Statistical Analysis Plan (Final, Version 1.2)

Principal Investigator: Prof. Xiujun Cai

Research Institution: Sir Run Run Shaw Hospital, Zhejiang University

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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 (SDT) versus ileostomy in rectal cancer patients. In this trial, SDT 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 outcome was the 90-day incidence of severe complications (Clavien-Dindo grade ⩾ III). Secondary outcomes included overall complication rate, anastomotic leakage rate (grade B/C), length of postoperative hospital stay, hospitalization costs, and 90-day postoperative quality of life.

Patients were randomized 1:1 to two groups:

- SDT group: rectal cancer surgery plus stent-based diverting technique
- Ileostomy group: rectal cancer surgery plus protective ileostomy

Follow-up concluded 90 days after the last patient underwent surgery.

2. Population

● 2.1 Intent-to-treat population

The intent-to-treat (ITT) population will include all randomized participants, with grouping according to their originally assigned treatment,

regardless of whether the allocated intervention was actually received or completed. Primary and secondary outcome analyses will be performed in the intent-to-treat (ITT) population. As randomization was performed intraoperatively, a modified ITT (mITT) population was not defined in this study.

- **2.2 Per-protocol population**

The per-protocol (PP) population includes all randomized participants who completed the study as planned, with no major protocol violations, adequate adherence to the assigned intervention, and sufficient follow-up data for the primary outcome assessment. Primary and secondary outcome analyses will be conducted in the PP population as sensitivity analyses.

- **2.3 As-treated population**

The as-treated (AT) population comprises all randomized patients who actually received the intervention to which they were assigned, regardless of their original randomization group. In this trial, participants randomized to the SDT group but who ultimately underwent ileostomy for various reasons were included in the ileostomy group in the as-treated analysis, and vice versa. All as-treated analyses were conducted as sensitivity analyses.

- **2.4 Safety population**

The safety population comprises all randomized patients in this trial, except those who withdrew prior to surgery. Patients were categorized

based on the treatment actually received, on which safety monitoring was performed. As this is a surgical study with the primary outcome focused on perioperative complications, all eligible patients were included in the safety population. Adverse events were monitored and reviewed by the Data Safety and Monitoring Board (DSMB).

3. Data Management

3.1 Summary

Data are entered remotely via electronic Case Report Form (eCRF) within an Electronic Data Capture (EDC) system. The database is designed and validated by the data manager to ensure accuracy. Only authorized site staff may enter or edit data, with each entry logged by a unique user ID and confirmed by electronic signature. All corrections are traceable (cross-out notation, reason, signature, date) without erasing original records, and a full audit trail is maintained. Unless specified, eCRF is not a source document; monitors verify its consistency with source data.

3.2 Data management

Data management includes logic checks, queries for inconsistent/missing data, and ongoing quality control. Treatment-emergent adverse events and concomitant medications are coded.

3.3 Data Verification

Data verification includes logical, manual, medical, and statistical checks. Queries are issued via the EDC system and resolved by the investigator/CRC until all data are validated. 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.

3.4 Database Lock

After all source data are entered and reviewed by the Principal Investigator, statistician, and data manager with no unresolved queries, the database lock form is signed, and the database is locked. Locked data are exported for statistical analysis and cannot be edited. Minor post-lock discrepancies are corrected and documented in the statistical program.

4. Data Analysis

4.1 Timing of Analysis

The final statistical analysis will be performed after database lock, which will occur after all patients have completed the 90-day follow-up and all data have been verified, cleaned, and resolved with no outstanding queries. There were no planned interim analyses for the primary outcome in this trial.

4.2 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 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 2 decimal places. The primary outcome will be performed one-sided at $\alpha = 0.025$, with results presented as treatment differences and corresponding 97.5% one-sided confidence intervals. Other comparisons will be two-sided at $\alpha = 0.05$, with 95% two-sided confidence intervals reported.

4.3 Missing data

For missing baseline data (age, BMI, etc.), multiple imputation by chained equations (MICE) will be used. The number of imputed datasets, imputation variables, and diagnostic checks will be fully documented. For quality of life (QoL) data with missing values, only observed cases will be included in the analysis (missing values excluded from denominator). For crossover or treatment-switching patients, the ITT principle will be strictly maintained in the primary analysis; treatment switching will be summarized descriptively and explored in the as-treated sensitivity analysis. For protocol deviations, all major violations will be listed by center and patient, with impact on the primary outcome assessed in PP and AT analyses.

