this trial will be derived from data acquired during the long-term follow-up, requiring high levels of follow-up compliance and challenging coordination between surgeons, oncologists, visitors, and patients.

## INTRODUCTION

Pancreatic cancer is a highly fatal malignancy with poor responses to therapy and is estimated to be the fourth leading cause of cancer mortality[1]. Among all types of pancreatic cancer, the vast majority are pancreatic ductal adenocarcinoma (PDAC)[2]. Pancreaticoduodenectomy (PD), the standard procedure for resectable pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures[2 3]. Compared with traditional open surgery, minimally invasive surgery has several advantages, such as small incision, minimal intraoperative bleeding, and fast postoperative recovery, among others[4], which are essential factors promoting the development of surgical treatments. However, the long-term survival benefits of minimally invasive surgery in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival (OS) and disease-free survival (DFS) than open surgery for patients with early-stage cervical cancer[5].

Since its inception by Gagner et al. in 1994, laparoscopic PD (LPD) has been increasingly performed owning to its potential technical advantages[6 7]. As shown by the ISGPS Evidence Map of Pancreatic Surgery[8], an increasing number of studies, including 4 large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for treatment of periampullary or pancreatic tumours[9-13]. Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) by highly experienced surgeons who have passed the learning curve[12 14]. However, the application of LPD to PDAC treatment is concerning. Several studies have focused on the comparison of LPD and OPD for PDAC treatment and suggested that LPD was associated with equivalent oncologic outcomes and promising superior long-term survival outcomes compared with OPD[15]. However, retrospective studies are associated with inherent limitations, including patient selection biases, missing or incomplete data, and unaccounted-for variables, making results difficult to interpret definitively. No RCTs have investigated the effects of LPD and OPD on survival in patients with PDAC.

To explore the long-term safety and efficacy of LPD in patients with PDAC using high-level evidence, the Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM) designs and conducts this prospective large-scale multicentre RCT to analyse outcomes of interest, immediately after the TJDBPS01 trial, which interpreted the safety and feasibility of LPD compared with those of OPD. Accordingly, this trial aims to compare the long-term oncological and short-term surgical outcomes of LPD and OPD performed by highly experienced surgeons that have surmounted the learning curve for PDAC treatment.

## METHODS AND ANALYSIS

## Trial design

This trial is characterized as a prospective, multicentre, randomised controlled, and open-label study comprising two parallel groups of patients undergoing OPD and LPD. Patients diagnosed with pancreatic malignant tumours requiring PD will be consecutively recruited. This study will be conducted at ten high-volume pancreatic surgery centres in China, with surgeries being conducted by experienced surgeons. After providing written informed consents, 200 patients will be preoperatively allocated in a 1:1 ratio to either the LPD or OPD arm. The recruitment duration is estimated to be 2 years and the follow-up duration will be 5 years. The primary endpoint of this trial is the 5-year OS rate. The study will be prepared, analysed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines[16], as presented in Figure 1.

## Qualifications of participating surgeons and centres

The responsible participating surgeons shall satisfy the following qualifications as previously described in the TJDBPS01 study[12]: (1) having completed no less than 104 cases of LPDs; (2) having completed no less than 104 cases of OPDs[14]; and (3) having completed trainings of the Tongji Hospital LPD training program. Moreover, the participating centres shall perform more than 50 PDs annually. Surgeons willing to participate shall offer one recently unedited LPD and OPD surgery video, respectively, to the TJDBPS07 research council for evaluation. If the research council approves the surgical techniques, the surgeon and the centre will be permitted to participate in this study as a collaborator. Eligible patients will be discussed at regularly scheduled multidisciplinary team (MDT) meetings. Randomisation and assignment of a study-specific ID will be performed by the study sponsor.

## Population and eligibility criteria

All adult patients indicated for elective PD because of a pancreatic mass will be screened for eligibility. Eligible patients will be assessed by the pancreatic MDTs of the participating centres. The MDTs should confirm that the pancreatic mass is highly suspected to be a pancreatic malignant tumour and of sufficient concern to require resection. Imaging data of contrast enhanced multi-thin sliced computed tomography (CT) scan (1mm) with or without endoluminal ultrasonography (EUS) will be regarded as the standard evaluation for each PD candidate. The last CT imaging should be performed within 4 weeks before the surgery. Histological diagnoses of malignancies are encouraged to be acquired but not a necessity[17]. All patients will sign the informed consent and be allowed to leave the trial at any time. The exact inclusion and exclusion criteria are below.

Inclusion criteria

1) Age between 18 years and 75 years.
2) Histologically confirmed PDAC or clinically diagnosed PDAC by an MDT without histopathologic evidence.
3) Patients feasible to undergo both LPD and OPD according to MDT evaluations.
4) Patients understanding and willing to comply with this trial.
5) Provision of written informed consent before patient registration.
6) Patients meeting the curative treatment intent in accordance with clinical guidelines.

Exclusion criteria

1) Pregnant or breast-feeding women.
2) Patients with serious mental disorders.
3) Patients treated with neoadjuvant therapy.
4) Patients requiring left, central or total pancreatectomy or other palliative surgery.
5) Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.
6) Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs.
7) Preoperative American Society of Anaesthesiologists (ASA) score $\geq 4$.
8) History of other malignant disease.
9) Body mass index $> 35$ kg/m$^2$.
10) Patients participating in any other clinical trials within 3 months.

**Endpoints**

The primary endpoint of this trial is the 5-year overall survival rate, which is defined as the percentage of patients in this trial who are alive 5 years postoperatively [time frame: 5 years postoperatively].

Other crucial indicators are included as secondary endpoints, including (1) overall survival (i.e., the interval between the day of surgery and the day of death for various reasons [time frame: 5 years postoperatively]); (2) disease-free survival (i.e., the interval between the day of surgery and the day of tumour recurrence [time frame: 5 years postoperatively]; (3) 90-day mortality (i.e., the percentage of patients who died within 90 days postoperatively). Mortality will be calculated by dividing the number of patients who died by the number of all patients undergoing surgical treatment; (4) complication rate (complications related to PD are defined according to the

International Study Group of Pancreatic Surgery; complication grades are defined according to the Clavien-Dindo classification system) (5) comprehensive complication index[18] (CCI, calculated as the sum of all complications that are weighted for their severity, available at www.assessurgery.com); (6) length of stay (i.e., the number of nights spent in the hospital from the end of the surgical procedure until discharge or death); and (7) intraoperative indicators, including estimated blood loss and operation time.

## Sample size

The sample size calculation was performed according to the primary endpoint, the 5-year OS rate, and the non-inferiority design of this trial. Assumptions were made based on a previous study by Kuesters et al.[19], which compared LPD with OPD for PDAC treatment with the 5-year OS rate being 20% in the LPD group and 14% in the OPD group. Based on the 6% decrease in 5-year OS rate in the OPD group compared with the LPD group, the sample size required for each group was estimated to be 86 patients to achieve a non-inferiority limit of 10% at a one-tailed significance level of 2.5% with a power of 80% and a balanced design (1:1 ratio). Moreover, the primary analyses will be based on the modified intention to treat (mITT), per protocol (PP), and as treated (AT) sets. We aimed to reach a statistical power of 80% when analysing the smallest population, namely the PP set.

Patients converted from LPD to open surgery will not be included in the PP set. Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group and 91 patients in the OPD group will be needed for analysis using the one-sided *t* test at a one-sided significance level of 0.025. PASS version15.0.5 will be used for the calculations. An additional 10% of patients will be needed to be randomised considering the non-resectable patients, patients withdrawing from the study, and patients lost to follow-up. Accordingly, 100 patients in the LPD arm and 91 patients in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1, requiring 100 patients in each arm and 200 patients in total to be included for randomisation.

## Patient timeline and description of trial visits

The study duration is estimated to be 7 calendar years, with an enrolment schedule of 2 years and a follow-up period of 5 years for each patient. The end of the trial was defined as 5 calendar years since the last enrolled patient received surgery. This protocol is reported in accordance with the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Table 1, supplemental file 1)[20].

