# A Prospective, Multi-center, Randomized, Open, Parallel-controlled Clinical Study of BD Pre-filled Flush Syringes

Study Protocol No./Version No.: MDS-21FLUSHCN01/V1.0

Sponsor: BD Medical Technology (Jiangsu) Co., Ltd.

# Statistical Analysis Plan

(Version: Final 1.0)

Statistical Analysis Institution: GCP ClinPlus Co., Ltd.

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# Signature Page of Statistical Analysis Plan

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# 1. ABBREVIATIONS AND STATISTICAL TERMS (ENGLISH) USED IN THIS REPORT

| Abbreviation | Detailed explanation |
|---|---|
| AE | Adverse Event |
| CMH | Cochran-Mantel-Haenszel Statistics |
| CI | Confidence Interval |
| Cr | Creatinine |
| CRF | Case Report Form |
| FAS | Full Analysis Set |
| IWRS | Interactive Web Randomization System |
| Max | Maximum |
| Mean | Mean |
| Min | Minimum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Median | Median |
| PPS | Per Protocol Set |
| Q1 | First Quartile |
| Q3 | Third Quartile |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Statistical Analysis Report |
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | System Organ Class |
| SOP | Standard Operation Procedure |
| SS | Safety Set |

# 2. STUDY PURPOSE

To compare the BD Pre-filled Flush Syringes (manufactured by [BD, USA]) and evaluate the effectiveness and safety of the BD Pre-filled Flush Syringes (manufactured by [BD Medical Technology (Jiangsu) Co., Ltd.]) for locking and flushing the end of catheter line.

# 3. STUDY DESIGN

## 3.1 Description of overall design

Selection of trial method: The trial is a prospective, multi-center, randomized, open, parallel-controlled clinical trial. The trial is a premarket clinical trial for registration in China. A statistical design is performed using non-inferiority statistics comparison.

Prospective: The study method with signed informed consent form as the starting point and follow-up to 1 hours after the end of the locked and flushed catheter treatment.

Randomization: A block randomization method is used and SAS 9.4 software or the higher version is adopted to generate the random assignment list for subjects. After confirming that the subjects meet the eligibility evaluation of the inclusion and exclusion criteria, the investigator or authorized personnel logs in to the randomization system to obtain the random number and corresponding group information, then the study nurse perform the trial intervention according to the random assignment results.

Open: Due to the difference in appearance between the test device and the control device (the printed content on the smallest package is inconsistent), and the use of incomplete packaging is prohibited, the investigators and subjects cannot be blinded in the trial, so this trial adopts an open design.

Parallel control: Since there are already equivalent devices on the market, the parallel-controlled design is selected. The equivalent devices are the BD Pre-filled Flush Syringes with proven effectiveness and safety.

Multi-center: Three study sites with clinical trial qualifications are selected to carry out this clinical trial. Subjects are enrolled at multiple sites and have a wide range of sources to avoid bias in trial results due to systematic errors at a single site.

Non-inferiority trial: To evaluate the overall performance of the test device BD Pre-filled Flush Syringes for flushing and/or locking the catheter is non-inferior to the control device BD Pre-filled Flush Syringes.

After signing of informed consent form, all subjects who meet the inclusion criteria and do not meet the exclusion criteria are randomized into the test or control group at the ratio of 1:1.

The ends of catheter lines for all subjects are flushed and/or locked by study nurses using investigational medical devices (test device and control device). The effectiveness and BD Pre-filled Flush Syringes shall be assessed.

The study process includes three periods: screening period, flush syringe treatment period, and follow-up period. The screening period is up to 3 days. Follow-up is conducted 1 hours after the end of flush syringe treatment to assess safety and effectiveness.

## 3.2 Study population and sample size

The study population includes subjects who require locking and flushing the end of catheter line at the intervals of different drug treatment. Specific inclusion and exclusion criteria are described in the 5.2 Selection of subjects of Protocol.