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.

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 quality of life questionnaires). 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.

4.5 Baseline characteristics

Baseline clinical data (including age, gender, body mass index, smoking status, alcohol consumption, etc.) documented in the baseline assessment form will be summarized separately for each treatment group, presented as means with standard deviations, and as counts and percentages. No statistical testing will be performed on these baseline variables (see appendix Table 1).

4.6 Primary outcome

The primary endpoint will be analyzed in the ITT population and defined as the rate of severe complications (Clavien-Dindo grade $\geqslant$ 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).

The primary non-inferiority analysis will be based on the risk difference (RD) with a predefined non-inferiority margin of 2.8%. The RD and its 97.5% one-sided confidence interval will be estimated using binomial regression with identity link. For the relative risk (RR), binomial regression with log link will be used to estimate the RR and two-sided 95% confidence interval. The RR is reported as a supplementary effect measure and will not be used for the non-inferiority test ((see appendix Table 2).

Non-inferiority margin justification: The non-inferiority margin of 2.8% was determined based on clinical relevance and pilot data. This margin was defined such that the severe complication rate in the SDT group would not exceed 120% of that in the ileostomy group (i.e., a 20% relative increase). Given the expected severe complication rate of 14% in the ileostomy group in our pilot study, the absolute non-inferiority margin was calculated as 14% × 0.2 = 2.8%. In clinical practice, an absolute increase of no more than 2.8% in severe complications is considered acceptable, as it is negligible compared with the substantial benefits of SDT: avoidance of stoma creation and reversal, shorter hospital stay, lower medical costs, and improved quality of life.

Subgroup analysis will be performed according to: Age (≥60y or <60y), Gender (female or male), Body mass index (≥24.0 or <24.0), Diabetes (Yes or No), Use of neoadjuvant radiotherapy (Yes or No), Tumor to anal verge (≥7cm or <7cm), Multiple high-risk factors (Yes or No), Pathological T stage (0-2 or 3-4), Pathological N stage (positive or negative), Presence of prior abdominal surgery (Yes or No), Center effect (High-volume centers≥50 cases versus low-volume centers <50 cases) . For subgroup analyses, between-group differences and corresponding 97.5% CIs will also be presented. The RRs will be reported with corresponding 95% CIs (see appendix Table 3).

4.7 Secondary outcomes

Secondary outcomes will be analyzed in the ITT population. Continuous variables (e.g., operation time, estimated blood loss, distance from anastomosis to anal verge, length of postoperative hospital stay, hospitalization cost, quality of life score) will be compared using the Student's t-test (for normally distributed data) or Wilcoxon rank-sum test (for non-normally distributed data), with the median difference and corresponding 95% confidence interval reported. For categorical variables (e.g., surgical approach, surgical type, anastomotic technique, overall/mild/severe complication rate, Clavien-Dindo grade), the two-

sided Pearson's χ^2 test or Fisher's exact test will be used as appropriate (see appendix Table 4).

4.8 Sensitivity analysis

Sensitivity analyses will be conducted for the PP and AT populations. Sensitivity models will replicate the primary analysis to ensure consistency across populations. The statistical methods used in these sensitivity analyses will be consistent with those applied to the ITT population. Results will be compared and interpreted across the ITT, PP, AT 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 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.

6. Appendix tables

Table 1

Characteristics	Stent-based Diverting Technique (n=)	Ileostomy (n=)
Age, y		
Mean ± SD	XX ± XX	XX ± XX
Group, No. (%)		
< 60	XX (XX)	XX (XX)
≥60	XX (XX)	XX (XX)
Gender, No. (%)		
Male	XX (XX)	XX (XX)
Female	XX (XX)	XX (XX)
Body mass index*		
Mean ± SD, kg/m2	XX (XX)	XX (XX)
Group, No. (%)		
<18.5 (Underweight)	XX (XX)	XX (XX)
18.5-23.9 (Normal)	XX (XX)	XX (XX)
≥24.0 (Overweight/Obese)	XX (XX)	XX (XX)
Smoking	XX (XX)	XX (XX)
Drinking	XX (XX)	XX (XX)
Concomitant, No. (%)		
Hypertension	XX (XX)	XX (XX)
Diabetes	XX (XX)	XX (XX)
Cardiovascular system diseases	XX (XX)	XX (XX)
Respiratory system diseases	XX (XX)	XX (XX)
Urinary system diseases	XX (XX)	XX (XX)

