Clinical Trial Protocol for Medical Device

Protocol No.: MDS-21FLUSHCN01

A prospective, Multi-center, Randomized, Open-label, Parallel-controlled Clinical Study of Pre-filled Flush Syringes

Name of the investigational medical device: Pre-filled Flush Syringes

Model and Specification: BD 10 mL PosiFlush Pre-filled Flush Syringes

Class III medical device that requires clinical trial approval Yes□ No☑

Protocol version No. and date: V1.0/ May 26, 2022

Clinical trial leading institution: Beijing Hospital

Principal investigator: Sun Chao

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

Study Protocol Version Update Record

Protocol/Amendment No.	Original version No. / Version date	Description of changes	Reasons for revision

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List of Abbreviations

Abbreviations	Definition
AE	Adverse Event
CRC	Clinical Research Coordinator
CRO	Contract Research Organization
D	Day
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
FAS	Full Analysis Set
GCP	Good Clinical Practice (Medical Device)
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NMPA	National Medical Products Administration
PASS	Power Analysis and Sample Size (Statistics Software)
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious Adverse Event
SAS	Statistical Analysis System (Statistics Software)
SOC	System Organ Class
SS	Safety Set
°C	Celsius

Synopsis

Study Title	A Prospective, Multi-center, Randomized, Open-label, Parallel-controlled Clinical Study of Pre-filled Flush Syringes
Protocol No.	MDS-21FLUSHCN01
Sponsor	BD Medical Technology (Jiangsu) Co., Ltd.
Study Sites	3 study sites
Planned Study Period	April 2022 to September 2023
Subject Population	Subjects requiring locking and flushing the end of catheter line at the intervals of different drug treatment.
Study Objective	To compare the BD PosiFlush™ Pre-filled Flush Syringes (manufactured by BD, USA) with the pre-filled flush syringes (manufactured by BD Medical Technology (Jiangsu) Co., Ltd.) and evaluate the effectiveness and safety for locking and flushing the end of catheter line.
Study Design	This prospective, multi-center, randomized, open, and parallel-controlled clinical study is intended to evaluate the effectiveness and safety of 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 investigational group or control group in a 1:1 ratio. This study is performed by 63 trial nurses using the study device (investigational device and control device) to lock and flush the end of catheter line for all subjects, each nurse will randomly use 3 investigational devices and 3 control devices.
Number of subjects planned to be enrolled	Sample size calculation assumptions: • Overall performance success rate in the investigational device group is 98% • Overall performance success rate in the control device group is 98% • Non-inferiority margin is 5% • Allocation ratio of 1:1 • Type I error rate is 0.025 one-side • Power is 90% • Attrition rate is 10% A total of 368 subjects are required. This study will be performed by 63 study nurses using the study device, each nurse will randomly use 3 investigational devices and 3 control devices, so a total of 378 subjects will be enrolled in this clinical trial.

Efficacy Evaluation	**Primary efficacy indicator:** The primary objective is to investigate the overall performance for flushing and/or locking the catheters. **<u>Evaluation method:</u>** Overall performance is assessed by a Nurse, who need to answer the following questions: 1) Can air in the BD Pre-filled Flush Syringes be expelled successfully? 2) Can BD Pre-filled Flush Syringes be connected to the catheter smoothly? 3) Can BD Pre-filled Flush Syringes flush and /or lock the catheter successfully? 4) Can BD Pre-filled Flush Syringes disconnect from the catheters smoothly? 5) Any leakage observed at any part of the Flush syringe at any time during the usage? Overall performance for flushing and/or locking the catheter deemed as "**success**" if: Question 1 to 4 answered with “YES”, and question 5 answered with “NO”. **Secondary efficacy indicator:** The second objective is to investigate the pushability of plunger during flushing and/or locking. **<u>Evaluation method:</u>** Pushability will be assessed by a Nurse who needs to score the following question: 1) Is the plunger easy to push forward when flushing or locking (pushability)? Score on a 5-point scale: • 5 points: Very easy; • 3 points: Easy; • 1 point: Difficult.
Safety Evaluation	The safety objective is to investigate the incidence of adverse events and serious adverse events.
Other Evaluation	Device defects.

Selection Criteria of Subjects	**Inclusion criteria:** 1. Age >or equal to 18, no limitation on gender; 2. Hospitalized patients; 3. Patients who are anticipated to need or have vascular access catheter devices [This may include: Peripheral Intravenous Catheter (PIVC), Central Venous Catheter (CVC) and Peripherally Inserted Central Catheter (PICC)]; 4. Patients who are expected to require flushing the vascular access catheter with saline at the beginning, during, or end of infusion therapy, or who require to flush and/or lock vascular access catheters at the beginning, during, the end of drug therapy; 5. Patients who can understand the purpose of the trial, agree to participate in this clinical trial and voluntarily sign the informed consent form. **Exclusion criteria:** 1. Patient reports pregnancy or lactation (self-report); 2. Subjects who are known to have blockage or recanalization of vascular access prior to this trial; 3. Subjects who are known to have uncomfortable symptoms such as redness and pain, or common complication associated with indwelling catheter such as phlebitis and infection at the localized insertion site prior to this trial; 4. Patient who has participated in a drug or medical device clinical trial within three months before enrollment; 5. Any other situation that, in the opinion of the Investigator would make the patient considered unfit for this study.
Withdrawal Criteria	**Subjects voluntarily withdraw from the study:** According to the provisions of the informed consent form, subjects have the right to withdraw from the study at any phase of the study, or the subjects do not explicitly propose to withdraw from the study, but they no longer receive flush syringe treatments or examinations and are lost to follow-up, which also a category of "withdrawal" or "drop out". For subjects withdrawing from the trial for any reason, it is required to record reasons for their withdrawal as far as possible, complete and report all observations in detail. **Investigators decide to withdraw the subject from study:** If subjects enrolled have conditions during the study that the investigator considers inappropriate for continuation of the study, the subject needs to withdraw from the study.
Suspension / Termination Criteria of Study	The major purpose of suspending/terminating the study is to protect the rights and interests of the subjects, ensure the quality of the trial and avoid unnecessary economic losses. Reasons for suspension/early termination of the study are as follows: 1. The sponsor may suspend/terminate the study for any scientific,

	medical or ethical reasons, but must fully consider the rights, safety and health of the subjects in the group; 2. The sponsor voluntarily requests suspension/termination for other reasons; 3. Drug authority, ethics committee, sponsor or investigator consider that there are significant safety risks; 4. Other reasons judged by the sponsor or investigator that are considered inappropriate to proceed with the trial. The suspension arising therefrom can be a permanent "termination" or a temporary "suspension". The study can be restarted after the problem that caused the suspension of the study is resolved. Suspension/termination of the study or restarting the study after suspension must be reported to the Ethics Committee.
Investigational Group Device	**Product name: Pre-filled Flush Syringes** Model and specification: BD 10 mL PosiFlush Pre-filled Flush Syringes Product components: The product mainly consists of barrel, plunger, plunger stopper, nozzle cap and 0.9% sodium chloride injection (conforming to ChP and USP) Storage conditions: 15-25°C, it can be extended to 15-30°C; do not freeze Manufacturer: BD Medical Technology (Jiangsu) Co., Ltd.
Control Group Device	**Product name: BD Pre-filled Flush Syringes** Specification/Model: BD 10mL PosiFlush Pre-filled Flush Syringes Product components: the product mainly consists of barrel, plunger, plunger stopper, nozzle cap and 0.9% sodium chloride injection (conforming to USP) Storage conditions: 20-25°C, it can be extended to 15-30°C; do not freeze Registration Certificate No.: GXZJ20163142809 Manufacturer: Becton, Dickinson and Company Agent name: Becton Dickinson Medical Devices (Shanghai) Co., Ltd.
Statistical Analysis Method	**Statistical analysis:** This study will use SAS9.4 or above for statistical analysis. For quantitative variables, descriptive statistics will include number of subjects, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For qualitative variables, descriptive statistics will include the number of subjects and percentages. Test hypotheses for the primary efficacy indicators: Null hypothesis H_0: The overall performance success rate p_1 in the

	investigational device group is inferior to the p_2 of the control device group ($p_1 \leq p_2-\delta$). Alternative hypothesis H_1: The overall performance success rate p_1 in the investigational device group is non-inferior to the p_2 of the control device group ($p_1 > p_2-\delta$). Where δ = 5% is the non-inferiority margin, which is the range of differences not considered clinically significant. For the comparison of the main efficacy indicators between groups, the chi-square test or Fisher's exact test is adopted, and the confidence interval method is used for statistical inference to separately calculate the success rate of each group and the rate difference as well as two-sided 95% confidence interval between the two groups. If the lower limit of two-sided 95% CI > -5%, H_0 is rejected and the overall performance success rate of the investigational device group can be considered non-inferior to the control device group. Descriptive analysis (quantitative or qualitative description) is performed for the secondary efficacy indicator, the safety evaluation indicator and other evaluation indicators. For categorical variables, summary statistics will include the number of subjects and percentage. For the description of adverse event, the cases of adverse events will also be summarized. For continuous variables, summary statistics will include the number of subjects, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For indicators that require statistical inference, inter-group comparison of quantitative indicators is verified by t-test or Wilcoxon rank sum test based on data distribution characteristics; categorical indicators are verified by χ^2 test or Fisher's exact test; ranked data is verified by Wilcoxon rank sum test.