Data collection and assessment are recommended to be conducted at the responsible

surgical centre. Baseline data will be collected during the screening/baseline visit, and surgical data will be collected intra- and postoperatively.

Short-term follow-ups will be conducted 1 day, 1 week, 1 month, and 3 months postoperatively, and follow-up contents will include laboratory inspection indicators, Eastern Cooperative Oncology Group (ECOG) score, Karnofsky Performance Scale (KPS) score, postoperative wound recovery, wound pain level, drainage of each drainage tube postoperatively, postoperative recovery (i.e., time until getting out of bed, imported food, and so on), weight, adverse events, combined medication, and postoperative complications.

Long-term follow-ups will be conducted every 3 months within the first postoperative year and every 6 months from the second postoperative year onwards. The following follow-up contents will be tracked and recorded: clinical evaluations including internal inspections (such as weight, KPS score, and ECOG score), chemotherapy-related adverse events, imaging items to prove the existence of tumour recurrence or metastasis (record the date of recurrence, location and follow-up treatment), the date of death, and the cause of death (i.e., disease- or treatment-related mortality).



## Randomisation and blinding

Eligible patients signed the informed consent form will be screened within one week prior to randomisation. Randomisation will be assigned on the day the preoperative evaluation is finished and the patient is diagnosed with PDAC, eligible for PD. We will employ a 1:1 randomisation pattern for arms A and B, stratified by participating centres. Random numbers will be generated by SAS software version 9.40 (SAS Institute, Inc., Cary, NC) and randomisation will be performed through a centralized computer-generated system by providing random numbers using dynamic blocks. Within each block, randomisation is balanced, and every patient is assigned to a treatment using the randomisation scheme.

This is an open-label trial, and randomisation procedure and outcome will not be blinded to patients and surgeons. However, data collectors, outcome assessors, and data analysts will be blinded during statistical analysis. Surgeons will not participate in the data collection process which will be conducted by an independent team. Analysis processes will be blinded, and the statistician will be provided with only group codes instead of group names.

## Intervention

Surgical procedures need to comply with PD technique standards as previously described[21]. Any appropriate changes in surgical procedures according to the surgeon's own experience and preference are permitted, including changes in procedure order, surgical approach, and anastomosis method. All changes will be recorded in the case report form.

### Experimental intervention-LPD techniques

Patients will take a supine position and undergo general anaesthesia. Five trocars in total will be used. Routine and standard lymph node dissections will be maintained as recommended by guidelines. The pancreatic stump will be sent for quick frozen pathological examination intraoperatively; moreover, it is necessary to confirm that the pancreatic margin specimen is pathologically negative before digestive tract reconstruction. Surgeons will determine the reconstruction type according to their experiences and preferences. After reconstruction, two drainage tubes are routinely placed, with one near the anastomosis of the pancreaticojejunostomy and the other near the anastomosis of the bile jejunum.

Conversion to open surgery is defined as the use of any skin incision during LPD for other than trocar placement or surgical specimen removal. For cases of conversion, data will be analysed in the LPD group in an intention-to-treat manner. However, reasons for conversion shall be realistically registered and carefully recorded.

### Control intervention-OPD techniques

Open surgery shall be performed by the same group of surgeons as LPD. Key steps are performed essentially as described in the LPD group. Methods used for reconstruction during OPD must be consistent with those during LPD in the same single centre.

### Concomitant treatment

The TJDBPS07 trial follows TJDBPS01 which compared LPD and OPD; accordingly, the principles of perioperative management are similar to those previously described[21]. Whatever medical devices and materials that are most used in daily practice of each participant centre can be used if recorded carefully in surgical records. Antibiotics are given to patients 30 min before skin incision and 2 h after incision. Patient-controlled analgesia will be used to control postoperative pain. Time to remove the nasogastric tube depends on each patients' situation evaluated by doctors of each participating centre; early removal is encouraged. The abdominal drains will be placed routinely for patients. The timepoint of drain removal depends on every patient's manifestation, laboratory examination results (the concentration of drain fluid amylase (DFA) on postoperative days (PODs) 1 and 3), and imaging findings. In patients with a DFA concentration of less than 5000 U/L on POD 1, early drain removal at 72 h is recommended. In patients with a DFA concentration of more than 5000 U/L on POD 1, drain removal will be decided by the corresponding surgeon according to the patient's situation. Patients can be discharged if they meet the following discharge criteria: no need for intravenous infusion, well tolerance of oral solid or semisolid food, no need for intravenous analgesics, well wound healing, well tolerance of

independent walking at least 250 m in a plain road, well major organ function with near-normal haematological parameters.

After surgical resection, patients pathologically diagnosed with PDAC will receive adjuvant chemotherapy according to the National Comprehensive Cancer Network (NCCN) guideline[22]. Written informed consent for adjuvant chemotherapy should be obtained. Different regimens recommended in the aforementioned guideline are permitted, and the treatment duration is at the discretion of the responsible treating oncologist. Detailed information on adjuvant chemotherapy will be recorded. Relapse cases will be treated according to the recommendations of the NCCN guideline at the corresponding participating centres.

**Data collection and management**

All data will be collected using an electronic case report form. The datasets generated during the study will be stored in a local database, which is managed by the data collection group of Tongji Hospital. Investigators from each participating institution will have access to the data of their respective patients. All data are pseudonymized, and patient details are encoded.

Data collection will include variables related to patient demographics, intraoperative information, histopathological information, postoperative clinical findings, adjuvant chemotherapy, and follow-up.

Patient demographics: age, gender, height (cm), weight (kg), smoking, drinking, main complaint, clinical diagnosis, comorbidities, surgical history, underlying malignant disease, ECOG score, ASA score, imaging results, preoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and carcinoembryonic antigen (CEA)), preoperative biliary drainage, and date of admission.

Intraoperative information: operation date, surgical approach (laparoscopic or open), conversion to open surgery, intraoperative death, texture of pancreas, diameter of the main pancreatic duct, placement of intra-abdominal drain, type of reconstruction, anastomosis approach (intracorporeal or extracorporeal), anastomosis performance (linear stapler, circular stapler, hand-sewn, or combinations), total operative time, each anastomosis time (pancreaticojejunostomy, cholangiohepaticojejunostomy, and gastroenterostomy), intraoperative complications, estimated blood loss, and intraoperative blood transfusion.

Histopathological information: tumour location, tumour size, histological type, surgical margin status (R0 resection rates), number of lymph nodes, number of positive lymph nodes, depth of invasion (T classification), lymph node status (N classification), and American Joint Committee on Cancer staging.

Postoperative clinical findings: length of postoperative stay, postoperative blood

transfusion, length of intravenous analgesic use, drain production and amylase, postoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA), date of patient mobilization, date of liquid diet, date of drain removal, postoperative complication, reoperation, Clavien-Dindo grade, adverse event, cost of surgery, and cost of hospitalization.

Adjuvant chemotherapy: date of adjuvant chemotherapy, chemotherapy regimens, side effects, imaging results, haemoglobin level, white blood cell count, and related tumour markers (i.e., CA19–9, CA125, and CEA).

Follow-up: date of follow-up visit, patient status (alive, dead or lost to follow-up), ECOG score, KPS score, imaging results, related tumour markers (i.e., CA19–9, CA125, and CEA), DFS, and OS.

## Data Availability Statement

The final datasets will not be available to the public. However, researchers will have access to the study data in de-identified form from the corresponding author after reasonable request when the study is completed.

## Risk of bias

All adult patients with pancreatic masses eligible for PD will be screened in all participating centres. The recruited patients will be expected to be generalizable and representative to the wider population. Standard randomisation will be conducted to ensure comparable baseline characteristics between each group. To minimize confounding, allocations will be stratified by centre.