A total of 378 subjects are proposed to be enrolled in this clinical trial. The study is a parallel-controlled, non-inferiority design in which the control device is the BD Pre-filled Flush Syringes, a kind of prevalent product already on the market. The study intends to investigate the overall performance of the test device for flushing and/or locking the catheter that shall be non-inferior to that of the control device. Based on previous clinical experience, the overall performance pass rate of control device for flushing and/or locking the catheter is about 98%, and the study assumes the same treatment completion rate for the test device and control device. This study adopts a non-inferiority design, with $\alpha$=0.025 (one-sided), $\beta$=0.1 (power of 90%), and the non-inferiority margin is 5%. The test group and the control group are allocated 1:1 in equal proportions. The sample size shall be calculated by using the PASS software and 165 subjects shall be enrolled into each of the test group and the control group. However, 368 subjects shall be included in this clinical study considering factors such as drop-outs (drop-out rate of 10%) during the trial and other factors.

This study will be performed by 63 authorized nurses who participate in using the investigational device, each nurse will randomly use 3 test devices and 3 control devices, so a total of 378 subjects are proposed to be enrolled in this clinical trial.

## 3.3 Assignment or randomization for flush syringe treatment

The random numbers of 378 subjects will be provided by the statistical analysis institution commissioned by the sponsor, and the random assignment list of the subject will be generated using SAS 9.4 software or the higher version. A block randomization method is used. Given the number of seeds and block length, subjects are randomly assigned to the test and control groups at the ratio of 1:1 ratio, so the test group has 189 subjects and the contol group has 189 subjects. The two groups are treated with the following devices:

The test device is BD Pre-filled Flush Syringes (specification & model: BD 10 ml PosiFlush Pre-filled Flush Syringes);

The contol device is BD Pre-filled Flush Syringes (specification & model: BD 10 ml Pre-filled Flush Syringes with Standard Plunger Rod).

## 3.4 Study period

This clinical trial is divided into three phases: screening period, flush syringe treatment period and follow-up period.

The first phase is the screening period with a maximum of 3 days; the screening period and the flush syringe treatment period can be the same day. During this period, a visit will be set up to review the inclusion/exclusion criteria of the subjects to ensure that the subjects meet the enrollment conditions. All enrolled subjects shall be randomly assigned to the test group or the control group at the ratio of 1:1.

The second phase is the flush syringe treatment period. During this period, a fixed visit is set up on the day of flush syringe treatment to complete the operation and record the effectiveness and safety of devices as per the protocol.

The third phase is the follow-up period. Follow-up will be conducted 1 h after the end of flush syringe treatment.

Table 3.1 Trial flowchart

| Item / Time | Screening period (D-2, -1, 0) | Flush syringe treatment period (D1) | Follow-up period (1 h after flush syringe treatment) |
|---|---|---|---|
| Signing of informed consent form | ▲ | | |
| Admission diagnosis/demographics | ▲ | | |
| Review of inclusion/exclusion criteria | ▲ | | |
| Randomization | ▲ | | |
| Vital signs[1] | ▲ | | |
| Evaluation of effectiveness | | ▲ | |
| Record of adverse events/severe adverse events[2] | ▲ | ▲ | ▲ |
| Record of combined medication/treatment[3] | ▲ | ▲ | ▲ |
| Device deficiency | | ▲ | |

Note: The screening period and the treatment period can be the same day.

1. Vital signs: Record the last examination result prior to flush syringe treatment.
2. Record adverse events: Collect and record the adverse events from each subject during the period from the signing of informed consent to the termination of follow-up. For adverse events related to the test device, follow-up shall be conducted until the adverse events recover (return to normal state or to baseline state), or until the condition is stable, or until a reasonable explanation is available. For adverse events irrelevant with the test device, follow-up shall be conducted until the end of the follw-up, and the status of adverse events at the end of the trial shall be recorded.
3. Combined medication/treatment: Collect and record the combined medication before and after the use of the test device during the trial (the closest one to such use, twice in total), and the medication and the test device shall pass through the same vascular access (excluding oral medication); medication/treatment related to adverse events shall be recorded.