1. Information of Sponsor

1.1 Name of sponsor

BD Medical Technology (Jiangsu) Co., Ltd.

1.2 Address of sponsor

No. 888-8, Lvyuan Road, Xinjie Street, Yixing

1.3 Contact information of sponsor

Project leader of the clinical trial: Ma Juanjuan

Contact number: 010-58139097

2. Information of Clinical Trial Institutions and Principal Investigators

No.	Name of clinical trial institution	Investigator	Title	Contact information
1	Beijing Hospital	Sun Chao	Assistant director nurse	18601924876
2	Beijing Friendship Hospital, Capital Medical University	Luo Jinkai	Assistant director nurse	010-63139021
3	Beijing Jishuitan Hospital	Lu Xuemei	Director nurse	010-58516783

3. Background of the Clinical Trial

3.1 R&D background

Infusion is one of the necessary measures for the diagnosis and treatment of patients in the hospital. Due to the needs of the disease, some patients need to use intravenous catheters or catheters to open up intravenous access, which facilitates rapid clinical administration of drugs and emergency resuscitation, while protecting patients' vascular and reducing the pain caused by repeated cannulation. However, when using intravenous catheters or catheters for infusion, it is necessary to lock the catheter with the flushing solution, usually, a manually configured heparin flushing solution is used. Whereas some problems are also encountered in clinical applications, such as blockage of intravenous catheters or catheters, and increased heparin concentration in the blood, resulting in short retention time of intravenous catheters or catheters, high re-cannulation rate, increasing patients’ pain, nursing workload and consumables, and also increasing the incidence of phlebitis. In clinical practice, locking of venous catheter is an important part of intravenous catheters infusion technology and the key to the success of intravenous catheters indwelling. BD PosiFlush™ Pre-filled Flush Syringes (manufactured by BD, USA), which is currently on the market, has a good locking effect and can effectively prevent the blockage of the peripheral intravenous catheter, thereby prolonging the use time of the intravenous catheter and reducing the pain of repeated cannulation for patients, protecting patients' vascular, reducing their medical costs, and also improving the efficiency of nurses.

The pre-filled flush syringes developed and manufactured by BD Medical Technology (Jiangsu) Co., Ltd. has passed the inspection of Shandong Institute of Medical Device and Pharmaceutical Packaging Inspection, and the conclusion is that the product conformed to the technical requirements of the *Pre-filled Flush Syringes*. According to the *Good Clinical Practice for Medical Devices* of the National Medical Products Administration, in accordance with relevant national regulations and ethical requirements, as well as the characteristics and principles of pre-filled flush syringes, a clinical study is conducted on the safety and effectiveness of the pre-filled flush syringes manufactured by BD Medical Technology (Jiangsu) Co., Ltd. for locking and flushing the end of the catheter line, and this protocol is formulated.

3.2 Basic information of product

3.2.1 Structure and composition

The product consists of barrel, plunger, plunger stopper, nozzle cap and 0.9% sodium chloride injection (conforming to ChP and USP).

The pre-filled flush syringes contain sterile, pyrogen-free and preservative-free 0.9% sodium chloride injection, conforming to ChP and USP. The sodium chloride injection is filled in a plastic, single-use latex-free flush syringe. The solution is sterile. The pH of solution is 4.5-7.0. The osmotic pressure of the solution is 0.308 mOsm/mL (calculated).

3.2.2 Principle of work and action

Sodium chloride is an electrolyte replacement drug. Sodium and chloride are important electrolytes in the body, mainly present in extracellular fluid, and play a very important role in maintaining normal blood and extracellular fluid volume and osmotic pressure.

The mechanism/mode of action of pre-filled flush syringes used to flush and/or lock vascular access devices is mechanical. Because the 0.9% sodium chloride injection in the pre-filled flush syringes can “clean out” or displace fluid from other IV catheters and fill the IV catheter as the locking solution. When used in conjunction with the recommended clamping technique, it prevents blood from entering the catheter and clotting. The 0.9% sodium chloride solution in the pre-filled flush syringes is used as a fluid replacement solution because of basic compatibility with the blood and has no intended therapeutic effect of its own (no actual drug mode of action). The 0.9% sodium chloride in the pre-filled flush syringes does not damage blood components.

3.2.3 Characteristics of the product

- Used as a flushing/locking device for vascular access devices without the risk of heparin-induced thrombocytopenia (HIT);
- The pre-filled flush syringes eliminate the steps and time involved in manually preparing saline syringes, increasing the efficiency of clinical nurses and optimizing workflow;
- Pre-filled flush syringes can reduce the risk and/or degree of blood reflux caused by the syringe.

3.3 Scope of application and related information

Pre-filled flush syringes are intended to lock and flush the end of the catheter line at the intervals of different drug treatment.

3.3.1 Indications

Not applicable.

3.3.2 Intended population

Subjects requiring locking and flushing the end of catheter line at the intervals of different drug treatment.

3.3.3 Site used

The end of the catheter line used by the subject.

3.3.4 Contact mode and duration of contact with human body

The pre-filled flush syringes do not contact with the human body directly, but the sterile, pyrogen-free and preservative-free 0.9% sodium chloride injection (conforming to ChP and USP) contained in it will eventually enter the human body.

3.3.5 Severity and stage of the disease

Not applicable.

3.3.6 Conditions of use

Used by clinicians and nurses. Do not use on sterile interface or in sterile environment.

3.3.7 Repeated use

The pre-filled flush syringes are a single-use product, not reusable.

3.3.8 Use method

1. Tear open package and take out the pre-filled flush syringe.
2. Depress plunger (do not open white tip cap) with tip cap on to relieve the resistance between the stopper and the barrel.
3. Use aseptic technique, and remove tip cap by twisting off.
4. If connecting with a needleless I.V. system, please attach directly. If for traditional ports, please connect a needle with safety engineered feature as required by OSHA bloodborne Pathogens Standard.
5. Hold the syringe upright and expel the air in the syringe.
6. Attach the syringe to the port, valve or needleless system and flush following institution's policy and indwelling device manufacturer's recommendations.
7. Discard used syringe and any unused portion of the solution according to institution policy. Do not reuse.

3.3.9 Contraindications

Not yet clear; not found yet.

3.3.10 Cautions

1. Do not use if the packaging is incomplete.
2. Do not use if the pre-filled flush syringe is damaged and leaking.
3. Do not use if the nozzle cap is installed incorrectly or detached.
4. Do not use if any form of suspended particles is inspected visually or the solution is discolored, turbid, and precipitated.
5. Do not re-sterilize.
6. Check the expiration date on the packaging label and do not use if the product is expired.
7. Do not place the pre-filled flush syringe on a sterile interface or in sterile environment.
8. Do not reuse. Single use only. Discard any remaining parts of the unused.
9. Do not contact the solution with medicines incompatible. Please refer to the compatibility literature.

4. Trial Objective

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

5. Trial Design

5.1 Overall design and determination basis

Overall design

Selection of trial method: this trial is a prospective, multi-center, randomized, open, parallel-controlled clinical trial. The investigational product is the Pre-filled Flush Syringes (specification and model: BD 10 mL PosiFlush pre-filled flush syringes), and the control product is the BD Pre-filled Flush Syringes (specification and model: BD 10 mL PosiFlush pre-filled flush syringes), a statistical design will be performed using non-inferiority statistical comparisons.

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

Randomization: A block randomization method is used and SAS9.4 or above software 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 nurses perform the trial intervention according to the random assignment results.

Open: Due to the difference in the appearance between the investigational product and the control product (the printing 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 an open design is used for this trial.

Parallel control: Because there are already equivalent products on the market, the design of parallel control is selected. The equivalent products are the BD Pre-filled Flush Syringes with proven efficacy and safety.

Multi-center: Three institutions with clinical trial qualifications are selected to carry out this clinical trial. The subjects are enrolled in multiple sites and come from a wide range of subjects to avoid the bias of trial results caused by systematic errors at a single site.

Non-inferiority test: To evaluate that the overall performance of the pre-filled flush syringes for flushing and/or locking the catheter is non-inferior to that of the 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 investigational group or control group in a 1:1 ratio.

The end of catheter line for all subjects is flushed and/or locked by the study nurse using study devices (investigational device and control device) to evaluate the effectiveness and safety of pre-filled flush syringes.

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

5.2 Selection of subjects

5.2.1 Inclusion criteria

1) Age >or equal to 18, no limitation on gender;
2) Hospitalized patients;
3) Patients who are anticipated to need or have vascular access catheter devices [This may include: Peripheral Intravenous Catheter (PIVC), Central Venous Catheter (CVC) and Peripherally Inserted Central Catheter (PICC)];
4) Patients who are expected to require flushing the vascular access catheter with saline at the beginning, during, or end of infusion therapy, or who require flush and/or lock vascular access catheters at the beginning, during, the end of drug therapy;
5) Patients who can understand the purpose of the trial, agree to participate in this clinical trial and voluntarily sign the informed consent form.