ASA classification, No. (%)†		
I (Healthy)	XX (XX)	XX (XX)
II (Mild systemic disease)	XX (XX)	XX (XX)
III (Severe systemic disease)	XX (XX)	XX (XX)
Eastern cooperative oncology group score		
0	XX (XX)	XX (XX)
1	XX (XX)	XX (XX)
Prior abdominal surgery, No. (%)	XX (XX)	XX (XX)
High-risk factors of anastomosis leakage, No. (%)		
Neoadjuvant radiotherapy	XX (XX)	XX (XX)
Tumor to anal verge≤7cm	XX (XX)	XX (XX)
Intraoperative factors‡	XX (XX)	XX (XX)
Others§	XX (XX)	XX (XX)
Number of high-risk factors, No. (%)		
Single	XX (XX)	XX (XX)
Multiple	XX (XX)	XX (XX)
Pathological TNM stage, No. (%)‖		
0	XX (XX)	XX (XX)
I	XX (XX)	XX (XX)
II	XX (XX)	XX (XX)
III	XX (XX)	XX (XX)

Table 2

Outcomes	Stent-based Diverting Technique (n=)	Ileostomy (n=)	P value
Primary outcome			
Events (severe complications), No	XX	XX	
Incidence of severe complications, % (95% CI)*	XX (95% CI, XX–XX)	XX (95% CI, XX–XX)	
Between-group difference in incidence, % (97.5% CI)	-XX (–∞, XX%)	-	XX
Relative ratio, % (95% CI)*	XX (XX–XX)	-	XX
Secondary outcomes			
Incidence of total complications, No. (%)*	XX (XX)	XX (XX)	XX
Incidence of mild complications, No. (%)*	XX (XX)	XX (XX)	XX
Complications (Events)	XX (XX)	XX (XX)	-
General complications, No. (%)	XX (XX)	XX (XX)	-
Anastomotic leakage (Grade B)	XX (XX)	XX (XX)	XX
Anastomotic leakage (Grade C)	XX (XX)	XX (XX)	XX
Anastomotic stenosis	XX (XX)	XX (XX)	XX
Intestinal obstruction	XX (XX)	XX (XX)	XX
Intestinal perforation	XX (XX)	XX (XX)	XX
Abdominal infection	XX (XX)	XX (XX)	XX
Bleeding	XX (XX)	XX (XX)	XX
Others†	XX (XX)	XX (XX)	XX
Stent or Tube-related complications, No. (%)	XX (XX)	XX (XX)	-
Stent displacement	XX (XX)	XX (XX)	-
Intestinal fistula‡	XX (XX)	XX (XX)	-
Mushroom-shaped tube-related dermatitis	XX (XX)	XX (XX)	-
Mushroom-shaped tube displacement	XX (XX)	XX (XX)	-
Stoma-related complications, No. (%)	XX (XX)	XX (XX)	-

Parastomal hernia	XX (XX)	XX (XX)	-
Dermatitis	XX (XX)	XX (XX)	-
Stoma obstruction	XX (XX)	XX (XX)	-
Stoma bleeding	XX (XX)	XX (XX)	-
Grade of complications			
I	XX (XX)	XX (XX)	XX
II	XX (XX)	XX (XX)	XX
III	XX (XX)	XX (XX)	XX
IV	XX (XX)	XX (XX)	XX
V§	XX (XX)	XX (XX)	XX
Converse to Stent-based Diverting Technique, No. (%)	-	XX (XX)	-
Converse to ileostomy, No. (%)	XX (XX)	-	-
Converse to salvage ileostomy, No. (%)‖	XX (XX)	-	-
Time of stent degradation			
No stent	XX (XX)	XX (XX)	-
Stent displacement	XX (XX)	XX (XX)	-
Before 3 weeks	XX (XX)	XX (XX)	-
3-4 weeks	XX (XX)	XX (XX)	-
5-6 weeks	XX (XX)	XX (XX)	-
Stoma ending, No. (%)#			
No stoma	XX (XX)	XX (XX)	-
Reversal on time (stage II)	XX (XX)	XX (XX)	-
Delayed reversal	XX (XX)	XX (XX)	-

