Statistical Analysis Plan

Principal Investigator: Prof. Xiujun Cai

Research Institution: Sir Run Run Shaw Hospital, Zhejiang University

Register Number: NCT06204497

Date: 2025-10-06

Version: 1.1

1. Introduction

This trial is a multicenter, prospective, randomized, controlled, open label, parallel-group, non-inferiority trial to evaluate the safety and efficacy of stent-based diverting technique versus ileostomy in rectal cancer patients. In this trial, stent-based diverting technique is considered to reduce the overall length of post-operation hospital stay and medical costs, improve patients' quality of life, while not increasing the peri-operative complication rate. The primary endpoint is the incidence of severe complications within 90-day (Clavein-Dindo ≥ III), and the secondary endpoints are the incidence of total complications, the incidence of anastomotic leakage (Grade B/C), and the postoperative hospital stays and cost, and the postoperative quality of life. Patients are randomly assigned into two groups in a 1:1 ratio: stent-based diverting technique receiving rectal cancer surgery followed by stent-based diverting technique, ileostomy group receiving rectal cancer surgery followed by ileostomy. The follow-up period finishes 90 days after the last patient is receiving the final surgery.

2. Population

2.1 Intent-to-treat population

The intent-to-treat (ITT) population will include all patients who participated in this trial after randomization, and will be grouped based on the treatment they were randomized to receive.

1.2 Per-protocol population

The per-protocol (PP) population will consist of patients who participated in this trial and fully complied with the protocol, and will be used for sensitivity analysis.

2.3 The as-treated (AT) population will consist of patients who received the actual surgical procedure, and will be used for sensitivity analysis.

2.4 Safety population

The safety population will consist of all randomized patients in this trial, excluding those who withdrew prior to the surgery. Patients will be grouped according to the treatment they actually received, and safety monitoring will be conducted on this population.

3 Data validation

Upon data entry, the database will validate data in real time based on pre-programmed validation rules. Each participating center will have a data manager who verifies the completeness, consistency, and timeliness of all data. For missing data, the data manager is also responsible for retrieving the original data, with a high likelihood of successful retrieval. Additionally,

the data manager will check and track data related to primary and key secondary outcomes at specified time points.

4 Data Analysis

4.1 General calculations

For the summary of population characteristics, all percentages will be calculated with the total number of the intent-to-treat (ITT) population as the denominator (including all patients with missing data for the relevant variable). For the summary of categorical outcome variables (e.g., complication rate), patients with missing data will be excluded from the denominator when calculating percentages. For the summary of continuous outcome variables (e.g., estimated blood loss, length of hospital stay, cost), patients with missing data will be excluded when calculating means or medians. When patients with missing data are excluded from the denominator, the number of patients included in the summary will be clearly reported.

All percentages, means, standard deviations (SDs), medians, interquartile ranges (IQRs), and ranges will be rounded to 1 or 2 decimal place. P-values will be rounded to 3 decimal places. Parameter estimates, standard errors (SEs), relative ratios (RRs), and 95% confidence intervals (CIs) will be reported to 1 or 2 decimal places. Hypothesis testing for

primary outcome will be one-sided at the 2.5% significance level, others will be two-sided at the 5% significance level.

4.4 Screening data

The CONSORT flow diagram will be used to summarize the progress of participants throughout the study. Participating sites are required to record details of all randomized participants, including those who no longer meet the eligibility criteria or do not undergo surgery. Protocol violations will also be summarized, along with the reasons for each deviation.

4.5 Withdrawals

The number of participants who withdraw consent from the study will be summarized, along with the reasons for their withdrawal. For patients who withdraw prior to surgery, no further data submission will be required. For those who withdraw after surgery, collection of treatment and follow-up data will still be required (including the administration of additional patient-reported questionnaires), but patients will not receive any further trial-specific interventions. With patients' permission, data collected before withdrawal may still be used for analysis. If a patient explicitly states that they do not wish to contribute further data to the trial, their wishes will be respected, and the patient will be handled as a censored case.

4.6 Baseline characteristics

Baseline clinical data, as documented in the baseline assessment forms, will be tabulated using frequencies and summary statistics for each treatment group and the overall population. No statistical testing will be performed on these data.

4.7 Primary outcome

The primary endpoint will be analyzed in the ITT population and defined as the rate of severe complications (Clavien-Dindo grade ⩾ III) within 90 days post-surgery, the primary endpoint will be assessed as follows (Time Frame: For the Study Group, from the SDT to 90 days after surgery; if the patient undergoes ileostomy as a salvage procedure, the time frame will be extended to 90 days after stoma reversal. For the Control Group, from ileostomy creation to 90 days after stoma reversal. For patients in both groups who do not undergo stoma reversal, the time frame will be defined as 90 days after the initial surgery). This endpoint will be analyzed using logistic regression to calculate the relative ratio (RR), with reporting of the between-group difference and corresponding 95% confidence interval (CI).

Subgroup analysis will be performed according to: Age, Gender, Body mass index, Use of noeoadjuvant radiotherapy, Tumor to anal verge, Multiple high-risk factors, Pathological T stage, Pathological N stage,

Presence of prior abdominal surgery. The RRs will be reported with corresponding 95% CI.

4.8 Secondary outcomes

Secondary outcomes will be analyzed in the ITT population. For categorical variables, a two-sided Pearson's χ^2 test or Fisher's exact test will be used, as appropriate; the rate difference and corresponding 95% CI will be calculated using the Miettinen-Nurminen method. For continuous variables, Student's t-test (for normally distributed data) or the Mann-Whitney U test (for non-normally distributed data) will be applied, as appropriate; the median difference and corresponding 95% CI.

4.9 Sensitivity analysis

Sensitivity analyses will be conducted for the per-protocol (PP) and as-treated (AT) populations. The statistical methods used in these sensitivity analyses will be consistent with those applied to the intent-to-treat (ITT) population. Results will be compared and interpreted across the ITT, and PP populations to determine whether protocol violations or missing data have an impact on the study outcomes.

5 Safety monitoring

Safety indicators will be monitored and analyzed in the safety population. Each participating medical center will designate independent monitors to

oversee safety indicators, including the postoperative severe complication rate and serious adverse events.

To ensure participant safety and trial rigor, an independent Data and Safety Monitoring Board (DSMB) was composed of a colorectal surgeon, a biostatistician, and an ethics consultant. The DSMB conducted blinded reviews (with no access to group allocation) of the primary outcome: the incidence of 90-day severe complications (Clavien-Dindo grade≥III) and all serious adverse events (SAEs) every 6 months. During these reviews, no protocol violations or safety signals warranting trial suspension were identified, and the DSMB consistently recommended that the trial continue as planned.

Signature: Yimin Zhu 

Date: 2025-10-06