5.2.2 Exclusion criteria

1) Patient reports pregnancy or lactation (self-report);
2) Subjects who are known to have blockage or recanalization of vascular access prior to this trial;
3) Subjects who are known to have uncomfortable symptoms such as redness and pain, or common complication associated with indwelling catheter such as phlebitis and infection at the localized insertion site prior to this trial;
4) Patient who has participated in a drug or medical device clinical trial within three months before enrollment;
5) Any other situation that, in the opinion of the Investigator would make the patient considered unfit for this study.

5.2.3 Criteria and procedures of subject withdrawal

5.2.3.1 Investigator-decided withdrawal

If subjects enrolled have conditions during the study that the investigator considers inappropriate for continuation of the study, the subject needs to withdraw from the study.

5.2.3.2 Subjects voluntarily withdraw from the study

According to the provisions of the informed consent form, subjects have the right to withdraw from the study at any phase of the study, or the subjects do not explicitly propose to withdraw from the study, but they no longer receive flush syringe treatments or examinations and are lost to follow-up, which is also a category of “withdrawal” or “drop-out”.

For subjects withdrawing from the trial for any reason, it is required to record reasons for their withdrawal as far as possible, complete and report all observations in detail.

5.2.3.3 Withdrawal (drop-out) handling

Drop-out refers to any subject who has signed the informed consent form (ICF), has passed the screening, and is enrolled in the clinical trial randomly but withdraws from the clinical trial at any time for any reason is considered a drop-out case.

For subjects who drop out of this trial, the reasons for withdrawal from the trial and the completed operations before drop-out shall be documented.

If the subject withdraws from this trial due to adverse events, timely and appropriate flush syringe treatments and follow-up examinations shall be performed until the adverse events are recovered (return to normal state or to baseline state), or until the condition is stable, or until a reasonable explanation is available.

5.2.4 Suspension / Termination criteria of study

The major purpose of suspending/terminating the study is to protect the rights and interests of the

subjects, ensure the quality of the trial and avoid unnecessary economic losses. Reasons for suspension/early termination of the study are as follows:

1. The sponsor may suspend/terminate the study for any scientific, medical or ethical reasons, but must fully consider the rights, safety and health of the subjects in the group;
2. The sponsor voluntarily requests suspension/termination for other reasons;
3. Drug authority, ethics committee, sponsor or investigator consider that there are significant safety risks;
4. Other reasons judged by the sponsor or investigator that are considered inappropriate to proceed with the trial.

The suspension arising therefrom can be a permanent “termination” or a temporary “suspension”. The study can be restarted after the problem that caused the suspension of the study is resolved. Suspension/termination of the study or restarting the study after suspension must be reported to the Ethics Committee.

5.3 Evaluation method

5.3.1 Evaluation of effectiveness

5.3.1.1 Primary efficacy indicators and evaluation time

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

  Definition: The success rate of the prefilled flush syringes for flushing and/or locking the catheter.

  Observation time: Flushing and/or locking the catheter during preparation, initiation, implementation, termination.

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

Evaluation method:

Overall performance is assessed by a Nurse, who need to answer the following questions:

1) Can air in the BD Pre-filled Flush Syringes be expelled successfully?
2) Can BD Pre-filled Flush Syringes be connected to the catheter smoothly?
3) Can BD Pre-filled Flush Syringes flush and /or lock the catheter successfully?
4) Can BD Pre-filled Flush Syringes disconnect from the catheters smoothly?
5) Any leakage observed at any part of the Flush syringe at any time during the usage?

Overall performance for flushing and/or locking the catheter is only considered as "**success**" if: Question 1 to 4 answered with “YES”, and question 5 answered with “NO”.

Justifications of indicators selected: The effectiveness of this product is mainly reflected in five aspects: priming, connection, flushing and/or locking catheters, disconnection from catheters and leakage.

Cautions: None.

5.3.1.2 Secondary efficacy indicators and evaluation time

- **Easy pushability of the plunger when flushing and/or locking.**

  Definition: Whether the plunger can be easily pushed forward when the pre-filled flush syringe is flushing and/or locking?

  Observation time: Flushing and/or locking the catheter during implementation,

termination.

Evaluation criteria: The pushability of the plunger when flushing and/or locking = (number of cases evaluated with score ≥ 3 points/total number of cases evaluated) × 100%.

Evaluation method:

Pushability will be assessed by a Nurse, who needs to score the following question:

1) Is the plunger easy to push forward when flushing and/or locking (pushability)?

   5-point scale will be used:

   - 5 points: Very easy;
   - 3 points: Easy;
   - 1 point: Difficult.

5.3.2 Safety evaluation

Observation purpose: To evaluate the safety of the pre-filled flush syringe for flushing and/or locking the end of catheter line.

(1) Safety

- Adverse events and serious adverse events

(2) Method and time selection for evaluating, recording and analyzing safety indicators

1) Evaluation method (calculation formula)

- Calculate the incidence of adverse events, serious adverse events: number of subjects experiencing the above events/total number of subjects × 100%.

2) Time selection

Adverse events/serious adverse events are recorded at all times.

3) Analytical method

See section 6.4 for statistical analysis method.

5.3.3 Other evaluations

(1) Device defects

- Device defects that occur during the trial.

(2) Method and time selection for evaluating, recording and analyzing safety indicators

1) Evaluation method (calculation formula)

- Calculate the incidence of device defects: subjects experiencing the above events/total number of subjects × 100%.

2) Time selection

Device defects are recorded at all times.

3) Analytical method

See section 6.4 for statistical analysis method.

5.4 Investigational medical device and control medical device

Investigational group device

Product name:	**Pre-filled flush syringes**
Specification/Model:	BD 10mL PosiFlush Pre-filled Flush Syringes

Registrant:	BD Medical Technology (Jiangsu) Co., Ltd.
Shelf life:	3 years
Storage conditions:	15°C-25°C. It can be extended to 15°C-30°C; do not freeze.
Intended use:	Used to lock and flush the end of a catheter. It is not suitable for subcutaneous injection and intramuscular injection.
Product composition:	The product consists of barrel, plunger, plunger stopper, nozzle cap and 0.9% sodium chloride injection (conforming to ChP and USP).

Control group device

Product name:	**BD Pre-filled Flush Syringes**
Specification/Model:	BD 10mL PosiFlush Pre-filled Flush Syringes
Registrant:	Becton, Dickinson and Company
Agent:	Becton Dickinson Medical Devices (Shanghai) Co., Ltd.
Registration Certificate No.:	GXZJ20163142809
Shelf life:	3 years
Storage conditions:	20°C-25°C. It can be extended to 15°C-30°C; do not freeze.
Intended use:	Intended to lock and flush the end of the catheter line at the intervals of different drug treatment. It is not suitable for subcutaneous injection and intramuscular injection.
Product composition:	The product consists of barrel, plunger, plunger stopper, nozzle cap and 0.9% sodium chloride injection (conforming to USP).

5.5 Trail procedures

5.51 Trial flow chart

Item / Time	Screening period (D-2,-1,0)	Flush syringe treatment period (D1)	Follow-up period (1h after the flush syringe treatment)
Sign the informed consent form	▲		
Hospital admission diagnosis/demographic data	▲		
Review inclusion/exclusion criteria	▲		
Randomization	▲		
Vital signs[1]	▲		
Evaluation of effectiveness		▲	
Record adverse events/serious adverse events[2]	▲	▲	▲
Record combined medications/treatments[3]	▲	▲	▲
Device defects		▲	

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

1. Vital signs: Record the recent last examination result prior to the flush syringe treatment.
2. Record adverse events: Collect and record the adverse events in each subject during the period from the signing the informed consent form to the termination of follow-up. Investigator should follow up the adverse events, follow up the subject undergoing such adverse events until the adverse events are recovered (return to normal state or to baseline state), or until the condition is stable, or until a reasonable explanation is available.
3. Combined medication/treatment: Collect and record the combined medication before and after the use of the study device during the trial (the closest one to such use, twice in total), and the medication and the study device shall pass through the same vascular access (excluding oral medication); medication/treatment for adverse events.

5.5.2 Implementation of the trial

Subjects will be trained for the use of Pre-filled flush syringes prior to enrollment. Investigators using the device (Investigational group device and/or Control group device) shall be specialized in intravenous infusion therapy for at least 2 years; maintain peripheral or central vascular access more than 10 times per month for the last 6 months; complete the product use of pre-filled flush syringes as required and complete assessment after training.

The informed consent form shall be signed by each subject before screening. Refer to the "trial flow chart" for the specific trial process.

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 the screening 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 selected subjects shall be randomly assigned to the investigational group or the control group in a 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 the flush syringe treatment to complete the operation of the treatment and record the effectiveness and safety as per the protocol.

The third phase is the follow-up period. A follow-up shall be performed at 1 hour after the flush syringe treatment.

The visiting investigators shall be required to observe, treat and record the subjects in each phase according to the flow chart.