# 4. EVALUATION INDICATORS

## 4.1 Effectiveness evaluation indicators

### 4.1.1 Primary effectiveness indicators

- **Overall performance of catheter flushing and/or locking**

**Definition:** The success rate of pre-filled flush syringe for flushing and/or locking the catheter.

**Observation time:** At the time of preparation, initiation, implementation, and completion of catheter flushing and/or locking.

**Evaluation criteria:** The success rate of flushing and/or locking the catheter = (number of cases evaluated as "pass"/total number of cases evaluated) × 100%.

Evaluation method:

Overall performance is assessed by the nurse, who is required to answer the following questions:

1) Whether the air in the pre-filled flush syringe can be removed successfully?

2) Whether the pre-filled flush syringe can be connected to the catheter smoothly?

3) Whether the pre-filled flush syringe can flush and/or lock the catheter successfully?

4) Whether the pre-filled flush syringe can be disconnected from the catheter smoothly?

5) Whether any sites of the flush syringe leak at any time during use?

The overall performance of catheter locking and flushing is only considered "**pass**" only if:

Questions 1 to 4 are answered "Yes" and question 5 is answered "No".

**Reason for indicator selection**: The effectiveness of the product is reflected in five main aspects: venting, catheter connection, catheter flushing and/or locking, disconnection from the catheter, and the presence of leaks.

**Precautions:** None.

4.1.2 Secondary effectiveness indicators

- **Ease of pushing of the plunger during catheter flushing and/or locking**

**Definition:** The pushability of the plunger when the pre-filled flush syringe is flushing and/or locking.

**Observation time:** At the time of implementation and completion of catheter flushing and/or locking.

**Evaluation criteria:** Ease of pushing of the plunger during catheter flushing and/or locking = (number of cases whose score ≥ 3/total number of cases evaluated) × 100%.

Evaluation method:

As assessed by a nurse, who is asked to answer the following questions:

Whether it is easy to push the plunger (ease of pushing) during catheter flushing and/or locking?

5-score scale:

- 5 scores: Very easy;
- 3 scores: Easy;
- 1 score: Difficult.

## 4.2 Safety indicators

- Adverse events and serious adverse events.

### 4.3 Other indicators

- Record device deficiencies that occur during the trial.

# 5. STATISTICAL ANALYSIS DATASETS

## 5.1 Full analysis set (FAS)

Dataset consisting of all subjects randomized and grouped according to the basic principles of intention-to-treat analysis.

Subjects are analyzed in randomly assigned treatment groups according to the intention-to-treat principle.

FAS is used as the population for analysis of baseline information in this study and also as the population for effectiveness evaluation.

## 5.2 Per protocol set (PPS)

Dataset consisting of subjects in the FAS with no serious violations of the test protocol*, good compliance, and no missing primary effectiveness indicators.

PPS is used as the primary population for the analysis of the primary effectiveness indicators in this study.

Note: *"No serious violations of the trial protocol" refers to violations of the trial protocol that do not affect the primary effectiveness evaluation.

## 5.3 Safety set (SS)

Dataset consisting of all subjects who have received at least one treatment with the investigational devices and had at least one safety evaluation."

Safety analysis is performed according to the actual assigned treatment groups.

SS is used as the primary population for the safety analysis in this study.

# 6. STATISTICAL ANALYSIS METHODS

## 6.1 General principles

This study will use SAS 9.4 software or the higher version for statistical analysis.

All statistical tests are conducted using two-sided tests and a P-value less than 0.05 will be considered statistically significant (unless otherwise specified). In this study, hypotheses and statistical inferences are made only for the primary effectiveness indicators, and the intergroup comparisons for the remaining indicators are exploratory analyses.

For the description of quantitative indicators, the number of cases (missing), mean, standard deviation, median, minimum, maximum, and first quartile and third quartile are calculated. The decimal places of the minimum and maximum are kept the same as the original data, but the decimal places of the mean, standard deviation, and median are one more than the original data, but usually, the maximum number of decimal places does not exceed four decimal places.