The primary outcome of this trial is the 5-year OS rate, which is objective and will be obtained from the planned follow-up data. The participants, surgeons, and nursing staff will not be blinded to interventions due to the characteristics of this trial, which compares minimally invasive surgery and conventional open surgery. The responsible surgeons will not be involved in the postoperative management of patients and determination of patients' discharge. Data collectors, outcome assessors, and data analysts will all be blinded to surgical techniques.

To minimize missing data bias, data for the primary outcome will be routinely collected and regularly reviewed.

Results of this trial will be reported in accordance with the CONSORT statement[16] to minimize reporting bias. In addition, the trial protocol is reported according to the SPIRIT statement[20] to assure full transparency throughout this trial and subsequent reporting.

### Assessment of cross-over patients

Conversion from LPD to OPD is closely associated with intraoperative situations, including technical infeasibility and significant bleeding, which is unavoidable even for experienced surgeons who have passed the learning curves, making it impossible to eliminate conversion by modifying inclusion and exclusion criteria. The conversion rate in our previous trial comparing LPD and OPD for pancreatic or periampullary tumours was 4%[12]. Considering the techniques complexity in LPD for PDAC, the maximum conversion rate within this trial is cautiously estimated to be 10%. Reasons for conversion will be recorded in detail and further evaluated in the subgroup analysis.

### Statistical analysis

A statistical analysis plan will be developed and agreed upon by the data collection group. All main statistical analyses will be performed according to an intention-to-treat principle, and the primary analysis will be based on the mITT, PP, and AT set. Patients deemed unresectable intraoperatively or who do not receive surgical resection will not be considered in any of the analysis sets. The mITT set will comprise all patients in the group to which they were randomised regardless of the actual received surgery. The PP set will include patients without major protocol violations. Patients converted from LPD to OPD will not be included in the PP set. The AT set will be analysed with considerations of the actual treatment of patients, rather than their randomisation. For robust interpretation, the results of the three primary analysis sets should lead to similar conclusions; otherwise, possible reasons behind discrepancies must be discussed. OS and DFS will be analysed from the date of pancreatic resection to the date of death (for OS) or date of regional recurrence or systemic spread (for DFS). The OS and DFS curves for the entire follow-up period will be estimated according to Kaplan-Meier method and compared using a log-rank test. Time-specific OS and DFS probabilities at appropriate time points will be derived from the survival curves and the Greenwood estimate will be used to construct corresponding a 95% confidence interval (CI). Hazard ratios (HRs) and two-sided 95% CIs will be estimated using a Cox regression model after confirming the proportional hazards assumptions.

In summary, continuous data will be presented as mean ± standard deviation and will be compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables will be compared using the $\chi^2$ test or Fisher's exact test, as appropriate. Statistical analyses will be conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). $P < 0.05$ will denote statistical significance.

This trial is registered at ClinicalTrials.gov (registration number: NCT03785743).

### Monitoring

Throughout the trial, a trained, qualified, and independent monitor will periodically visit each participating centre to randomly check protocol compliance, compliance with the inclusion and exclusion criteria, proper implementation, obtainment of informed consent forms, source data verification, and reporting of serious adverse events. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[23]. The Hospital Ethical Committee and Chinese Clinical Trial Registry are responsible for collection and management of these data. Moreover, an independent agency will handle the auditing every month.

## DISCUSSION

The TJDBPS07 trial is designed as a prospective, multicentre, randomised controlled, and open-label trial to assess the long-term oncological and short-term surgical outcomes of LPD and OPD for PDAC treatment. The results of our TJDBPS01 trial suggested that LPD is a safe and feasible procedure for treating pancreatic or periampullary tumours, with comparable short-term outcomes to OPD in highly experienced hands[12 21]. The TJDBPS07 trial follows TJDBPS01 and focuses on the comparison of LPD and OPD for treatment of resectable PDAC. In consideration of the complexity and difficulty of PD, surgeons participating in this trial are required to complete a structured training program for LPD and pass the learning curve by finishing a minimum of 104 LPDs, as suggested by the results of a retrospective study on the learning curve for LPD in China[14].

With rapid advances in minimally invasive technology, minimally invasive surgery is favoured by surgeons in more and more fields due to its minimal invasiveness and enhanced patient recovery[24]. Few RCTs focusing on the impact of minimally invasive surgery on the long-term survival of cancer patients have been conducted, and different conclusions have emerged from existing studies. A study by Yu et al. found that laparoscopic distal gastrectomy and open surgery had comparable DFS and OS in patients with locally advanced gastric cancer[25]. Moreover, a study by Kitano et al. concluded that laparoscopic D3 surgery was not inferior to open surgery in terms of OS in patients with stage II and III colon cancer[26]. However, research by Pedro et al. suggested that for patients with early cervical cancer, minimally invasive radical hysterectomy resulted in lower rates of DFS and OS than open radical hysterectomy[5]. The current guidelines of NCCN suggest that minimally invasive surgery and open surgery are both suitable for surgical treatment of several tumours[22 27-31], resulting in the widespread use of minimally invasive surgery. However, more high-quality RCTs are needed to verify whether minimally invasive surgeries can bring the same long-term benefits for patients with tumours as open surgeries do.

With a 5-year survival rate of approximately 10%, the highly fatal pancreatic cancer is becoming an increasingly common cause of cancer-related mortality. Surgical resection represents the only chance of cure for patients with resectable pancreatic cancer[32]. Moreover, the application of adjuvant chemotherapy significantly improves long-term survival in these patients[33]. Although an increasing number of researchers

are concerned about the therapeutic effects of LPD on patients with PDAC, current evidence is still based on a few observational studies with limited quality[34]. The data of 322 patients with PDAC (108 undergoing LPD and 214 undergoing OPD) demonstrated that LPD was technically feasible for PDAC treatment and was associated with better length of stay, postoperative recovery, and pursuing adjuvant treatment than OPD. This study simultaneously showed comparable OS but longer DFS in LPD than OPD[35], while other studies have indicated that the long-term survival and perioperative outcomes were comparable between LPD and OPD for treatment of selected PDAC patients[36-38]. Considering the controversies among existing publications and limitations of observational studies, doctors and researchers in the field of PDAC emphasize the necessity and importance of large-scale multicentre RCTs.

In conclusion, the TJDBPS07 trial is a multicentre randomised controlled, non-inferiority trial investigating the long-term survival and the preoperative safety of LPD and OPD for resectable PDAC. This trial aims to evaluate differences in the 5-year OS rate between LPD and OPD for PDAC treatment. The results of this trial will provide high-level evidence for guiding the daily practice of PDAC management.

## Trial status

The TJDBPS07 trial was registered on 10 March 2019 at the ClinicalTrials Registry (registration number: NCT03785743). The protocol of this trial was proposed by the investigator from Tongji Hospital, and the final version was approved by Tongji Institutional Review Board. The first enrolled patient has been given the randomised number in August 2019. All ten centres are actively recruiting patients by the time this protocol is submitted. Recruitment will approximately be completed by December 2021.

## Patient and public involvement

This trial will not involve either patients or the public in the design, recruitment, conduct of the study, or measurement of outcomes. The trial results will not be notified to every single patient, while instead, the results will be presented in academic conferences, and disseminated via open-access and peer-reviewed journals. This trial will investigate patient-reported outcomes, using tools such as questionnaires about quality of life.

## Ethics and dissemination

Each participant will sign an informed consent document before inclusion; this form is provided by a qualified team member and subsequently sent to and preserved by the data collection team. All participations are voluntary and have the right to withdraw

from the study for any reason whenever they want to. If they do withdraw, they will still receive standard treatment according to local hospital procedures. The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and its later amendments[39]. This trial was registered under the Tongji Hospital (trail ID: NCT03785743) and approved by Tongji Hospital Ethics Committee (approval number: TJ-IRB20190318) in March 2019. Local ethical approval was confirmed from each participating centre before recruiting at other centres. All authors have access to study data and reviewed and approved the final manuscript. The results of this trial will be presented in international meetings, and final trial results will be published in an open access, peer-reviewed journal.