Screening period (D-2,-1,0)

1) Sign the informed consent form (Note: Relevant screening examinations shall not be performed before the written informed consent form is obtained);
2) Demographic data collection: date of birth, gender, ethnicity, etc.;
3) Hospital admission diagnosis;
4) Register the subject screening number of the selected patients, and review the subject inclusion and exclusion criteria;
5) Randomization;
6) Vital signs: Respiration, blood pressure (systolic pressure, diastolic pressure), pulse, body temperature;
7) Record adverse events and serious adverse events;
8) Record combined medications/treatments.

Flush syringe treatment period (D1)

Flush syringe treatment period indicates the use and operation of pre-filled catheter flush syringes.

1) The operation shall be performed to flush and/or lock the end of the catheter line:

   The procedure shall be performed to flush and/or lock the end of the catheter line by the study nurse. Refer to section 3.3.8 Usage for the specific operation method.

   Record the time to start and end the flush syringe treatment.

   Before the priming preparation, if device defects and other problems are found, each subject can change a new study device; if such problems are found after the priming preparation, each subject can only use the current one without changing the device.

2) Evaluation of effectiveness:

   The use of the pre-filled flushing syringe shall be evaluated by the study nurse after flushing and/or locking the end of the catheter line. Refer to section 5.3.1 Evaluation of effectiveness for the specific evaluation method.

3) Record adverse events (AE/SAE);
4) Record combined medications/treatments;
5) Record device defects.

Follow-up

Follow-up is performed at 1 hour after the flush syringe treatment.

1) Record adverse events (AE/SAE);
2) Record combined medications/treatments.

5.6 Device operation specifications

5.6.1 Study device management

1) The relevant training shall be received by the users before using the device. And the users shall be familiar with the use of the device with the ability to identify the abnormality of the device. The users shall avoid results errors caused by human factors.
2) Inspect visually whether the package of the device is complete or damaged before using.

5.6.2 Recycling of study devices

The sponsor is responsible for recycling the study devices after the termination or at the end of the trial. The "Device Recycling Form" shall be signed by both parties, and all related materials shall be counted at the end of the trial. For specific device recycling matters, please contact the project manager of this clinical trial.

Conduct device recycling as follows and count the quantities:

1. Used study products

   Study products that are not invalid, damaged, defective or involved in adverse events, and those involved in adverse events but determined as definitely unrelated to adverse events according to the judgment of the investigator, can be destroyed according to the regulations of the study site after use, without any need for recycling. Destruction of study products shall be recorded.

2. Unused study products

   After the termination of the trial, the sponsor will collect all unused investigational and control medical devices. At the end of the study, all related materials must be counted.

3. Defective devices and devices related to adverse events:

   In the following cases, the device shall be recycled and the relevant form for recycling devices shall be filled in:

   - Damaged or defective products;
   - Products that fail or malfunction during the study;
   - Products that cannot be used due to improper storage conditions;
   - Products with incorrect information on the packaging, such as incorrect expiration date;
   - Products related to adverse events, regardless of whether they are damaged, defective or faulty.

In addition, the paper outer packaging of the study device shall be not recycled.

5.7 Combined treatment (medication) specifications

Collect and record the combined medication before and after the use of the study device during the trial (the closest one to such use, twice in total), and the medication and the study device shall pass through the same vascular access (excluding oral medication); medication/treatment for adverse events.

5.8 Measures to control bias

1) The sponsor shall provide relevant training for the investigator prior to the initiation of the study, so as to ensure that the investigators fully understand the study process and

are proficient in using the study product.

2) The operation shall be performed in strict accordance with the operation methods and procedures stipulated in the study protocol during the study process. And the quality control and supervision shall be conducted properly by the clinical research associate (CRA) to ensure that the investigators operate and implement in strict accordance with the study protocol. The above measures shall be implemented throughout the implementation phase of the study to reduce mistakes or operational errors.
3) The subjects shall be screened in strict accordance with the inclusion and exclusion criteria of the trial protocol to reduce selectivity bias for subjects.
4) The clinical study shall be performed by selecting trials or controls in a random way to reduce trial bias caused by sampling error.
5) The data shall be recorded properly during the process of the study. When the study is completed, the data shall be retained and organized properly. When any data problem is found, the data manager shall confirm the data through the data challenge form to avoid the data error.

6. Statistical Considerations

6.1 Estimation of sample size

A total of 378 subjects are proposed to be enrolled in this clinical trial. This study is a non-inferiority design with parallel control. The equivalent products already available on the market (BD Pre-filled Flush Syringes) are selected as the control group device. The study intends to investigate that the overall performance of the investigational device group device for flushing and/or locking the catheter is non-inferior to that of the control group device. According to previous clinical experience, the overall performance success rate of equivalent devices for flushing and/or locking catheters is about 98%. Hence, it is assumed that the treatment completion rate of the investigational device group is consistent with that of the equivalent device. This study adopts a non-inferiority design, with α=0.025 (one-sided), β=0.1 (power of test of 90%), and the non-inferiority margin of 5%. The subjects in the investigational device group and the control group are allocated in an equal ratio of 1:1. The sample size shall be calculated to each enroll 165 subjects into the investigational device group and the control group by using the PASS software. However, 368 subjects shall be included to participate in this clinical study considering factors such as drop-out of subjects (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 study device, each nurse will randomly use 3 investigational devices and 3 control devices, so a total of 378 subjects will be proposed to be enrolled in this clinical trial.

Minimum and maximum number of subjects and reasons for each clinical trial institution

This trial will be conducted simultaneously in multiple clinical trial institutions to enroll subjects. In principle, the subjects enrolled at each site will be distributed as evenly as possible to ensure adequate site representation. However, given the feasibility and enrollment progress, the number of subjects enrolled at each site will be properly adjusted according to the actual situation, so as to ensure the relative balance of the enrollment size of each site, and the final enrollment size of a particular site shall not exceed 50% of the total number of cases, and at least not less than half of the number of cases borne by the average distribution.

6.2 Analysis data sets

Full analysis set (FAS): a data set consisting of all randomized subjects according to the basic principle of intention-to-treat analysis.

Per protocol set (PPS): refers to the subjects in the FAS who are of no serious violation against

the trial protocol, good compliance, and no missing primary efficacy indicators.

Safety set (SS): refers to the subjects who receive at least one study device treatment and at least one safety evaluation.

Efficacy analysis is to be performed based on the full analysis set and per protocol set. PPS will be used as the primary population for analyzing primary efficacy indicators in this study; FAS will be used as the population for analyzing the baseline data of this study, as well as for efficacy evaluation. SS will be used as the primary population for the safety analysis in this study.

6.3 Subject exclusion criteria

Investigators, sponsors, data management and statistical analysis units comprehensively judge whether to exclude patients based on factors such as the degree to which subjects completed the trial and the reasons for withdrawal. FAS subjects shall be excluded from PPS if they meet one of the following:

(1) Subjects who do not meet the inclusion criteria or meet any of the exclusion criteria are mistakenly included in the trial;

(2) Subjects with missing primary efficacy indicators;

(3) Subjects who are in major violation of the trial protocol and with poor compliance;

(4) Subjects with other special reasons.

Specific subject exclusion will be determined through discussion between the investigator, sponsor, data administrator and statistician at the data review meeting.

6.4 Statistical methods

This study will use SAS9.4 or above for statistical analysis. Statistical description shall be performed for all data, including baseline data, all effectiveness indicators, and all safety indicators, etc.

For quantitative variables, descriptive statistics will include number of subjects, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum.

For qualitative variables, descriptive statistics will include the number of subjects and percentages.

Statistical test for the primary efficacy indicators is carried out with two-sided α=0.05. When P is less than 0.05, the inter-group difference is considered statistically significant.

Test hypotheses for the primary efficacy indicators:

Null hypothesis H_0: The overall performance success rate p_1 in the investigational device group is inferior to the p_2 of the control device group ($p_1 \leq p_2-\delta$).

Alternative hypothesis H_1: The overall performance success rate p_1 in the investigational device group is non-inferior to the p_2 of the control device group ($p_1 > p_2-\delta$).

Where δ = 5% is the non-inferiority margin, which is the range of differences not considered clinically significant.

For the comparison of the main efficacy indicators between groups, the chi-square test or Fisher's exact test is adopted, and the confidence interval method is used for statistical inference to separately calculate the success rate of each group and the rate difference as well as two-sided 95% confidence interval between the two groups. If the lower limit of two-sided 95% CI > -5%, H_0 is rejected and the overall performance success rate of the investigational device group can be considered non-inferior to the control device group.

Descriptive analysis (quantitative or qualitative description) is performed for the secondary efficacy indicator, the safety evaluation indicators and other evaluation indicators. For categorical variables, summary statistics will include the number of subjects and percentage. For

the description of adverse event, the cases of adverse events will also be summarized. For continuous variables, summary statistics will include the number of subjects, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. For indicators that require statistical inference, inter-group comparison of quantitative indicators is verified by t-test or Wilcoxon rank sum test based on data distribution characteristics; categorical indicators are verified by $\chi 2$ test or Fisher's exact test; ranked data is verified by Wilcoxon rank sum test.

