Statistical Analysis Plan (SAP)	
Study Title	Multi-center, prospective, open label, single arm post-market study of BD NRFit™ Spinal Needles, NRFit™ Spinal Introducer Needles, and NRFit™ Syringes on participants who are receiving neuraxial procedure.
Study ID	MDS-21NRFit001
Author(s)	Shuangshuang Fu
Report Date	08 August 2024
CIP Version	Version 2.0
Registration Number	NCT05953363 (ClinicalTrials.gov)

BD	**Statistical Analysis Plan**	
	Study ID: MDS-21NRFit001	Version No: **1.0**

GFM-10082C

General Information	
Report Date:	08-Aug-2024
Report Author:	Shuangshuang Fu
CIP/CPSP Version:	2.0

BD	**Statistical Analysis Plan**	
	Study ID: MDS-21NRFit001	Version No: **1.0**

GFM-10082C

Table of Contents

1.0 INTRODUCTION

1.1 Background and Rationale

A 2009 study of obstetric anesthesia practice found four deaths due to administration of tranexamic acid into the neuraxis. Errors of this type are referred to as misconnections or wrong-route drug delivery. This 2009 study is just one example of death or serious harm that can result from wrong-route drug delivery. Misconnections are often the result of accidental administration of substances, that are safe to deliver intravascularly, via the neuraxial route.

Authors across disciplines have concluded that the mortality and morbidity associated with such errors is secondary to the universal adoption of Luer lock equipment.

Furthermore, sentinel interest groups in the US and the EU have issued warnings about the risk of universal Luer connectors, that allow these misconnections. Therefore, implementation of devices with non-Luer connectors could improve patient safety and decrease the risk of misconnections.

The goal of the ISO 80369 standard for Small Bore Connectors is to reduce the risk of misconnections between medical devices or between accessories for different applications. ISO 80369-6:2016 specifies requirements for small bore connectors intended to be used for connections in neuraxial applications. Neuraxial applications involve the use of medical devices intended to administer medications to neuraxial sites, wound infiltration anesthesia delivery, other regional anesthesia procedures and monitoring or removing cerebrospinal fluid for therapeutic or diagnostic purposes. The neuraxial ISO 80369-6 devices have been designated as NRFit. They are visually identifiable by an NRFit label and yellow device components, both of which denote that the device is only for neuraxial use.

BD manufactured ISO 80369-6 compliant devices from medication preparation to delivery, such as the spinal NRFit™ needles, the spinal introducer NRFit™ needles, the spinal NRFit™ needle sets, the syringes NRFit™, the blunt fill and blunt filter NRFit™ needles.

This study is designed to assess the safety and performance of the BD Spinal NRFit™Needles, BD Spinal NRFit™Needle Sets, BD Spinal Introducer NRFit™ Needles, BD Syringes NRFit™ devices, mainly, but not limited to the purpose of providing clinical data required under European Union (EU) regulation 2017/745.

1.2 Objectives and Endpoints

Table 1. Objectives and Endpoints

Objective Types	Objectives	Endpoints
Primary Performance	• To assess the performance of the BD Spinal NRFit™ needles and BD NRFit™ introducers used in spinal anesthesia procedures.	• Percentage of participants with successful placement of the BD Spinal NRFit™ needle in the subarachnoid location defined as the spontaneous appearance of cerebrospinal fluid (CSF) emerging from the spinal needle hub. • Percentage of participants with successful placement of the BD Spinal NRFit™ needle in the subarachnoid location defined as the spontaneous appearance of cerebrospinal fluid (CSF) emerging from the spinal needle hub when an BD NRFit™ introducer is used.
	• To assess the performance of BD NRFit™ Syringes when used in spinal anesthesia procedures.	• Percentage of participants with successful aspiration and injection of anesthetic through a BD NRFit™ Syringe. • Percentage of participants with BD NRFit™ Syringes that do not leak at the connection point during medication administration.
Primary Safety	• To assess the incidence of post dural puncture headache (PDPH)	• Percentage of participants with a diagnosis of PDPH (defined as headache that worsens when standing/upright position and relieves when laying supine) for a period of up to 10 (± 3 days) days following the procedure.