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**Authors' contributions**

RYQ, MW, and FZ obtained funding for the study. RYQ, HZ, and MW designed the study. XJY, JiL, JuL, WXZ, XMC, DWL, JHL, JDL, YHL, and RYQ performed the operations. STP, TTQ, and TYY drafted the manuscript. RYQ, HZ, and MW contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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**Competing interests**

The authors and each study site declare no conflicts of interest.

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Not required.

## Provenance and peer review

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Table 1: Schedule of study enrolment, interventions, and assessments

| | Study Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Enrollment | Allocation | Treatment | Discharge | Post-allocation | | | | | | | | | | | Close-out |
| **Time point** | Outpatient clinic /Admission | Before Surgery | Surgery | After Surgery | Month 1 (T1) | Month 3 (T2) | Month 6 (T3) | Month 9 (T4) | Month 12 (T5) | Month 18 (T6) | Month 24 (T7) | Month 30 (T8) | Month 36 (T9) | Month 42 (T10) | Month 48 (T11) | Month 54 (T12) | Month 60 (T13) |
| **Enrollment** | | | | | | | | | | | | | | | | | |
| Eligibility screen | × | | | | | | | | | | | | | | | | |
| Informed consent | × | | | | | | | | | | | | | | | | |
| Allocation | | × | | | | | | | | | | | | | | | |
| **Interventions** | | | | | | | | | | | | | | | | | |
| LPD | | | × | | | | | | | | | | | | | | |
| OPD | | | × | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | × | | | | | | | | | | | | | | | | |
| **Assessments** | | | | | | | | | | | | | | | | | |
| Baseline characteristics | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Blood routine | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Blood biochemistry | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Tumor marker | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Abdominal CT scan | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Surgical record | | | × | | | | | | | | | | | | | | |
| Postoperative record | | | | × | | | | | | | | | | | | | |
| Pathological findings | | | | × | | | | | | | | | | | | | |
| Adjuvant therapy | | | | × | | | | | | | | | | | | | |
| Survival status | | | | | × | × | × | × | × | × | × | × | × | × | × | × | × |
| | | | | | | × | × | × | × | × | × | × | × | × | × | × | × |

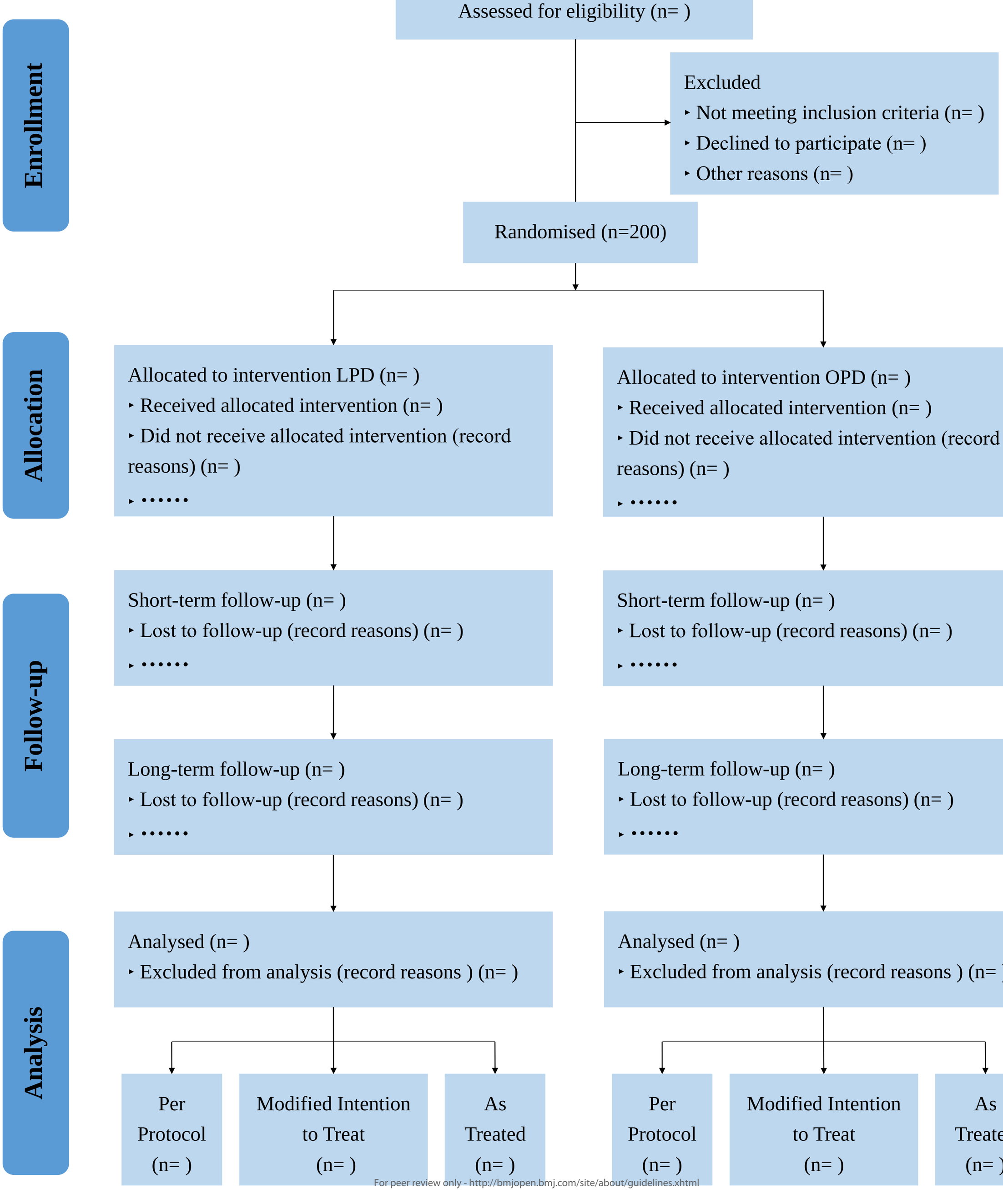
LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

**Figure legend.**

Figure 1: Flow diagram for TJDBPS07. CONSORT, Consolidated Standards of Reporting Trials; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

# CONSORT

## TRANSPARENT REPORTING of TRIALS



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3;15 |
| Protocol version | 3 | Date and version identifier | 15 |
| Funding | 4 | Sources and types of financial, material, and other support | 16 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | 2 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16 |
| | 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) | 13 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 5 |

| | | | |
|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6-7 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 9-10 |
| | 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) | 10 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10-11 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10-11 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-8 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8-9 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |

| | | | |
|---|---|---|---|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 9 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11-12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 11-12 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 11-12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 13 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 6 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6;10;15 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | - |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 11;15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 15 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 |
| | 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 | 12 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | annex |
| 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" license.

BMJ Open

# Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial



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| Secondary Subject Heading: | Oncology, Surgery |
| Keywords: | Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < ONCOLOGY |
| | |

# Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial

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## Abstract

**Introduction:** Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic head cancer. Minimally invasive surgery, which initially emerged as hybrid-laparoscopy and recently developed into total laparoscopy surgery, has been widely used for various abdominal surgeries. However, controversy persists regarding whether laparoscopic PD (LPD) is inferior to open PD (OPD) for resectable pancreatic ductal adenocarcinoma (PDAC) treatment. Further studies, especially randomised clinical trials, are warranted to compare these two surgical techniques.

**Methods and analysis:** The TJDBPS07 study is designed as a prospective, randomised controlled, parallel-group, open-label, multicentre noninferiority study. All participating pancreatic surgical centres comprise specialists who have performed no less than 104 LPDs and OPDs, respectively. A total of 200 strictly selected PD candidates diagnosed with PDAC will be randomised to receive LPD or OPD. The primary outcome is the 5-year overall survival rate, whereas the secondary outcomes include overall survival, disease-free survival, 90-day mortality, complication rate, comprehensive complication index, length of stay, and intraoperative indicators. We hypothesize that LPD is not inferior to OPD for the treatment of resectable PDAC. The enrolment schedule is estimated to be 2 years and follow-up for each patient will be 5 years.