6.5 Subject number, flush syringe treatment assignment or randomization

6.5.1 Subject number

Each subject will receive a unique screening number, and once a subject has been assigned a screening number, this screening number cannot be assigned to other subjects. This screening number must be recorded on the screening form at each site. Screening numbers will be assigned in the order in which subjects are screened. The screening results shall be recorded in a screening form. Data on the screened subjects, including reasons for screening failure, shall also be input into the electronic case report form (eCRF).

6.5.2 Flush syringe treatment assignment or randomization

The random number of the subject will be provided by the statistical analysis unit commissioned by the sponsor, and the random assignment table of the subject will be generated using SAS9.4 or above. Given the number of seeds and block length, subjects are randomly assigned to the trial and control groups in a 1:1 ratio through a block randomization method.

The random number of the subjects is a 3-digit "site number". If the serial number is less than 3 digits, "0" is added to the front so as to make up 3 digits.

Subject randomization is completed by an Interactive Web Response System (IWRS). Systematic randomization work will be carried out by the investigator or relevant personnel authorized by the investigator. After the successful screening of subjects in each center, the investigators or other authorized personnel log in to the randomization system to obtain the random number and corresponding group information, then study nurses perform the trial intervention according to the random assignment results.

6.6 Handling of missing values and outliers

All missing, unused or incorrect data (including midway withdrawal and exit) and unreasonable data will be discussed and finalized by the investigator, sponsor and biostatistician.

Unless otherwise stipulated, missing values of all analysis indicators will not be filled.

7. Monitoring Plan

According to the requirements in *Good Clinical Practice for Medical Devices*, the sponsor shall undertake monitoring responsibilities for the medical device clinical trial, formulate standard operating procedures for monitoring and select monitors who conform to the requirements to fulfill the responsibilities of monitoring:

The monitor number and monitoring frequency shall be commensurate with the complexity of the trial and the number of clinical trial institutions participating in this trial.

The monitors shall be properly trained, be familiar with GCP and relevant laws and regulations, have relevant professional background expertise, be familiar with relevant research materials of investigational medical devices and clinical information of similar products, clinical trial protocol and related documents, and be able to effectively perform monitoring responsibilities.

The monitors shall abide by the standard operating procedures for monitoring formulated by the sponsor, and urge the clinical trial of medical devices to be implemented in accordance with the clinical trial protocol. The aspects to be monitored include the compliance with clinical trial protocol, GCP and relevant laws and regulations by the clinical trial institutions and the

investigators during the conduct of the clinical trial, the signing of informed consent by subjects, screening, follow-up, rights and security protection, management and use of investigational device and control device, management and use of biological samples, handling of adverse events and device defects, reporting of safety-related information, data records of clinical trial and completion of case report forms etc. The monitors shall report to the sponsor in writing after each monitoring which shall include the name of the monitor, monitoring date, monitoring time, site monitored, aspects monitored, name of investigator, project completion information, issues identified, conclusion and the corrective measures taken for the mistakes and omissions etc.

8. Data Management

Data managers shall prepare a data management plan (DMP) according to project requirements and carry out various specific data management work according to the DMP to ensure the authenticity, integrity and traceability of clinical trial data.

8.1 Original data

The original data can confirm the real existence of the subject and the integrity and authenticity of the data. All data recorded in the Electronic Data Capture System (EDC) is derived from the original data and shall therefore be consistent with the original data. If the data in the EDC is inconsistent with the original data, it shall be modified according to the original data, or be provided with a reasonable explanation. The original data is stored in each trial site. Original data includes but are not limited to the following documents:

- Medical records;
- Informed consent form of the subjects;
- Related forms or documents that record information on efficacy and safety.

8.2 EDC system

This study will use the EDC system to collect data. It has been fully verified and can save the audit trail and manage accounts and permissions well.

The EDC system will automatically save the audit trail of the data, including the time of data entry and change, the operator, the reason for the change, the data value before the change, the data value after the change, etc., to ensure the traceability of the data.

System administrators separately create accounts for different roles, grant different permissions for them, and strictly manage and control account application and cancellation.

8.3 Design of eCRF

Data managers design case report forms according to the study protocol and with reference to the Clinical Data Acquisition Standards Harmonization (CDASH). Database designers build eCRF in EDC and set up logical verification procedures; data managers carry out testing of the database and can only be published online unless the testing is passed.

8.4 eCRF filling

The eCRF is filled out by the investigator or an authorized clinical study coordinator (CRC) based on the source documents (original medical records, examination reports, etc.) and the investigator is responsible for timely and accurate entry of the study data into the EDC. The monitor dispatched by the sponsor shall confirm that all data records and reports are correct and complete, and that the data in all EDCs is consistent with the original data.

8.5 Data verification

After the eCRF is filled out, the data will be verified by means of computer program verification and manual verification according to the data management plan. The suspicious data points found in the verification shall be managed in the form of query, and the investigator or CRC shall promptly reply to the query.

8.6 Data quality assurance

This study will employ quality control and data verification processes to ensure the reliability and accuracy of the clinical database. The monitoring plan and data management plan will detail the data entry, inspection, clarification and verification processes that all relevant study staff shall follow to ensure compliance with Good Clinical Practice.

8.7 Medical coding

The medical coders will be responsible for the medical coding of this study. adverse events, hospital admission diagnosis, etc. Those will be coded using MedDRA 24.0 or above. The medical coding operation will follow the "Medical Coding Plan" in which the contents of medical coding entry, dictionary version, dictionary update, coding review, etc. are specified in detail.

8.8 Blind review

Not applicable.

8.9 Database locking

After all doubts have been resolved and the data in the database are confirmed to be complete and accurate, the representatives of the sponsor, principal investigators, statistical analysts, and data managers will jointly approve the database, and then the database manager will lock the database.

8.10 Submission and filing of data management documents

After the database is locked, the data managers will prepare a data management report according to the actual implementation of the project, and complete the submission and filing of paper and electronic documents according to the management requirements of the project document.

9. Risk Benefit Analysis

9.1 Benefit analysis

Pre-filled Flush Syringes have been on the market for many years at home and abroad, and it has been proven that the use of Pre-filled Flush Syringes can improve the accuracy of drug administration, reduce the risk of drug administration and medication errors, as well as reduce the risk of microbial contamination to improve the safety and convenience of use. Therefore, it is intended that the safety performance of the trial product is reliable and can meet the requirements of clinical trials.

9.2 Risk analysis

Transient taste and/or odor disturbances may occur with the use of Pre-filled Flush Syringes. In the course of the trial, the effective cases may be insufficient if a significant number of subjects drop out from the trial, or the quality of the trial may be affected due to the non-standard operation of the trial personnel.

10. Quality Control of Clinical Trial

10.1 Quality control of site

The clinical study protocol shall be discussed and formulated by the principal investigators who participate in the trial prior to the initiation of the formal trial, so as to ensure the quality of the trial. Relevant training will be provided for the relevant medical staff participating in this trial.

The data collected shall be guaranteed to be accurate, consistent, complete and credible during the study conduct phase. All observed results and abnormal findings in clinical trials shall be carefully verified and recorded in a timely manner to ensure the reliability of the data.

All laboratories of each clinical site shall establish consistent criteria of test index, standard operating procedures and quality control procedures. The national legal measurement unit shall

be adopted for each trial test item and the items in the test report must be complete (including date, test items, test results and normal range) and signed by the relevant personnel. Special examination items shall be specially designated to the personnel who is responsible for testing.

The relevant training shall be received by the users of measuring equipment before using the equipment. They shall be familiar with the use of equipment to avoid measurement errors in trial data caused by human factors. Meanwhile, the proper maintenance of the equipment shall be carried out on a regular basis to ensure the measuring accuracy of clinical trial data and the normal operation of the equipment. All equipment used for trial data measurement shall acquire relevant access documents or certificates on sales in Chinese market, and its shelf life shall be within the warranty period and the equipment shall be in good condition. Calibration shall be performed before use to ensure measuring accuracy.

10.2 Monitoring

Sponsors shall dispatch trained monitors for regular and irregular monitoring in the course of the trial. The monitor is responsible for monitoring whether the clinical facilities of the study sites meet the requirements and whether the trial personnel follow the trial protocol and accurately record the trial results. The monitor must also review the eCRF with original documents and inform the investigator of any omissions or errors during each monitoring session, and must review the use record of the device to ensure compliance with the requirements of the protocol. The monitor shall confirm that all AEs are recorded, and SAEs are reported and recorded within the specified time. The monitor shall submit the written report to the sponsor in a timely manner after each monitoring.

Medical monitoring is completed by medical monitors and will be carried out throughout the entire process of the trial, including but not limited to review of enrollment qualifications, protocol violations, regular clinical trial data, and data during follow-up, etc.

According to the requirements of the GCP for medical devices, the study sites must also be audited by auditors appointed by the sponsor. The auditors will conduct systematic and independent inspection of activities and documents related to the clinical trial of medical device to determine that whether the implementation of such activities, recording, analysis and report of data conform to the clinical trial protocol, standard operating procedure, and relevant laws and regulations. Audits shall be performed by personnel who is not directly involved in the clinical trial.

Regulatory department could perform supervision and administration of relevant documents, facilities, records and other aspects of the clinical trial of medical devices.