	• To assess the incidence of any BD NRFit™ spinal needle and BD NRFit™ introducer and BD NRFit™ syringe and procedure-related adverse events (other than PDPH)	• Incidence of device/procedure-related adverse events

1.3 Acceptance Criteria and/or Investigation Hypothesis

Observed data in line with literature data:

- Successful needle placement ≥90%
- Incidence of PDPH ≤3%
- Incidence of misconnection 0%
- Incidence of medication leak at BD NRFitTM syringe connection point < 2%
- Incidence of aspiration/injection through a BD NRFit TM syringe > 80%

2.0 STUDY DESIGN

2.1 Study Design

This is a multi-center, prospective, open label, single arm post-market study that will enroll approximately 180 participants in order to have a minimum of 150 treated participants who will receive a spinal anesthesia procedure as part of their routine medical care. A minimum of 50 participants for each of the two needle tip types (Quincke and Whitacre tip) will be enrolled in the study. Data related to the safety and performance of the BD Spinal NRFit™ Needles, the BD Spinal Introducer NRFit™ Needles, the BD Spinal NRFit™ Needle Sets, the BD Syringes NRFit™ and ancillary devices will be captured when used as intended.

Participants will be screened against eligibility criteria and will be considered enrolled once the informed consent document is signed. The procedure(s) performed, and device(s) used, will be left to the discretion of the participant's physician investigator.

Participants will be followed from the time of spinal procedure for up to 10 days (± 3 days) post spinal procedure to assess for any adverse events/complications.

A participant is considered to have completed the study if he/she has completed all phases of the study including the day-10 (± 3 days) post procedure follow-up assessment.

The end of the study is defined as the date of the last study assessment of the last participant in the study.

2.2 Study Population

Participants will be recruited from the patient population treated at the investigational sites. Sites may choose to limit recruitment to specific areas of the hospital and/or to patients treated by specific healthcare providers.

2.2.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Any patient, regardless of age or gender, for which the investigator has decided that a neuraxial procedure must be performed utilizing BD NRFit™ Spinal Needles, NRFit™ Spinal Introducer Needles, and NRFit™ Syringes as part of their routine medical care.
2. Expected to be available for observation through the study period (10 days, ± 3 days, post procedure*).
3. Able and willing to provide signed and dated informed consent or legal authorized representative (LAR) authorized to give consent on behalf of the participant (Note: Consent of guardian or parent may be required for participants under the age of 18 years; participant assent may be required as well).

** The time window of ± 3 days must be used when the 10-day post-procedure occurs during the weekends or holidays.*

2.2.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Coagulopathy or bleeding disorder, where it is in the opinion of the investigator makes regional anesthetic of increased risk.
2. Subjects with a history of neurological impairment of the trunk or lower extremities.
3. Infection at the site of needle insertion.
4. Previous spine surgery at the level involved in the study procedure.

2.3 Randomization and Blinding

This is a single-arm and open label study, randomization and blinding are not applicable.

2.4 Sample Size

The planned sample size is approximately 150 subjects treated with BD NRFit™ Spinal Needle and BD NRFit™ Syringe, and approximately 100 subjects treated with BD NRFit™ Spinal Introducer. The sample size is based on the precision of endpoint estimates as well as the ability to detect adverse events. For a given endpoint with 90% rate, a sample size of 150 would lead to a precision of 4.8%, a sample size of 100 would lead to a precision of 6.0%. Table 2 below contains further detail. For an adverse event with 1% rate, there is a probability of 77.9% to observe at least 1 event in a sample of 150.