Qualitative indicators are described by the number of cases and percentages of each category. The percentages are calculated using the non-missing data in each analysis set. Percentages are retained to one decimal place.

All numerically derived variables are retained to two decimal places, unless otherwise specified.

The treatment of missing data will be described in Section 7, otherwise all missing data will be left unfilled.

## 6.2 Subject profile

### 6.2.1 Enrollment and progress

Summarize the number of individuals who have been screened, failed to be screened, and successfully been screened (randomized, non-randomized), and summarize the reasons for failure of subjects who failed the screening.

Summarize the number and proportion of subjects in each group in the randomized population who have not use the investigational device, used the investigational device, completed the trial, not complete the trial, and entered each analysis set (FAS, PPS, SS), and summarize in detail the main reason for non-completion for subjects who fail to complete the trial on the end page.

Summarize the number and proportion of subjects randomized into each analysis set (FAS, PPS, SS) by site.

List the details of subject screening, and subject completion of the trial in the randomized population. List details of subjects who are not included in the PPS and those who deviate from the protocol.

### 6.2.2 General information

(1) Evaluation Indicators

1) Demographics and vital signs: Age, gender, ethnicity, body temperature, pulse, respiration, systolic blood pressure, diastolic blood pressure;

2) Treatment procedure: The procedures to be performed with the investigational device, the vascular access device and its placement.

(2) Evaluation method

FAS is used for evaluation.

The age, body temperature, pulse, respiration and systolic blood pressure are quantitatively described, and the t-test/Wilcoxon rank sum test is used for comparison between groups; the gender, ethnicity, procedures to be performed with the inestigational device, vascular access device and its placement are qualitatively described, and the chi-square test/Fisher exact probability method is used for comparison between groups.

### 6.2.3 Intervention and treatment compliance

#### 6.2.3.1 Investigational devices

Based on FAS, quantitative descriptive statistics (number of cases, mean, standard deviation, median, first quartile and third quartile, minimum, and maximum) shall be used to describe the duration of investigational device use in each group. Qualitative descriptions of whether the drug is used before investigational device use during the trial (via the same vascular access) and whether the drug is used after investigational device use during the trial (via the same vascular access) shall be performed.

Duration of investigational device use (secs) = end of use - start of use.

#### 6.2.3.2 Combined medication

Prior medication is defined as combined medication prior to the start of investigational device use. Concomitant medication is defined as combined medication at or after the start of investigational device use. All combined medications are listed in the form of a list.

## 6.3 Effectiveness evaluation

### 6.3.1 Primary effectiveness evaluation

(1) Evaluation Indicators

Overall performance of catheter locking and/or flushing is considered "**pass**" only if: Questions 1 to 4 are answered "Yes" and question 5 is answered "No".

Subjects who do not answer any of questions 1-5 or who answer "not applicable (NA)" will not be entered into the per protocol set; they will be treated in accordance with Table 6.1 when entering the full analysis set.

Table 6.1 Definition of "pass" for different scenarios of primary effectiveness indicators

<table>
<tr><td>Questions related to the primary effectiveness indicators</td><td>Scenario 1</td><td>Scenario 2</td><td>Scenario 3</td><td>Scenario 4</td></tr>
<tr><td>Whether the effectiveness evaluation is performed?</td><td>No</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>1. Whether the air in the pre-filled flush syringe can be removed successfully?</td><td rowspan="5">NA</td><td rowspan="4">Yes</td><td rowspan="5">At least one of the answers is "No" for questions 1-4, or "Yes" for question 5</td><td rowspan="5">At least one of the answers in Scenario 2 is "NA" or not selected</td></tr>
<tr><td>2. Whether the pre-filled flush syringe can be connected to the catheter smoothly?</td></tr>
<tr><td>3. Whether the pre-filled flush syringe can flush and/or lock the catheter successfully?</td></tr>
<tr><td>4. Whether the pre-filled flush syringe can be disconnected from the catheter smoothly?</td></tr>
<tr><td>5. Whether any sites of the flush syringe leak at any time during use?</td><td>No</td></tr>
<tr><td>Primary effectiveness determination (pass/fail)</td><td>Missing</td><td>Pass</td><td>Fail</td><td>Missing</td></tr>
<tr><td>Whether to be included in FAS</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Whether to be included in PPS</td><td>No</td><td>Yes</td><td>Yes</td><td>No</td></tr>
</table>