**Ethics and dissemination:** This study received approval from the Tongji Hospital Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, and monitor from an independent third-party organization. Results of this trial will be presented in international meetings and published in a peer-reviewed journal.

**Trial registration:** Clinical Trials Register, NCT03785743. Registered on 10 Mar. 2019.

## Strengths and limitations of this study

This trial aims to compare long-term safety of LPD and OPD for resectable PDAC treatment in a large multicentre setting and will provide evidence on performance of PDAC resection.

All participating pancreatic surgical centres are qualified with experienced surgeons who have performed no less than 104 LPDs and OPDs, respectively.

Each patient will attend a follow-up of at least 5 years to determine the study primary outcome, the 5-year overall survival rate, which is the most used indicator for describing cancer survival.

This is an open-label trial; accordingly, participants and clinicians will not be blinded to interventions.

The primary outcome of this trial will be derived from data acquired during the long-term follow-up, requiring high levels of follow-up compliance and challenging coordination between surgeons, oncologists, visitors, and patients.

## INTRODUCTION

Pancreatic cancer is a highly fatal malignancy with poor responses to therapy and is estimated to be the fourth leading cause of cancer mortality[1]. Among all types of pancreatic cancer, the vast majority are pancreatic ductal adenocarcinoma (PDAC)[2]. Pancreaticoduodenectomy (PD), the standard procedure for resectable pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures[2 3]. Compared with traditional open surgery, minimally invasive surgery (MIS) has several advantages, such as small incision, minimal intraoperative bleeding, and fast postoperative recovery, among others[4], which are essential factors promoting the development of surgical treatments. However, the long-term survival benefits of MIS in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival (OS) and disease-free survival (DFS) than open surgery for patients with early-stage cervical cancer[5].

Since its inception by Gagner et al. in 1994, laparoscopic PD (LPD) has been increasingly performed owning to its potential technical advantages[6 7]. As shown by the ISGPS Evidence Map of Pancreatic Surgery[8], an increasing number of studies, including 4 large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for treatment of periampullary or pancreatic tumours[9-13]. Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) by highly experienced surgeons who have passed the learning curve[12 14]. However, the application of LPD to PDAC treatment is concerning. Several studies have focused on the comparison of LPD and OPD for PDAC treatment and suggested that LPD was associated with equivalent oncologic outcomes and promising superior long-term survival outcomes compared with OPD[15]. However, retrospective studies are associated with inherent limitations, including patient selection biases, missing or incomplete data, and unaccounted-for variables, making results difficult to interpret definitively. No RCTs have investigated the effects of LPD and OPD on survival in patients with PDAC.

To explore the long-term safety and efficacy of LPD in patients with PDAC using high-level evidence, the Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM) designs and conducts this prospective large-scale multicentre RCT to analyse outcomes of interest, immediately after the TJDBPS01 trial, which interpreted the safety and feasibility of LPD compared with those of OPD. Accordingly, this trial aims to compare the long-term oncological and short-term surgical outcomes of LPD and OPD performed by highly experienced surgeons that have surmounted the learning curve for PDAC treatment.

## METHODS AND ANALYSIS

## Trial design

This trial is characterized as a prospective, multicentre, randomised controlled, and open-label study comprising two parallel groups of patients undergoing OPD and LPD. Patients diagnosed with pancreatic malignant tumours requiring PD will be consecutively recruited. This study will be conducted at ten high-volume pancreatic surgery centres in China, with surgeries being conducted by experienced surgeons. After providing written informed consents, 200 patients will be preoperatively allocated in a 1:1 ratio to either the LPD or OPD arm. The recruitment duration is estimated to be 2 years and the follow-up duration will be 5 years. The primary endpoint of this trial is the 5-year OS rate. The study will be prepared, analysed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines[16], as presented in Figure 1.

## Qualifications of participating surgeons and centres

The responsible participating surgeons shall satisfy the following qualifications as previously described in the TJDBPS01 study[12]: (1) having completed no less than 104 cases of LPDs; (2) having completed no less than 104 cases of OPDs[14]; and (3) having completed trainings of the Tongji Hospital LPD training program. Moreover, the participating centres shall perform more than 50 PDs annually. Surgeons willing to participate shall offer one recently unedited LPD and OPD surgery video, respectively, to the TJDBPS07 research council for evaluation. If the research council approves the surgical techniques, the surgeon and the centre will be permitted to participate in this study as a collaborator. Eligible patients will be discussed at regularly scheduled multidisciplinary team (MDT) meetings. Randomisation and assignment of a study-specific ID will be performed by the study sponsor.

## Population and eligibility criteria

All adult patients indicated for elective PD because of a pancreatic mass will be screened for eligibility. Eligible patients will be assessed by the pancreatic MDTs of the participating centres. The MDTs should confirm that the pancreatic mass is highly suspected to be a pancreatic malignant tumour and of sufficient concern to require resection. Imaging data of contrast enhanced multi-thin sliced computed tomography (CT) scan (1mm) with or without endoluminal ultrasonography (EUS) will be regarded as the standard evaluation for each PD candidate. The last CT imaging should be performed within 4 weeks before the surgery. Histological diagnoses of malignancies are encouraged to be acquired but not a necessity[17]. All patients will sign the informed consent and be allowed to leave the trial at any time. The exact inclusion and exclusion criteria are below.

Inclusion criteria

1) Age between 18 years and 75 years.
2) Histologically confirmed PDAC or clinically diagnosed PDAC by an MDT without histopathologic evidence.
3) Patients feasible to undergo both LPD and OPD according to MDT evaluations.
4) Patients understanding and willing to comply with this trial.
5) Provision of written informed consent before patient registration.
6) Patients meeting the curative treatment intent in accordance with clinical guidelines.

Exclusion criteria

1) Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs.
2) Patients requiring left, central or total pancreatectomy or other palliative surgery.
3) Preoperative American Society of Anaesthesiologists (ASA) score ≥ 4.
4) History of other malignant disease.
5) Pregnant or breast-feeding women.
6) Patients with serious mental disorders.
7) Patients treated with neoadjuvant therapy.
8) Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.
9) Body mass index > 35 kg/m$^2$.
10) Patients participating in any other clinical trials within 3 months.

**Endpoints**

The primary endpoint of this trial is the 5-year overall survival rate, which is defined as the percentage of patients in this trial who are alive 5 years postoperatively [time frame: 5 years postoperatively].

Other crucial indicators are included as secondary endpoints, including (1) overall survival (i.e., the interval between the day of surgery and the day of death for various reasons [time frame: 5 years postoperatively]); (2) disease-free survival (i.e., the interval between the day of surgery and the day of tumour recurrence [time frame: 5 years postoperatively]; (3) 90-day mortality (i.e., the percentage of patients who died within 90 days postoperatively). Mortality will be calculated by dividing the number of patients who died by the number of all patients undergoing surgical treatment; (4) complication rate (complications related to PD, including major complications with

Clavien-Dindo ≥3[18], postoperative pancreatic fistula[19], postoperative bile leak[20], postpancreatectomy haemorrhage[21], delayed gastric emptying[22], and chyle leak[23], are defined according to the International Study Group of Pancreatic Surgery) (5) comprehensive complication index[24] (CCI, calculated as the sum of all complications that are weighted for their severity, available at www.assessurgery.com); (6) length of stay (i.e., the number of nights spent in the hospital from the end of the surgical procedure until discharge or death); and (7) intraoperative indicators, including estimated blood loss and operation time.

## Sample size

The sample size calculation was performed according to the primary endpoint, the 5-year OS rate, and the non-inferiority design of this trial. Assumptions were made based on a previous study by Kuesters et al.[25], which compared LPD with OPD for PDAC treatment with the 5-year OS rate being 20% in the LPD group and 14% in the OPD group. Based on the 6% decrease in 5-year OS rate in the OPD group compared with the LPD group, the sample size required for each group was estimated to be 86 patients to achieve a non-inferiority limit of 10% at a one-tailed significance level of 2.5% with a power of 80% and a balanced design (1:1 ratio). Moreover, the primary analyses will be based on the modified intention to treat (mITT), per protocol (PP), and as treated (AT) sets. We aimed to reach a statistical power of 80% when analysing the smallest population, namely the PP set.