Table 2. Sample Size and Precision

Sample Size	Rate	Precision (Half width of 95% CI)
150	90%	4.80%
100	90%	6.00%
150	80%	6.40%
150	3%	3.10%
150	2%	2.70%

2.5 Interim Analysis

No interim analysis is planned for the study.

2.6 Study Procedure

Study procedures and their timing are summarized in the “Schedule of Activities” Table below.

Table 3. Schedule of Activities

Procedure	Baseline	Spinal Procedure	Follow-Up Visit[2] 10 days (± 3 days) post spinal procedure
Informed consent process, incl. Informed consent signature date	X		
Inclusion and exclusion criteria	X		
Baseline assessment and Demography	X		
Limited Medical history	X		
Spinal procedure intervention		X	
Ease of use procedure survey		X	
Adverse Event monitoring and assessment[1]		==========	
Serious Adverse Event monitoring and assessment		==========	
Device deficiencies monitoring and assessment		==========	

[1] Participants will be monitored as required for their routine medical care and according to the hospital policy. Any adverse event or complication must be diagnosed and assessed by a study clinician.
[2] If the participant has been discharged from the hospital prior to day-10 (± 3 days) post-procedure, follow-up may be performed in a variety of ways including by telephone. The time window of ± 3 days must be used when the 10-day post-procedure occurs during the weekends or holidays. However, any adverse event or complication must be diagnosed and assessed by a study clinician.

3.0 INTENDED STATISTICAL SOFTWARE AND DATA INFORMATION

3.1 Intended Statistical Software

All the analyses will be performed using Statistical Analysis System (SAS) Version 9.4 or above or R.

3.2 Data Information

The input data will consist in several SAS files prepared by the Statistical Programming group and saved in H:\MDS\MDS-21NRFit001\Final\Data on SAS server.

4.0 ANALYSIS POPULATION SET(S)

4.1 Populations Definitions

The following populations are defined in the table below:

Table 4. Population Definitions

Population	Description
Enrolled	All participants who sign the ICF
Treated	All participants in whom a spinal anesthesia procedure is attempted, regardless of success
Safety	All participants in whom a spinal anesthesia procedure is successful

Treated population will include the following participants on the Spinal Procedure CRF page:

- 'Was spinal procedure performed or attempted using BD NRFit devices?' Equals 'Yes'.

Safety population will include the following participants on the Spinal Procedure Details - BD NRFit Needle CRF page:

- 'Was there a spontaneous appearance of cerebrospinal fluid (CSF) emerging from the needle hub?' Equals 'Yes'.

The primary performance endpoints analysis will be performed on the treated population. The primary safety endpoint analysis for PDPH incidence will be performed on the safety population. The primary safety endpoint analysis for device/procedure-related adverse events (other than PDPH) will be performed on the treated population.

5.0 STATISTICAL ANALYSIS / CALCULATIONS

5.1 Derived Variables

None.

5.2 Analysis Methods

5.2.1 Primary Performance Endpoints

5.2.1.1 Performance of the BD Spinal NRFit™ Needle and BD NRFit™ Introducer

- Rate of successful BD Spinal NRFit™ Needle placement

The successful placement of the BD Spinal NRFit™ needle in the subarachnoid location is defined as the spontaneous appearance of cerebrospinal fluid (CSF) emerging from the spinal needle hub. In case of multiple attempts, successful placement is determined by the last attempt.

It will be computed as the number of participants experiencing the event divided by the total number of subjects with needles attempted; 95% confidence interval (exact method) will be calculated. The analysis will be performed on the treated population as defined in section 4.1.

The incidence of successful needle placement will be based on counts of “Yes” response to the following question on the “Spinal Procedure Details - BD NRFit Needle” CRF page: “Was there a spontaneous appearance of cerebrospinal fluid (CSF) emerging from the needle hub?”