Table 3

	Stent-based Diverting Technique	Ileostomy	P value
PHS and Costs	n=	n=	
Unplanned readmission, No. (%)	XX ± XX	XX ± XX	XX
PHS (stage I), days	XX ± XX	XX ± XX	XX
PHS (stage II), days	XX ± XX	XX ± XX	XX
PHS (Readmission),	XX ± XX	XX ± XX	XX
Total PHS, days*	XX ± XX	XX ± XX	XX
Total PHS (Only patients with reversal), days*	XX ± XX	XX ± XX	XX
Cost (stage I), CNY	XX ± XX	XX ± XX	XX
Cost (stage II), CNY	XX ± XX	XX ± XX	XX
Cost (Readmission), CNY	XX ± XX	XX ± XX	XX
Total Cost, CNY*	XX ± XX	XX ± XX	XX
Total Cost (Only patients with reversal), CNY*	XX ± XX	XX ± XX	XX
Quality of life	n=	n=	
General Health*	XX ± XX	XX ± XX	XX
Physical Function*	XX ± XX	XX ± XX	XX
Role-Physical*	XX ± XX	XX ± XX	XX
Bodily Pain*	XX ± XX	XX ± XX	XX
Vitality*	XX ± XX	XX ± XX	XX
Social Functioning*	XX ± XX	XX ± XX	XX
Mental Health*	XX ± XX	XX ± XX	XX
Role-Emotional*	XX ± XX	XX ± XX	XX

Subgroup	Level	Events/total SDT	SDT_95%CI	Events/total ILE	ILE_95%CI	RD 97.5%CI	RR	Interaction_p
Age	＜60	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Age	≥60	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Gender	Female	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Gender	Male	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Body_mass_index	＜24.0	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Body_mass_index	≥24.0	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Diabetes	N	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Diabetes	Y	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Noeoadjuvant_radiotherapy	N	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Noeoadjuvant_radiotherapy	Y	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Tumor_to_anal_verge	＜7	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX

Tumor_to_anal_verge	≥7	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Number_of_high_risk_factors	Single	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Number_of_high_risk_factors	Multiple	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Prior_abdominal_surgery	N	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Prior_abdominal_surgery	Y	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Pathological_T_stage	0-2	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Pathological_T_stage	3-4	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Pathological_N_stage	Negative	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Pathological_N_stage	Positive	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Centers	Low-volume	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX
Centers	High-volume	XX/XX	XX (XX–XX)	XX/XX	XX (XX–XX)	XX (-∞–XX)	XX (XX-XX)	XX

Statistical Analysis Plan (Modified Version 1.1)

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 (Clavien-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.

2.2 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.

4.2 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.

4.3 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.

4.4 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.

4.5 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 neoadjuvant 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.

4.6 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.

4.7 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

Summary of Statistical Analysis Plan amendments

Version	Section	Revision Content	Reason for Revision
V1.1	Sensitivity analysis	Add the as-treated analysis as the sensitivity analysis	To meet high-standard SAP requirements for crossover data
V1.2	Missing data	Specified multiple imputation (MICE) for baseline missing data; clarified observed-case analysis for QoL; standardized handling of crossover, protocol deviations, and center-specific violations	To meet high-standard SAP requirements for missing and crossover data
V1.2	Primary outcome	Unified primary analysis as risk difference (RD); non-inferiority based on RD with 97.5% one-sided CI	Ensure non-inferiority analysis is statistically correct
V1.2	Primary outcome	Added Relative risk (RR) estimation method: binomial regression with log-link, reported with two-sided 95% CI as supplementary measure	Clearly define RR analysis without interfering with non-inferiority testing
V1.2	Primary outcome	Added non-inferiority margin justification (2.8%): derived from 20% relative increase (14% × 0.2 = 2.8%) and clinical acceptability	Address clinical relevance of margin required
V1.2	Subgroup analysis	Added subgroup by center volume: high-volume vs low-volume	Support comparison between high-and lowvolume centers
V1.2	Appendix	Added templates for statistical analysis tables	Standardized and formalized output.