Patients converted from LPD to open surgery will not be included in the PP set. Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group and 91 patients in the OPD group will be needed for analysis using the one-sided *t* test at a one-sided significance level of 0.025. PASS version15.0.5 will be used for the calculations. An additional 10% of patients will be needed to be randomised considering the non-resectable patients, patients withdrawing from the study, and patients lost to follow-up. Accordingly, 100 patients in the LPD arm and 91 patients in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1, requiring 100 patients in each arm and 200 patients in total to be included for randomisation.

## Patient timeline and description of trial visits

The study duration is estimated to be 7 calendar years, with an enrolment schedule of 2 years and a follow-up period of 5 years for each patient. The end of the trial was defined as 5 calendar years since the last enrolled patient received surgery. This protocol is reported in accordance with the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Table 1, supplemental file 1)[26].

Data collection and assessment are recommended to be conducted at the responsible surgical centre. Baseline data will be collected during the screening/baseline visit, and surgical data will be collected intra- and postoperatively.

Short-term follow-ups will be conducted 1 day, 1 week, 1 month, and 3 months postoperatively, and follow-up contents will include laboratory inspection indicators, Eastern Cooperative Oncology Group (ECOG) score, Karnofsky Performance Scale (KPS) score, postoperative wound recovery, wound pain level, drainage of each drainage tube postoperatively, postoperative recovery (i.e., time until getting out of bed, imported food, and so on), weight, adverse events, combined medication, and postoperative complications.

Long-term follow-ups will be conducted every 3 months within the first postoperative year and every 6 months from the second postoperative year onwards. The following follow-up contents will be tracked and recorded: clinical evaluations including internal inspections (such as weight, KPS score, and ECOG score), chemotherapy-related adverse events, imaging items to prove the existence of tumour recurrence or metastasis (record the date of recurrence, location and follow-up treatment), the date of death, and the cause of death (i.e., disease- or treatment-related mortality).



## Randomisation and blinding

Eligible patients signed the informed consent form will be screened within one week prior to randomisation. Randomisation will be assigned on the day the preoperative evaluation is finished and the patient is diagnosed with PDAC, eligible for PD. We will employ a 1:1 randomisation pattern for arms A and B, stratified by participating centres. Random numbers will be generated by SAS software version 9.40 (SAS Institute, Inc., Cary, NC) and randomisation will be performed through a centralized computer-generated system by providing random numbers using dynamic blocks. Within each block, randomisation is balanced, and every patient is assigned to a treatment using the randomisation scheme.

This is an open-label trial, and randomisation procedure and outcome will not be blinded to patients and surgeons. However, data collectors, outcome assessors, and data analysts will be blinded during statistical analysis. Surgeons will not participate in the data collection process which will be conducted by an independent team. Analysis processes will be blinded, and the statistician will be provided with only group codes instead of group names.

## Intervention

Surgical procedures need to comply with PD technique standards as previously described[27]. Any appropriate changes in surgical procedures according to the surgeon's own experience and preference are permitted, including changes in procedure order, surgical approach, and anastomosis method. All changes will be

recorded in the case report form.

**Experimental intervention-LPD techniques**

Patients will take a supine position and undergo general anaesthesia. Five trocars in total will be used. Routine and standard lymph node dissections will be maintained as recommended by guidelines. The pancreatic stump will be sent for quick frozen pathological examination intraoperatively; moreover, it is necessary to confirm that the pancreatic margin specimen is pathologically negative before digestive tract reconstruction. Surgeons will determine the reconstruction type according to their experiences and preferences. After reconstruction, two drainage tubes are routinely placed, with one near the anastomosis of the pancreaticojejunostomy and the other near the anastomosis of the bile jejunum.

Conversion to open surgery is defined as the use of any skin incision during LPD for other than trocar placement or surgical specimen removal. For cases of conversion, data will be analysed in the LPD group in an intention-to-treat manner. However, reasons for conversion shall be realistically registered and carefully recorded.

**Control intervention-OPD techniques**

Open surgery shall be performed by the same group of surgeons as LPD. Key steps are performed essentially as described in the LPD group. Methods used for reconstruction during OPD must be consistent with those during LPD in the same single centre.

**Concomitant treatment**

The TJDBPS07 trial follows TJDBPS01 which compared LPD and OPD; accordingly, the principles of perioperative management are similar to those previously described[27]. Whatever medical devices and materials that are most used in daily practice of each participant centre can be used if recorded carefully in surgical records. Antibiotics are given to patients 30 min before skin incision and 2 h after incision. Patient-controlled analgesia will be used to control postoperative pain. Time to remove the nasogastric tube depends on each patients' situation evaluated by doctors of each participating centre; early removal is encouraged. The abdominal drains will be placed routinely for patients. The timepoint of drain removal depends on every patient's manifestation, laboratory examination results (the concentration of drain fluid amylase (DFA) on postoperative days (PODs) 1 and 3), and imaging findings. In patients with a DFA concentration of less than 5000 U/L on POD 1, early drain removal at 72 h is recommended. In patients with a DFA concentration of more than 5000 U/L on POD 1, drain removal will be decided by the corresponding surgeon according to the patient's situation. Patients can be discharged if they meet the following discharge

criteria: no need for intravenous infusion, well tolerance of oral solid or semisolid food, no need for intravenous analgesics, well wound healing, well tolerance of independent walking at least 250 m in a plain road, well major organ function with near-normal haematological parameters.

After surgical resection, patients pathologically diagnosed with PDAC will receive adjuvant chemotherapy according to the National Comprehensive Cancer Network (NCCN) guideline[28]. Written informed consent for adjuvant chemotherapy should be obtained. Different regimens recommended in the aforementioned guideline are permitted, and the treatment duration is at the discretion of the responsible treating oncologist. Detailed information on adjuvant chemotherapy will be recorded. Relapse cases will be treated according to the recommendations of the NCCN guideline at the corresponding participating centres.

**Data collection and management**

All data will be collected using an electronic case report form. The datasets generated during the study will be stored in a local database, which is managed by the data collection group of Tongji Hospital. Investigators from each participating institution will have access to the data of their respective patients. All data are pseudonymized, and patient details are encoded.

Data collection will include variables related to patient demographics, intraoperative information, histopathological information, postoperative clinical findings, adjuvant chemotherapy, and follow-up.

Patient demographics: age, gender, height (cm), weight (kg), smoking, drinking, main complaint, clinical diagnosis, comorbidities, surgical history, underlying malignant disease, ECOG score, ASA score, imaging results, preoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and carcinoembryonic antigen (CEA)), preoperative biliary drainage, and date of admission.

Intraoperative information: operation date, surgical approach (laparoscopic or open), conversion to open surgery, intraoperative death, texture of pancreas, diameter of the main pancreatic duct, placement of intra-abdominal drain, type of reconstruction, anastomosis approach (intracorporeal or extracorporeal), anastomosis performance (linear stapler, circular stapler, hand-sewn, or combinations), total operative time, each anastomosis time (pancreaticojejunostomy, cholangiohepaticojejunostomy, and gastroenterostomy), intraoperative complications, estimated blood loss, and intraoperative blood transfusion.

Histopathological information: tumour location, tumour size, histological type, surgical margin status (R0 resection rates), number of lymph nodes, number of positive lymph nodes, depth of invasion (T classification), lymph node status (N

classification), and American Joint Committee on Cancer staging.

Postoperative clinical findings: length of postoperative stay, postoperative blood transfusion, length of intravenous analgesic use, drain production and amylase, postoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA), date of patient mobilization, date of liquid diet, date of drain removal, postoperative complication, reoperation, Clavien-Dindo grade, adverse event, cost of surgery, and cost of hospitalization.