(2) Evaluation method

The study hypotheses for the primary evaluation indicators are:

Null hypothesis $H_0$: The overall performance pass rate $p_1$ in the test device group is inferior to $p_2$ in the control device group ($p1 \leq p2-\delta$);

Alternative hypothesis $H_1$: The overall performance pass rate $p_1$ of the test device group is not inferior to $p_2$ of the control device group ($p1 > p2-\delta$).

Where $\delta = 5\%$ is the non-inferiority margin, i.e., the range of differences considered not clinically significant.

FAS and PPS are used for evaluation.

**Main analysis:**

Describe the number and percentage of subjects for whom the two kind of pre-filled flush syringes are used to flush and/or lock the catheter successfully for groups in each study site and all study sites.

For the primary effectiveness indicator, i.e., overall performance of catheter flushing and/or locking, intergroup comparisons are performed using the Breslow-Day test for parity of effectiveness across sites. The Breslow-Day test is not required if the rate is 100% for both groups in each site, and the effectiveness is considered not statistically different between sites.

A Breslow-Day test with a P > 0.05 means that there is no statistical difference between sites, and the effectiveness data of each site can be combined for analysis. For the difference in the pass rate of the pre-filled flush syringes used to flush and/or lock the catheter in the combined test and control device groups, the 95% confidence interval (CI) for the difference in the pass rate between the two groups is calculated using the Wald method.

A Breslow-Day test with a P <= 0.05 indicates a statistical difference between sites, and that the effectiveness data may not be combined for analysis and need to be statistically described separately for each site. Point estimates corrected for site factors are obtained by weighting the difference in the pass rate of the pre-filled flush syringes used to flush and/or lock the catheter by the minimal risk method[1] for the test device group and the control device group in each site, and the 95% confidence interval (CI) for the difference in the pass rate between the two groups is calculated using the Wald method.

If the pass rate is 100% in both groups, the Newcombe Wilson method [2] is used to calculate the 95% confidence interval (CI) for the difference in the pass rate between the two groups.

If the results show that the lower limit of the bilateral 95% confidence interval (CI) for the difference in the pass rate between the test device group and the control device group for pre-filled flush syringes used to flush and/or lock the catheter is greater than -5% (a pre-defined non-inferiority limit), $H_0$ is rejected and the test device group can be considered non-inferior to the control device group in terms of overall performance pass rate.