11. Ethical Issues and Informed Consent of Clinical Trial

11.1 Ethical considerations

This study will be performed in accordance with the ethical guidelines of the *Declaration of Helsinki*, GCP for medical devices, all applicable laws and regulations to protect the rights, safety and health of the subjects.

Before the start of the study, the clinical trial protocol, informed consent form, all information provided to the subjects, and other relevant materials related to the ethical review must be submitted to the Ethics Committee, which will take effect after review and approval or filing by the Ethics Committee. Investigators shall report the study progress to the Ethics Committee on a regular basis in accordance with the requirements of the Ethics Committee.

Any modification to the clinical trial protocol, informed consent form and other documents shall be implemented after obtaining the written consent of the Ethics Committee again.

If any document submitted to the Ethics Committee is modified after submission, the Ethics Committee must be notified in time. In addition, any serious/unexpected adverse events

occurring in the study that affect the rights and safety of subjects, or deviations from the clinical trial protocol must be reported to the Ethics Committee.

11.2 Informed consent process

All subjects are required to sign an informed consent form before starting to participate in the study. Informed consent form shall be obtained in accordance with the ethical guidelines of the *Declaration of Helsinki*, GCP, and other applicable laws and regulations.

Clinical trial, inform the subjects of the ; Prior to the participation of the subjects in this clinical trial, the investigator shall explain in detail to each subject about the investigational medical device and the clinical trial, the possible benefits and predictable risks; after explaining the basic contents of this clinical trial, the investigator shall confirm that each subject who will participate in this trial understands the purpose of this trial, then the investigator shall request each subject to sign their name on the informed consent form and indicate the date, and the investigator sign his/her own name and indicate the date accordingly.

Written informed consent shall be obtained from the subject's guardian if the subject is an individual with no legal capacity or with limited legal capacity; an impartial witness shall be required to witness the whole informed consent process, sign his/her name on the informed consent form and indicate the date if the subject is lacking in reading ability.

Each subject or his/her guardian must know that the participation in the trial is voluntary, and they may refuse to participate or have the right to withdraw from the trial at any stage of the trial and withdraw their informed consent without discrimination or retaliation, and their medical treatment and rights will not be affected etc.

Subjects shall read and consider carefully before signing the informed consent form, and sign it after understanding the trial process and agreeing to participate in this study. The informed consent form will be provided in two copies, and one copy will be kept at the study center as the original data and one copy will be retained by the subject. Subjects whose informed consent is not obtained and/or subjects who do not sign the informed consent form will not be included in this trial.

The informed consent process and specific matters in the ICF can be found in the ICF of this protocol.

12. Regulations on Reporting of Adverse Events

12.1 Definition and reporting requirements of adverse events

12.1.1 Definition of adverse event

Adverse event refers to any adverse medical event that occurs during the clinical trial of medical devices, whether or not it is related the investigational medical device.

12.1.2 Classification of adverse event

Mild: The adverse event is tolerable, does not affect the diagnosis and treatment, does not require special treatment, and has no impact on the subject's health.

Moderate: The adverse event is intolerable, requires special treatment, and has a direct impact on the subject's health.

Severe: The adverse event endangers the subject's life, causing death or disability, and immediate emergency treatment is required.

12.1.3 Correlation of adverse event with devices

Five criteria that investigators will use for judging the relationship between adverse events and study devices. Among them, "definitely related, probably related, and possibly related" will be determined to be adverse events related to the study devices.

(1) Definitely related: It conforms to the known reaction type of the device used, conforms to a reasonable time sequence after treatment, the adverse event cannot be explained by other reasons, the adverse event is alleviated or disappear after the treatment is stopped, the adverse event reappears after reuse, and the adverse event cannot be explained by the subject's current disease;

(2) Probably related: It conforms to the known reaction type of the device used, conforms to a reasonable time sequence after treatment, the adverse event cannot be explained by other reasons, the adverse event is alleviated or disappear after the treatment is stopped, and it is impossible to judge whether the adverse event will occur again after reuse, the adverse event cannot be explained by the subject's current disease;

(3) Possibly related: It conforms to the known reaction type of the device used, conforms to a reasonable time sequence after treatment, the adverse event cannot be explained by other reasons, the adverse event may be alleviated or disappear after treatment is stopped, and it is impossible to judge whether the adverse event will occur again after reuse, the adverse event can be explained by the subject's current disease;

(4) Possibly unrelated: It conforms to the known reaction type of the device used, conforms to a reasonable time sequence after treatment, the adverse event can be explained by other reasons, the adverse event may be alleviated or disappear after treatment is stopped, and it is impossible to judge whether the adverse event will occur again after reuse, the adverse event can be explained by the subject's current disease;

(5) Unrelated: It does not conform to the known reaction type of the device used, does not conform to a reasonable time sequence after treatment, the adverse event can be explained by other reasons, the adverse event does not alleviate or disappear after treatment is stopped, and the adverse event does not occur again after reuse, adverse events can be explained by the subject's current disease.

12.1.4 Observation and recording of adverse events

The investigator shall collect and record the adverse events from each subject during the period from the signing of informed consent form to the termination of follow-up. Any adverse event, regardless of its severity, or whether it is related to the medical device, is required to be recorded and described on the adverse event form for study medical records. Investigators need to determine the date of occurrence, severity, whether to take corresponding measures, and to judge the correlation between the adverse events and the medical devices.

The subject undergoing such adverse events shall be followed up until the adverse events are recovered (return to normal state or to baseline state), or until the condition is stable, or until a reasonable explanation is available.

12.1.5 Outcome of adverse events

Investigators shall report the outcomes of adverse events recorded at the last visit in the eCRF, such as:

(1) Symptoms disappear (with or without sequela, record the performance of sequela);

(2) Symptoms improve;

(3) Symptoms persist;

(4) Death (record the direct cause of death and the time of death);

(5) Unknown.

12.1.6 Possible adverse events and their prevention and treatment

Transient taste and/or odor disturbances may occur with the use of Pre-filled Flush Syringes. Special treatment is not necessary.

12.2 Device defects and reporting

Device defects refer to the unreasonable risks of medical devices under normal use during clinical trials that may endanger human health and safety, such as label errors, quality issues, and malfunctions.

If a device defect occurs during the trial, regardless of whether it causes injury to the subject/investigator, the investigator shall promptly notify the sponsor, the Ethics Committee, and clinical study monitor and other relevant personnel, and record the device defect in the eCRF.

If adverse events or serious adverse events occur due to device defects, refer to the handling methods for adverse events or serious adverse events for proper handling.

12.3 Definition of serious adverse events

Serious adverse events (SAE) refers to those that result in death or serious deterioration of health conditions during clinical trial, including:

Life-threatening diseases or injuries;

Permanent defects of body structure or body function;

Hospitalization or prolonged hospitalization required;

Medical or surgical intervention required to prevent permanent defects of body structure or body function;

Resulting in fetal distress, fetal death or congenital abnormality, congenital defects, etc.

In this trial, subjects who will undergo a pre-planned medical/surgical procedure or are admitted to a hospital for a pre-planned medical/surgical procedure during their participation in the trial are not classified as SAEs.

12.4 Reporting procedures, contact information

In case of any serious adverse events occurring during the clinical trial, the investigators shall immediately take appropriate therapeutic measures for subjects, and report the serious adverse event to the sponsor, the administrative authority for clinical trial of medical device of the study site and the Ethics Committee within 24 hours after learning the occurrence of the serious adverse event; and the investigator shall follow up with the serious adverse event as per the clinical trial protocol and submit the follow-up report for the serious adverse event.

When it is found that the risks of the medical device clinical trial exceed the possible benefits and it is necessary to suspend or terminate the clinical trial, the principal investigator shall report to the sponsor, the administrative department of the clinical trial institution of medical device, and the Ethics Committee, notify the subjects in a timely manner, and ensure that the subjects receive appropriate treatment and follow-up.

The sponsor shall report to the other clinical trial institutions of medical device, Ethics Committee, and principal investigators participating in clinical trials, report to the drug regulatory departments of the province, autonomous region and municipality directly under the central government where the sponsor is located, report to the drug regulatory departments and health management departments of the province, autonomous region and municipality directly under the central government where the clinical trial institutions of medical device are located within 7 days of learning the death-causing or life-threatening medical device-related serious adverse event in the clinical trial, within 15 days of non-death-causing or non- life-threatening medical device-related serious adverse event and other serious safety risk information and take appropriate risk control measures; when information that may affect the safety of the subjects, the implementation of the medical device clinical trial or may change the approval of the Ethics Committee arises, modifications shall be made to the clinical trial protocol, informed consent form and other information provided to the subjects as well as other relevant documents in a timely manner and then submitted to the Ethics Committee for review.

When multiple serious adverse events related to the medical devices in the clinical trial occur or any other significant safety issues arise, the sponsor shall suspend or terminate the clinical trial, report to the administrative departments, ethics committees and principal investigators of all clinical trial institutions of medical device, report to the drug regulatory departments of the province, autonomous region and municipality directly under the central government where the sponsor is located, report to the regulatory authorities and health management departments of the province, autonomous region and municipality directly under the central government where the clinical trial institutions of medical device are located.