Adjuvant chemotherapy: date of adjuvant chemotherapy, chemotherapy regimens, side effects, imaging results, haemoglobin level, white blood cell count, and related tumour markers (i.e., CA19–9, CA125, and CEA).

Follow-up: date of follow-up visit, patient status (alive, dead or lost to follow-up), ECOG score, KPS score, imaging results, related tumour markers (i.e., CA19–9, CA125, and CEA), DFS, and OS.

## Data Availability Statement

The final datasets will not be available to the public. However, researchers will have access to the study data in de-identified form from the corresponding author after reasonable request when the study is completed.

## Risk of bias

All adult patients with pancreatic masses eligible for PD will be screened in all participating centres. The recruited patients will be expected to be generalizable and representative to the wider population. Standard randomisation will be conducted to ensure comparable baseline characteristics between each group. To minimize confounding, allocations will be stratified by centre.

The primary outcome of this trial is the 5-year OS rate, which is objective and will be obtained from the planned follow-up data. The participants, surgeons, and nursing staff will not be blinded to interventions due to the characteristics of this trial, which compares MIS and conventional open surgery. The responsible surgeons will not be involved in the postoperative management of patients and determination of patients' discharge. Data collectors, outcome assessors, and data analysts will all be blinded to surgical techniques.

To minimize missing data bias, data for the primary outcome will be routinely collected and regularly reviewed.

Results of this trial will be reported in accordance with the CONSORT statement[16] to minimize reporting bias. In addition, the trial protocol is reported according to the SPIRIT statement[26] to assure full transparency throughout this trial and subsequent

reporting.

**Assessment of cross-over patients**

Conversion from LPD to OPD is closely associated with intraoperative situations, including technical infeasibility and significant bleeding, which is unavoidable even for experienced surgeons who have passed the learning curves, making it impossible to eliminate conversion by modifying inclusion and exclusion criteria. The conversion rate in our previous trial comparing LPD and OPD for pancreatic or periampullary tumours was 4%[12]. Considering the techniques complexity in LPD for PDAC, the maximum conversion rate within this trial is cautiously estimated to be 10%. Reasons for conversion will be recorded in detail and further evaluated in the subgroup analysis.

**Statistical analysis**

A statistical analysis plan will be developed and agreed upon by the data collection group. All main statistical analyses will be performed according to an intention-to-treat principle, and the primary analysis will be based on the mITT, PP, and AT set. Patients deemed unresectable intraoperatively or who do not receive surgical resection will not be considered in any of the analysis sets. The mITT set will comprise all patients in the group to which they were randomised regardless of the actual received surgery. The PP set will include patients without major protocol violations. Patients converted from LPD to OPD will not be included in the PP set. The AT set will be analysed with considerations of the actual treatment of patients, rather than their randomisation. For robust interpretation, the results of the three primary analysis sets should lead to similar conclusions; otherwise, possible reasons behind discrepancies must be discussed. OS and DFS will be analysed from the date of pancreatic resection to the date of death (for OS) or date of regional recurrence or systemic spread (for DFS). The OS and DFS curves for the entire follow-up period will be estimated according to Kaplan-Meier method and compared using a log-rank test. Time-specific OS and DFS probabilities at appropriate time points will be derived from the survival curves and the Greenwood estimate will be used to construct corresponding a 95% confidence interval (CI). Hazard ratios (HRs) and two-sided 95% CIs will be estimated using a Cox regression model after confirming the proportional hazards assumptions.

In summary, continuous data will be presented as mean ± standard deviation and will be compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables will be compared using the $\chi^2$ test or Fisher's exact test, as appropriate. Statistical analyses will be conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). $P < 0.05$ will denote statistical significance.

This trial is registered at ClinicalTrials.gov (registration number: NCT03785743).

## Monitoring

Throughout the trial, a trained, qualified, and independent monitor will periodically visit each participating centre to randomly check protocol compliance, compliance with the inclusion and exclusion criteria, proper implementation, obtainment of informed consent forms, source data verification, and reporting of serious adverse events. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[29]. The Hospital Ethical Committee and Chinese Clinical Trial Registry are responsible for collection and management of these data. Moreover, an independent agency will handle the auditing every month.

## DISCUSSION

The TJDBPS07 trial is designed as a prospective, multicentre, randomised controlled, and open-label trial to assess the long-term oncological and short-term surgical outcomes of LPD and OPD for PDAC treatment. The results of our TJDBPS01 trial suggested that LPD is a safe and feasible procedure for treating pancreatic or periampullary tumours, with comparable short-term outcomes to OPD in highly experienced hands[12 27]. The TJDBPS07 trial follows TJDBPS01 and focuses on the comparison of LPD and OPD for treatment of resectable PDAC. In consideration of the complexity and difficulty of PD, surgeons participating in this trial are required to complete a structured training program for LPD and pass the learning curve by finishing a minimum of 104 LPDs, as suggested by the results of a retrospective study on the learning curve for LPD in China[14].

Minimally invasive surgeries have gained increasing popularity in recent years because they have shown some promise in improving perioperative outcomes[30]. Nevertheless, their long-term effects on patients with malignant diseases require further exploration. Several RCTs focused on this topic and reported different conclusions. A study by Yu et al. found that laparoscopic distal gastrectomy and open surgery had comparable DFS and OS in patients with locally advanced gastric cancer[31]. Moreover, a study by Kitano et al. concluded that laparoscopic D3 surgery was not inferior to open surgery in terms of OS in patients with stage II and III colon cancer[32]. However, research by Pedro et al. suggested that for patients with early cervical cancer, minimally invasive radical hysterectomy resulted in lower rates of DFS and OS than open radical hysterectomy[5]. The current guidelines of NCCN suggest that minimally invasive surgeries are feasible and safe for patients with hepatobiliary cancer[33], colon cancer[34], rectal cancer[35], ovarian cancer[36], cervical cancer[37], and pancreatic cancer[28], among others. Meanwhile, many of these guidelines state that their long-term safety needed to be further evaluated in more high-quality researches.

With a 5-year survival rate of approximately 10%, the highly fatal pancreatic cancer is becoming an increasingly common cause of cancer-related mortality. Surgical

resection represents the only chance of cure for patients with resectable pancreatic cancer[38]. An increasing number of researchers are interested in the therapeutic effects of LPD on patients with PDAC in recent years[39], but there is still a lack of prospective research supporting its long-term safety in these patients. Available evidence is based on a few retrospective studies with limited quality[40]. The data of 322 patients with PDAC (108 undergoing LPD and 214 undergoing OPD) demonstrated that LPD was technically feasible for PDAC treatment and was associated with better length of stay, postoperative recovery, and pursuing adjuvant treatment than OPD. This study simultaneously showed comparable OS but longer DFS in LPD than OPD[41], while other studies have indicated that the long-term survival and perioperative outcomes were comparable between LPD and OPD for treatment of selected PDAC patients[42-44]. Considering the controversies among existing publications and limitations of observational studies, doctors and researchers in the field of PDAC emphasize the necessity and importance of large-scale multicentre RCTs.

In conclusion, the TJDBPS07 trial is a multicentre randomised controlled, non-inferiority trial investigating the long-term survival and the preoperative safety of LPD and OPD for resectable PDAC. This trial aims to evaluate differences in the 5-year OS rate between LPD and OPD for PDAC treatment. The results of this trial will provide high-level evidence for guiding the daily practice of PDAC management.

## Trial status

The TJDBPS07 trial was registered on 10 March 2019 at the ClinicalTrials Registry (registration number: NCT03785743). The protocol of this trial was proposed by the investigator from Tongji Hospital, and the final version was approved by Tongji Institutional Review Board. The first enrolled patient has been given the randomised number in August 2019. All ten centres are actively recruiting patients by the time this protocol is submitted. Recruitment will approximately be completed by December 2021.