The procedure code for calculating confidence interval (CI) about the site-adjusted CMH rate difference is shown below:

```
/*Variable description: dataset is the input dataset, siteid represents the study site, nurseid represents the nurse, trtp represents the treatment factor, y represents the outcome variable*/
data dataset;
   set dataset;
    if group="test group" then trt=1;else trt=2;
/*group is the group variable in the analyzed dataset, and "test group" is generally the value of the group variable, which represents the investigational test device*/
    if main="pass" then var=1;else var=2;
/*main is the analyzed variable, and "pass" is generally the dichotomous value of the main variable, which represents the study effect */
run;
ods select print;
ods output CrossTabFreqs=CrossTabFreqs;
proc freq data=dataset;
table siteid*trt*var.*Generate a four-cell table;
run;
quit;
proc sort data = dataset;
      by siteid trt;
run;
ods select print;
ods output BinomialCLs=BinomialCLs;
proc freq data=a;
by siteid trt;
table var/bin(cl=wilson level="1");*Wilson confidence interval is generated in preparation for newcombe method;
run;
quit;
/*******Calculate site-adjusted CMH rate difference by using the minimum risk method****************************************/
proc sql undo_policy=none;
   create table n11 as
      select distinct siteid,Frequency as n11
```

```
      from CrossTabFreqs where trt=1 and var=1;
   ;
quit;
proc sql undo_policy=none;
   create table n12 as
      select distinct siteid,Frequency as n12
      from CrossTabFreqs where trt=1 and var=2;
   ;
quit;
proc sql undo_policy=none;
   create table n21 as
      select distinct siteid,Frequency as n21
      from CrossTabFreqs where trt=2 and var=1;
   ;
quit;
proc sql undo_policy=none;
   create table n22 as
      select distinct siteid,Frequency as n22
      from CrossTabFreqs where trt=2 and var=2;
   ;
quit;
data n1234;
   merge n11 n12 n21 n22;*Generate the number of four cells in a four-cell table;
   p1=n11/sum(n11,n12);p2=n21/sum(n21,n22);*Calculate the pass rates of test and control groups: p1,p2;
   p1_p2=p1-p2;
   n=sum(n11,n12,n21,n22);
   diffn=p1_p2*n;
   var=p1*(1-p1)/sum(n11,n12)+p2*(1-p2)/sum(n21,n22); *The variance of the rate difference;
   if var=0 then var_1=1;else var_1=1/var;
 ***If both groups of studies are analyzed at 100%, the variance of the rate difference is 0 and the inverse of
the variance is set to 1;
   dvar_1=p1_p2*var_1;
run;

proc sql undo_policy=none;
   create table riskdiff0 as
      select *,sum(n) as s_n,sum(diffn) as s_diffn,
          sum(var_1) as s_var_1,sum(dvar_1) as s_dvar_1
      from n1234;
quit;
data riskdiff;
   set riskdiff0;
   alaph=diffn*s_var_1-s_dvar_1;
   beta=var_1*(1+alaph*s_diffn/s_n);
run;
proc sql undo_policy=none;
   create table riskdiff    as
      select *,sum(alaph*dvar_1) as s_advar_1,
          sum(beta*p1_p2) as s_betadif
      from riskdiff;
quit;
data riskdiff;
   set riskdiff;
   w_diff=beta/s_var_1-(alaph*var_1/(s_var_1+s_advar_1))*(s_betadif/s_var_1);***Calculate the weights
   for rate difference in each site by the minimal risk method;
run;
proc sql undo_policy=none;
   create table a_riskdiff    as
      select *,sum(p1_p2*w_diff) as a_riskdiff
```

```
    from riskdiff;
    quit;**Perform weighted estimation of the rate difference between the two groups in each site;
/*****Calculate the confidence interval of rate difference by using Newcombe and Wald method**********************************************************************/
data BinomialCLs1 BinomialCLs2;
  set BinomialCLs;
  if trt=1 then output BinomialCLs1;
  if trt=2 then output BinomialCLs2;
run;
data newcombe0;
merge a_riskdiff
BinomialCLs1(keep=siteid LowerCL uppercl
                rename=(LowerCL=LowerCL1 uppercl=uppercl1))
BinomialCLs2(keep=siteid LowerCL uppercl
                rename=(LowerCL=LowerCL2 uppercl=uppercl2));

run;
proc sql undo_policy=none;
  create table newcombe as
    select *,sum(LowerCL1*(1-LowerCL1)*w_diff**2/sum(n11,n12)) as part1,
           sum(uppercl2*(1-uppercl2)*w_diff**2/sum(n21,n22)) as part2,
           sum(LowerCL2*(1-LowerCL2)*w_diff**2/sum(n21,n22)) as part3,
           sum(uppercl1*(1-uppercl1)*w_diff**2/sum(n11,n12)) as part4,
           sum(w_diff*var) as part
    from newcombe0
  ;
quit;* Calculate the prepared parts of the formula by using newcombe and wald methods;
data newcombe wald;
  set newcombe;
  a_newcombe_l=a_riskdiff-probit(1-0.025)*sqrt(part1+part2);
  a_newcombe_u=a_riskdiff+probit(1-0.025)*sqrt(part3+part4);
  a_wald_l=a_riskdiff-probit(1-0.025)*sqrt(part);
  a_wald_u=a_riskdiff+probit(1-0.025)*sqrt(part);
run;*Substitute into the formula;
```

6.3.2 Secondary effectiveness evaluation

(1) Evaluation Indicators

1) Criteria for overall performance of catheter flushing and/or locking;

2) Ease of pushing of the plunger during catheter flushing and/or locking

(2) Evaluation method

FAS and PPS are used for evaluation.