- Rate of successful BD Spinal NRFit™ Needle placement when a BD Spinal NRFit™ Introducer is used

The successful placement of the BD Spinal NRFit™ needle in the subarachnoid location is defined as the spontaneous appearance of cerebrospinal fluid (CSF) emerging from the spinal needle hub for subjects who used BD NRFit™ introducer. In case of multiple attempts, successful placement is determined by the last attempt. If a subject uses BD NRFit™ introducer for the last attempt, the subject will be considered as part of the introducer population.

The incidence rate for the primary performance endpoints will be calculated as the number of participants experiencing the event divided by the total number of treated participants using BD NRFit™ introducer; 95% confidence interval (exact method) will be calculated.

A subject will be included in the analysis population if both of the following two conditions are met:

- Spinal Procedure CRF page: ‘Was spinal procedure performed or attempted using BD NRFit devices?’ Equals ‘Yes’

- AND
- 'Device Used' Equals 'BD Spinal NRFit Needle Set' OR ('Device Used' Equals 'BD Spinal NRFit Needle' AND 'Was a BD NRFit introducer used?' Equals 'Yes') OR ('Device Used' Equals 'Same as previous attempt' AND either of the previous two conditions is met)

5.2.1.2 Performance of the BD NRFit™ Syringes

- Rate of successful aspiration of anesthetic through BD NRFit™ Syringes

  A subject will be included in the analysis population if the following condition is met:
  - Spinal Procedure Details – Syringe CRF page: 'Was a BD syringe NRFit used?' Equals 'Yes'

A successful aspiration of anesthetic through BD NRFit™ Syringe is defined as follows:

- 'Was anesthetic medication successfully aspirated through the BD NRFit syringe?' Equals 'Yes'

The incidence rate for this endpoint will be calculated as the number of participants experiencing the event divided by the total number of treated participants using the BD NRFit™ Syringes; 95% confidence interval (exact method) will be calculated.

- Rate of successful injection of anesthetic through BD NRFit™ Syringes

  A subject will be included in the analysis population if the following condition is met:
  - Spinal Procedure Details – Syringe CRF page: 'Was a BD syringe NRFit used?' Equals 'Yes'

A successful injection of anesthetic through BD NRFit™ Syringe is defined as follows:

- 'Was anesthetic medication successfully injected through the BD Syringe NRFit?' Equals 'Yes'

The incidence rate for this endpoint will be calculated as the number of participants experiencing the event divided by the total number of safety population using the BD NRFit™ Syringes; 95% confidence interval (exact method) will be calculated.

- Rate of BD NRFit™ Syringes that do not leak at the connection point during medication administration
  A subject will be included in the analysis population if the following condition is met:
  - Spinal Procedure Details – Syringe CRF page: 'Was a BD syringe NRFit used?' Equals 'Yes'

  A success of the endpoint for the BD NRFit™ Syringe is defined as follows:
  - 'Did the BD Syringe NRFit leak at the connection point during medication administration?' Equals 'No'

The incidence rate for this endpoint will be calculated as the number of participants experiencing the event divided by the total number of safety population using the BD NRFit™ Syringes; 95% confidence interval (exact method) will be calculated.

5.2.2 Primary Safety Endpoints

- Incidence of post dural puncture headache (PDPH)

The event of PDPH is defined as headache that worsens when standing/upright position and relieves when laying supine for a period of up to 10 (± 3 days) days following the procedure.

The incidence of PDPH will be based on response to the following question:

- "Post-dural Puncture Headache" CRF page: "Did the subject develop post-dural puncture headache (PDPH)?" Equals 'Yes'

Participants experiencing any severity (mild/moderate/severe) of PDPH will contribute to the incidence count in the numerator.

The incidence rate for the above primary safety endpoints will be calculated as the number of participants experiencing the event divided by the total number of safety participants defined in section 4.1; 95% confidence interval (exact method) will be calculated.