## Patient and public involvement

This trial will not involve either patients or the public in the design, recruitment, conduct of the study, or measurement of outcomes. The trial results will not be notified to every single patient, while instead, the results will be presented in academic conferences, and disseminated via open-access and peer-reviewed journals. This trial will investigate patient-reported outcomes, using tools such as questionnaires about quality of life.

## Ethics and dissemination

Each participant will sign an informed consent document before inclusion; this form

is provided by a qualified team member and subsequently sent to and preserved by the data collection team. All participations are voluntary and have the right to withdraw from the study for any reason whenever they want to. If they do withdraw, they will still receive standard treatment according to local hospital procedures. The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and its later amendments[45]. This trial was registered under the Tongji Hospital (trail ID: NCT03785743) and approved by Tongji Hospital Ethics Committee (approval number: TJ-IRB20190318) in March 2019. Local ethical approval was confirmed from each participating centre before recruiting at other centres. All authors have access to study data and reviewed and approved the final manuscript. The results of this trial will be presented in international meetings, and final trial results will be published in an open access, peer-reviewed journal.

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**Authors' contributions**

RYQ, MW, and FZ obtained funding for the study. RYQ, HZ, and MW designed the study. XJY, JiL, JuL, WXZ, XMC, DWL, JHL, JDL, YHL, and RYQ performed the operations. STP, TTQ, and TYY drafted the manuscript. RYQ, HZ, and MW contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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**Disclaimer**

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**Competing interests**

The authors and each study site declare no conflicts of interest.

## Patient consent for publication

Not required.

## Provenance and peer review

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Table 1: Schedule of study enrolment, interventions, and assessments

| | Study Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Enrollment | Allocation | Treatment | Discharge | Post-allocation | | | | | | | | | | | Close-out |
| **Time point** | Outpatient clinic /Admission | Before Surgery | Surgery | After Surgery | Month 1 (T1) | Month 3 (T2) | Month 6 (T3) | Month 9 (T4) | Month 12 (T5) | Month 18 (T6) | Month 24 (T7) | Month 30 (T8) | Month 36 (T9) | Month 42 (T10) | Month 48 (T11) | Month 54 (T12) | Month 60 (T13) |
| **Enrollment** | | | | | | | | | | | | | | | | | |
| Eligibility screen | × | | | | | | | | | | | | | | | | |
| Informed consent | × | | | | | | | | | | | | | | | | |
| Allocation | | × | | | | | | | | | | | | | | | |
| **Interventions** | | | | | | | | | | | | | | | | | |
| LPD | | | × | | | | | | | | | | | | | | |
| OPD | | | × | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | × | | | | | | | | | | | | | | | | |
| **Assessments** | | | | | | | | | | | | | | | | | |
| Baseline characteristics | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Blood routine | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Blood biochemistry | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Tumor marker | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Abdominal CT scan | × | | | × | | × | × | × | × | × | × | × | × | × | × | × | × |
| Surgical record | | | × | | | | | | | | | | | | | | |
| Postoperative record | | | | × | | | | | | | | | | | | | |
| Pathological findings | | | | × | | | | | | | | | | | | | |
| Adjuvant therapy | | | | × | | | | | | | | | | | | | |
| Survival status | | | | | × | × | × | × | × | × | × | × | × | × | × | × | × |
| | | | | | | × | × | × | × | × | × | × | × | × | × | × | × |

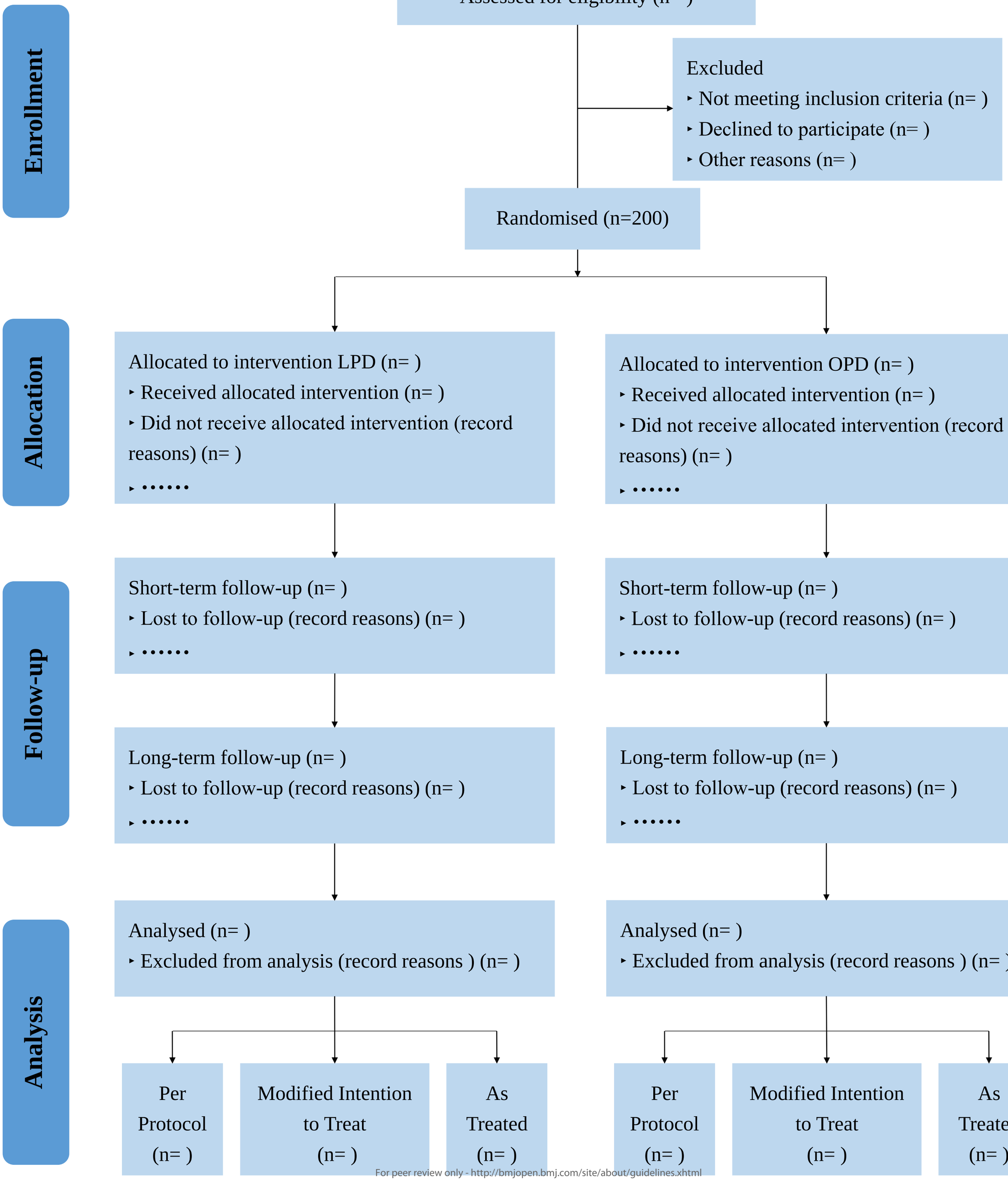
LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

**Figure legend.**

Figure 1: Flow diagram for TJDBPS07. CONSORT, Consolidated Standards of Reporting Trials; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

# CONSORT

## TRANSPARENT REPORTING of TRIALS



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 3;15 |
| Protocol version | 3 | Date and version identifier | 15 |
| Funding | 4 | Sources and types of financial, material, and other support | 16 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | 2 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16 |
| | 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) | 13 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 5 |

| | | | |
|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6-7 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 9-10 |
| | 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) | 10 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10-11 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 10-11 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-8 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8-9 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |

| | | | |
|---|---|---|---|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 9 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11-12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 11-12 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 11-12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 13 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 13 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 15 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 6 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6;10;15 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | - |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 16 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 11;15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 15 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 15 |
| | 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 | 12 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | annex |
| 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" license.