Calculate the criteria for overall performance of catheter flushing and/or locking, as well as the number and percentage of cases in each category for ease of pushing of the plunger (including a score of ≥ 3) during flushing or locking. A chi-square test/Fisher's exact probability method is used for inter-group comparison on the criteria for overall performance of catheter flushing and/or locking, as well as for the scores of ≥ 3 for ease of pushing of the plunger during flushing or locking. The rank correlation rank sum test is used to compare between groups for the ease of pushing of the plunger during flushing or locking.

### 6.4 Safety evaluation

(1) Evaluation Indicators

Adverse events and serious adverse events

(2) Evaluation method

Safety analysis is conducted based on safety set (SS).

The Medical Dictionary For Regulatory Activities (MedDRA) version 25.1 is used for adverse event coding. Adverse events that occur prior to the start of the flush syringe treatment are only shown in the list.

Adverse events that occur not earlier than the use of investigational device or that exist before the use of investigational device but get severe at or after the use of the investigational device are considered TEAEs. If multiple adverse events of the same preferred term (PT) occur in the same subject, the most serious one is used for the final intergroup comparison.

The number, frequency and proportion of TEAEs and investigational device-related TEAEs occurring in each group are tabulated and summarized according to system organ classification (SOC), preferred term (PT) and severity. If the same adverse event occurs multiple times in the same subject, the most serious one is used for analysis.

Severe TEAEs, TEAEs leading to study discontinuation, and TEAEs leading to death are summarized for each group by system organ classification (SOC) and preferred term (PT), respectively.

Adverse events related to the investigational device include those judged as "definitely related, likely related, and probably related" in relation to the investigational device.

Adverse events leading to study discontinuation (including whether the adverse event leads to withdrawal from the trial) are judged as "yes".

Adverse events leading to death (including prognosis) are selected as "Death".

All adverse events during the study are detailed in the list.

### 6.5 Other indicators

The number, frequency and proportion of all device deficiencies, device deficiencies leading to adverse events, and device deficiencies leading to serious adverse events occurring during the study period in each group are tabulated and summarized based on SS. All device deficiencies during the study period are detailed in the list.

## 7. DATA PROCESSING AND CONVERSION

### 7.1 Processing of missing data regarding primary effectiveness

The primary effectiveness indicators are not filled.

### 7.2 Missing of severity of adverse events

The severity of adverse events prior to flush syringe treatment is missing and is filled using "moderate". Missing of severity of adverse events occurring after the start of flush syringe treatment is filled using "severe" and these filled-in values are used for summary of occurrence rate only and are presented as original values in the final list.

# 8. INTERIM ANALYSIS

There will be no interim analysis in this trial.

# 9. REMARKS ON THIS PLAN

This Statistical Analysis Plan (SAP) provides a more technical and detailed description of the effectiveness and safety indicators than those in the study protocol (version v1.0, date <May 31, 2022>), and proposes specific statistical analysis methods for the relevant evaluation indicators, taking into account the numerical characteristics of the indicators in the study protocol, and in the context of the specific requirements of this study. Tables, graphs, and lists related to this plan will be provided in a separate, stand-alone document.

# 10. REFERENCES

1. Methods of Estimating Rate Difference and Associated Confidence Interval in Clinical Trials. Han Jingjing, Zeng Xin, Wang Jun. Chinese Journal of New Drugs and Clinical Remedies, April 2016

2. SAS Implements of Calculating Rate Differences Confidence Intervals in Clini-cal Trials with Rates of 0% or 100% in Both Groups. Huang Yaohua, Tang Xinran, Duan Chongyang, Chen Pingyan et al. Chinese Journal of Health Statistics, February 2017