Subjects who experience serious adverse events shall be followed up until their conditions return to normal, or premorbid conditions, or return to the condition deemed reasonable by the investigators, and the final follow-up report shall be reported in accordance with the reporting procedures for serious adverse events.

Serious adverse events that occur at the final visit must also be reported in accordance with the reporting procedures for serious adverse events.

In the event of recurrence, complications or worsening of a serious adverse event, the investigator shall follow up the primary serious adverse event and submit a follow-up report within 24 hours of receiving the information. If a new serious adverse event occurs at a different time period or is otherwise determined to be completely unrelated to the original serious adverse event due to other reasons, it must be reported as a new serious adverse event separately.

Contacts

Current unit	Name	Contact number	E-mail
BD Medical Technologies (Jiangsu) Co., Ltd.	Ma Juanjuan	010-58139097	Jessica.Ma@bd.com
GCP ClinPlus Co., Ltd.	Xie Yuanyuan	13263414232	yuanyuan.xie@gcp-clinplus.com

13. Deviation from Clinical Trial Protocol and Regulations for Clinical Trial Protocol Revision

13.1 Definition of deviation

Deviation refers to the situation where the requirements of the clinical trial protocol are not followed intentionally or unintentionally.

Investigators shall strictly follow the clinical trial protocol and shall not intentionally deviate from the protocol or substantially change the protocol. Where there is emergency in which the subject faces the direct risk and which needs to be immediately tackled, report can be submitted in writing afterwards.

If the investigator unintentionally fails to follow the clinical trial protocol, the investigator shall promptly report to the medical device clinical trial management department of the clinical trial institution after discovery, and be promptly informed by it to the sponsor and reported to the Ethics Committee.

For all protocol deviations, investigators must record their cause, date, and severity in the original document.

Protocol deviations include, but are not limited to:

- Enrolled subjects do not meet the inclusion criteria or meet the exclusion criteria;

- Failure to perform or inaccurately perform the treatment, follow-up or examination specified in this clinical trial protocol;

- Failure to report adverse events within the period specified in the clinical trial protocol.

The severity of protocol deviation shall be classified by the following definitions:

- Serious protocol deviation: protocol deviation that affects trial data and results, or endangers the rights and interests, safety or health of subjects.

- Mild protocol deviation: protocol deviation that will not affect the trial data and results, nor will it jeopardize the rights and interests, safety or health of subjects.

The sponsor will continue to review and evaluate the situation of protocol deviation, and if necessary, the sponsor will take appropriate corrective and preventive measures, including but not limited to: notifying, retraining the trial center or investigator, terminating the qualification of the trial center, and reporting to the local drug regulatory authorities and the National Medical Products Administration where the clinical trial institution is located.

13.2 Measures to control deviations

13.2.1 Sponsor

The protocol will be designed with concise and clearly written descriptions and possible protocol deviations will be considered as much as possible, so that deviations are minimized in the design of the protocol and possible deviations can be easily and clearly identified and confirmed.

In the meeting and training before the conduct of the trial, the implementation details of the protocol shall be trained to reduce the possible protocol deviation during the implementation.

The rectification of the protocol deviation that has occurred shall be implemented in time. If necessary, the trial project shall be suspended in time, and the protocol or trial plan shall be revised. After the protocol is revised, the trial will be continued after the obtaining the approval of the Ethics Committee and the completion of retraining.

13.2.2 Investigator

The trial protocol will be designed and formulated together with the sponsor, and the investigator will fully discuss the feasibility of the protocol in the institution with the sponsor.

The investigator shall explain to the subjects the importance of the compliance with protocol when informed consent is given.

The investigator shall comply with protocol approved by the Ethics Committee. Once a deviation from the protocol is recognized, the situation shall be recorded and explained immediately and be reported to the relevant department as required.

13.2.3 Subjects

When signing the ICF, the trial protocol and requirements of the trial shall be explained in detail to the subjects, and the investigator shall inform the subjects of precautions such as operation and follow-up.

13.2.4 Protocol deviation reporting

If there is a deviation from the protocol, the investigator shall immediately report to the sponsor, and at the same time, to the Ethics Committee to determine whether the trial can be continued.

13.3 The provisions of the clinical trial protocol amendments

The medical device study protocol shall be based on the principle of maximizing the protection of subjects' rights and interests, safety and health, and shall be jointly designed and formulated by the medical institution in charge of the clinical trial and the sponsor, and shall be submitted to the Ethics Committee for approval before implementation. If there is any modification to the study protocol, informed consent form and case report form during the study, the revised materials must be approved by the Ethics Committee before proceeding with the clinical trial.

14. Direct Access to Source Data and Documents

Source data refers to the original records of clinical findings, observations and other activities in clinical trials and all the information in their approved copies, which can be used for clinical trial reconstruction and evaluation.

Source document refers to printed, visual, or electronic documents containing source data.

The authorized monitor has the right to access and verify the source data or source documents of the subjects to determine whether the investigator conduct clinical trials in accordance with protocol requirements, and whether the source data or source documents are timely recorded in the subjects' medical records. The monitor needs to confirm that the source data or source documents are traceable and verifiable. At the same time, the data filled in the eCRF shall correspond to the source data or source documents.

When any person involved in the clinical trial questions the clinical trial data, the investigator shall provide the source data or source documents in time for the relevant personnel to verify and carefully answer the relevant questions.

The source data or source documents shall be maintained for 10 years after the end of the clinical trial in accordance with relevant laws and regulations. If the regulations are updated, the retention period shall be updated accordingly. Destruction requires the signature of the sponsor for confirmation and shall meet the requirements of relevant laws and regulations.

15. Contents to be Covered in the Clinical Trial Report

The clinical trial report shall fully, completely and accurately reflect the clinical trial results, and the safety and efficacy data of the clinical trial report shall be consistent with the clinical trial source data.

The clinical trial report generally contains general information about the clinical trial of medical devices, implementation, statistical analysis methods used, clinical trial results, adverse events and device defect report and their handling information, analysis and discussion of clinical trial results, clinical trial conclusion, ethical information description, issued found and suggestions for improvement etc.

16. Confidentiality Principle

All data generated in this study is confidential to the sponsor. The sponsor has the right to publish the results of the study. The investigators shall maintain the confidentiality of information and data related to this trial, and the investigators must be aware of the potential commercial value to the sponsor of scientific or medical information derived from this trial.

If the investigators expect to publish the information related to this trial or the conclusions drawn from the trial, it is necessary to consult with the sponsor in advance and obtain the written consent of the sponsor, and provide the attachment to the manuscript for review by the sponsor. The sponsor has the right to request the investigators not to publish information about the trial before the trial product is approved for marketing.

The sponsor has the right to publish or release information and data related to this trial, or to report it to the drug regulatory authorities. Sponsors shall obtain the investigator's prior consent if they wish to include the investigator's name in publications, releases or advertisements.

All personal information of the subjects participating in this clinical trial is confidential, however, the administrative department of the clinical trial institutions of the medical device, the Ethics Committee, the drug regulatory authorities, the health management departments or monitors, auditors are allowed to access the information of the subjects according to the specified procedures. Participating investigators, staff and sponsors jointly take intervention measures to strictly protect the privacy of subjects and the confidentiality of their related information.

17. Responsibilities of All Parties

17.1 Responsibilities of sponsor

The sponsor is responsible for the truthfulness and compliance of the clinical trial. If the sponsor is a foreign organization, an enterprise legal person in China shall be designated as an agent in accordance with relevant laws and regulations, and the agent shall assist the sponsor to perform its responsibilities.

The sponsor's quality management system shall cover the entire process of the clinical trial of medical devices, and the quality management measures shall be adapted to the risks of the clinical trial.

Before the initiation of the clinical trial of medical devices, the sponsor shall ensure that the product design has been finalized, complete the pre-clinical study of the investigational medical device, including performance validation and qualification, product inspection report based on product technical requirements, risk-benefit analysis, etc., and the results should be able to support the clinical trial of the medical device; select the registered clinical trial institutions of medical device, majors and principal investigators according to the characteristics of the investigational medical device; organize the formulation of investigator’s brochure, clinical trial protocol, informed consent form, case report form, standard operating procedures and other related documents, and provide them to clinical trial institutions of medical device and principal investigators.

The sponsor shall sign contracts with the clinical trial institutions of medical device and the principal investigator to clarify the rights and obligations of each party in the clinical trial of the medical device.

The sponsor shall file the clinical trial project with the drug regulatory department of the province, autonomous region or municipality directly under the central government where the sponsor is located after the clinical trial of the medical device has passed the ethics review and signs a contract with the clinical trial institutions of the medical device.

Before the clinical trial of the medical device begins, the sponsor shall be responsible for organizing training related to the clinical trial of the medical device, such as the principle, scope of application, product performance, operation method, installation requirements, technical indicators, and clinical trial protocol, standard operating procedures for the medical device and other related documents.

The sponsor shall provide the investigational medical device free of charge, and ensure that the investigational medical device shall be produced in accordance with the relevant requirements of the Good Manufacturing Practice for Medical Devices and of accepted quality; determine the transportation conditions, storage conditions, storage time, expiry date, etc. of the investigational medical device; the investigational medical device shall be properly packaged and stored in accordance with the requirements of the clinical trial protocol; the product information shall be marked on the packaging label, with an easily identifiable and correctly coded mark, indicating that it is only used for clinical trial of the medical device; after clinical trial of the medical device is approved by the Ethics Committee, the sponsor is responsible for transporting the investigational medical device to the clinical trial institution of the medical device under specified conditions; for investigational medical devices recovered from clinical trial institutions

of medical devices, the sponsor is responsible for maintaining records of recovery and disposal.

The sponsor shall pay the cost related to the clinical trial of medical devices for the subjects. When a subject suffers injuries or death related to the clinical trial of the medical device, the sponsor shall bear the corresponding treatment costs, compensation or indemnity, but not including the injuries caused by the investigator's and the clinical trial institution of medical device's own negligence and the subject's own disease progression.

The sponsor shall be responsible for the evaluation and reporting of safety information during medical device trial.

The sponsor shall assume the responsibility for the monitoring of clinical trials of medical devices, formulate the standard operating procedures for monitoring, and select monitors who meet the requirements to perform the monitoring duties.

The sponsor may organize auditors who are independent of medical device clinical trials and have corresponding training and experience to conduct audits on the implementation of clinical trials and assess whether the clinical trials comply with the clinical trial protocol, GCP and relevant laws and regulations.

The sponsor shall ensure that the implementation of the clinical trial of medical devices is carried out in accordance with the clinical trial protocol, and if it is found that the clinical trial institutions of medical devices and investigators fail to comply with the clinical trial protocol, GCP and relevant laws and regulations, the sponsor shall point out and correct them in a timely manner; if the non-compliance is serious or persists, the clinical trial institution and the investigator shall be terminated from continuing to participate in the clinical trial, and a written report shall be submitted to the drug regulatory department of the province, autonomous region, or municipality directly under the central government where the clinical trial institution is located.

The sponsor shall, within 10 working days after the medical device clinical trial is suspended, terminated or completed, report in writing to all the principal investigators, the administrative department of the clinical trial institution of medical device, and the Ethics Committee.

The sponsor shall, within 10 working days after the termination or completion of the clinical trial of medical devices, report to the drug regulatory department of the province, autonomous region or municipality directly under the central government where the sponsor is located.

17.2 Responsibilities of clinical trial institutions of medical device

The administrative department of clinical trial institution of medical device shall be responsible for filling in, managing and changing the clinical trial institution of medical device’s registration information in the registration management information system for clinical trial institutions of clinical trial, including the clinical trial specialty, principal investigator and other information; responsible for submitting the summary report on the implementation of clinical trials of medical devices in the previous year online in the registration system; responsible for organizing the evaluation of the qualifications of the principal investigators of the clinical trial and completing its filing before the ethics committee reviews the clinical trial of medical devices.

Clinical trial institutions of medical device shall establish a quality management system, covering the entire process of the implementation of medical device clinical trials, to ensure that the principal investigators perform their clinical trial-related duties, to ensure that subjects receive proper medical treatment, and to ensure the authenticity of the data generated by the trials.

Before accepting clinical trials of medical devices, clinical trial institutions of medical device shall evaluate relevant resources according to the characteristics of the investigational medical devices to ensure that they are provided with proper qualifications, personnel, facilities, and conditions.

Clinical trial institutions of medical device and investigators shall cooperate with the monitoring and audits organized by the sponsor, as well as the inspections carried out by the drug regulatory department and the health management department.

Clinical trial institutions of medical device shall properly maintain clinical trial records and basic documents in accordance with relevant laws and regulations and contracts signed with the sponsor.

17.3 Responsibilities of investigators

The principal investigator shall ensure that the clinical trial of medical device follows the latest version of the clinical trial protocol agreed by the Ethics Committee; carry out the clinical trial of medical devices in accordance with the provisions of GCP and relevant laws and regulations.

The principal investigator may, according to the needs of the clinical trial of medical device, authorize investigators who have received training related to clinical trials to organize subject recruitment, informed consent, screening and follow-up; management and use of investigational devices and control devices; management and use of biological samples; handling of adverse events and device defects; clinical trial data recording and case report form filling, etc.

Investigators participating in clinical trials of medical devices shall: have the corresponding professional technical qualifications, training experience and relevant experience to undertake clinical trials of medical devices; participate in the training related to the clinical trial of the medical device organized by the sponsor, and participate in the clinical trial of the medical device within the scope authorized by the principal investigator; be familiar with the principle, scope of application or intended use, product performance, operation method, installation requirements and technical indicators of the investigational medical device, and understand the relevant information of the preclinical study of the investigational medical device; fully understand and comply with the clinical trial protocol, GCP and relevant laws and regulations, as well as responsibilities related to clinical trials of medical devices; master the prevention and emergency treatment methods of risks that may arise in clinical trials.

Investigators shall abide by the ethical guidelines and relevant ethical requirements of the *Declaration of Helsinki of the World Medical Assembly*.

Investigators are responsible for the management of the test medical device and the control medical device (if applicable) provided by the sponsor, and shall ensure that it is only used for the subjects participating in the clinical trial of the medical device, and is stored and kept as required during the clinical trial. After the clinical trial is completed or terminated, they shall be disposed in accordance with relevant laws and regulations and the contract with the sponsor.

Investigators shall ensure that the collection, processing, preservation, transportation, and destruction of biological samples in medical device clinical trials comply with the clinical trial protocol and relevant laws and regulations.

When an adverse event occurs in the clinical trial of the medical device, the investigators shall provide the subject with adequate and timely treatment; when the subject develops a concurrent disease requiring treatment, the investigators shall promptly inform the subject. Investigators shall record adverse events and device defects found during the clinical trial of medical device.

Investigators shall report safety information in the clinical trials of medical device in a timely manner.

The principal investigator shall deal with the received safety information in a timely manner.

The principal investigator shall report the progress of the clinical trial of medical device to the Ethics Committee as scheduled, and promptly report events affecting the rights and safety of subjects or deviations from the clinical trial protocol.

Clinical trial institutions of medical device and investigators shall report in writing to the drug

regulatory department of the province, autonomous region or municipality directly under the central government where the sponsor is located for the sponsor's serious or persistent violation of GCP and relevant laws and regulations, or the requirement to change the trial data and conclusions.

17.4 Responsibilities of CRO

The CRO shall comply with the current regulations and guidelines such as the GCP for medical devices, the *Declaration of Helsinki*, and the obligations and responsibilities for the contract research organization in the trial protocol and sponsor contract.

The CRO shall be responsible for the related work of the management of the trial project and clinical monitoring affairs, establish the quality control and quality assurance system for the clinical trial, and assign professionals personnel to monitor the whole process of the clinical trial in accordance with the requirements of the company's quality system to ensure the authenticity, completeness and standardization of the entire trial process.

18. Other Contents Required to be Described

18.1 Basic document management

Clinical trial institutions, investigators, and sponsors shall establish a basic document preservation system. The basic documents of clinical trial are divided into three parts according to the clinical trial stage: the document of preparation stage, the document of progress stage and the document of termination or post-completion.

Investigators shall properly maintain the basic clinical trial documents during the clinical trial of medical devices. The clinical trial institutions shall preserve the clinical trial data for 10 years after the completion or termination of the clinical trial. The Ethics Committee shall keep all records of the ethics review until 10 years after the completion or termination of clinical trials of medical devices. The sponsor shall keep the basic documents of the clinical trial until there is no use of this medical device.

The basic documents of clinical trial can be used to evaluate the implementation of this specification and the relevant requirements of the drug regulatory authorities by the sponsors, clinical trial institutions and investigators. The drug regulatory department can inspect the basic documents of clinical trials.

18.2 Finance and insurance

The sponsor is responsible for the cost of medical treatment and corresponding compensation of subjects participating in clinical trials for injury or death related to the clinical trials. The sponsor shall provide the investigators and the clinical trial institutions with legal and financial insurance or guarantees, related to the clinical trial, which should be commensurate with the nature and degree of risk of the clinical trial. However, it does not cover injury caused by the investigators and the clinical trial institution's own negligence.

Investigator's Statement

I agree:

1. To carry out this clinical trial in strict accordance with the *Declaration of Helsinki*, the current laws and regulations in China and the requirements of the trial protocol.

2. To accurately record all required data in the Case Report Form (CRF) and provide cooperation in the completion of clinical trial reports.

3. To only use the investigational medical devices for this clinical trial. Completely and accurately record the receipt and use of the investigational medical devices during the clinical trial and save the records.

4. To allow sponsors to authorize or dispatch monitors, auditors and regulatory authorities to monitor, audit and inspect the clinical trial.

5. To strictly fulfill the clinical trial contract/protocol terms signed by the parties.

I have read the clinical trial protocol and the statement above, and I agree with all of them.

Principal investigator Signature (YYYY/MM/DD)

Clinical trial institution of medical device Signature and seal (YYYY/MM/DD)

Sponsor Signature (YYYY/MM/DD)