- Incidence of any BD NRFit™ spinal needle and BD NRFit™ introducer and BD NRFit™ syringe and procedure-related adverse events (other than PDPH)

  Subject will be considered as having an event if the subject has the following responses for the questions on the AE CRF Page listed below:

- Relationship to procedure: Equals 'Possible' or 'Probable' or 'Causal' OR Relationship to spinal needle: Equals 'Possible' or 'Probable' or 'Causal' OR Relationship to syringe: Equals 'Possible' or 'Probable' or 'Causal' OR Relationship to introducer: Equals 'Possible' or 'Probable' or 'Causal'

The incidence rate for the above primary safety endpoints will be calculated as the number of participants experiencing the event divided by the total number of treated participants; 95% confidence interval (exact method) will be calculated.

6.0 SUMMARY OF GENERAL STUDY DATA

6.1 Subject/Sample Disposition

The summary of the number of subjects in the enrolled population, treated population, safety population, as well as those that completed the study, and withdrew from the study with reason for withdrawal will be provided. Screen Failures will be summarized for each inclusion/exclusion criteria that was not met. Summary table will also be provided by site.

6.2 Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol requirements. Any and all protocol deviations must be documented regardless of whether medically justifiable, Sponsor-approved or taken to protect the subject in an emergency. Details regarding protocol deviations will be listed for enrolled participants.

6.3 Demographics and Baseline Variables

Demographics and baseline characteristics will be summarized with descriptive statistics for treated population. Summary statistics for categorical variables will include frequency and percentages, and for continuous variables will include mean, standard deviation (SD), minimum, median, and maximum. Demographic data (age (at signing informed consent), gender, race, body height, body weight, body mass index (BMI)) will be tabulated.

The demographic variables will include:

- Age (at signing informed consent)
- Sex
- Race
- BMI
- Body Weight
- Body Height

6.4 Concurrent Illnesses and Medical Conditions

Medical history will be summarized with descriptive statistics for the treated population.

6.5 Prior and Concurrent Medications

Not Applicable.

6.6 Study Device Procedure

The data related to study device details and placement are recorded on the Procedure section of eCRF page. The device procedure data will be summarized separately for spinal procedure, syringe, BD NRFit™ Needle type, BD NRFit™ Introducer type and ease of use procedure survey for the treated population. The reason for surgery and

for neuraxial procedure as well as the ASA classification will be also listed and tabulated.

6.7 Follow-up Visit Summary

Follow-up visit summary and listing will be presented for the treated population.

6.8 Device Failure, Malfunctions and Defects

Device failures, malfunctions or defects will be tabulated and presented on participant level for treated population. Details regarding device deficiencies will be listed.

7.0 SAFETY ANALYSIS

An overall summary including the number and percentage of subjects with at least one AE, total number of AEs, total number of SAEs, AEs by relationship to the Device/Index Procedure, and AEs by severity of the event will be summarized for the treated population.

AEs will be coded by using the medical dictionary for regulatory activities version 26.0 (MedDRA). All verbatim terms will be coded to the lowest level term (LLT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus. AEs will be tabulated by SOC and Preferred Term (PT). The number of entries, as well as the number and rate of affected participants will be reported. Additionally, AEs will be presented by severity.

SAEs and AEs which are related to device (adverse device effects [ADEs]), AEs which are related to procedure, or related to accessories (stylet and introducer) will be presented separately. All AEs will be listed together with start date of AE as well as duration of AE for AEs with complete dates.

8.0 INTERIM ANALYSIS PLAN

No interim analysis is planned for the study.

9.0 REFERENCES

None.

10.0 APPENDIX

Appendix 1 Tables/Listing/Figures Shell for Final Reporting

Appendix 2 Derived Data Specification

11.0 VERSION HISTORY

Vers #	Date (DD-MMM-YYYY)	Change Owner	Description of Change(s)
1.0	08-Aug-2024	Shuangshuang Fu	Original

Signature Page for VV-TMF-316780 v1.0

Reason for signing: Finalize	Name: Shuangshuang Fu Role: Clinical Statistician Date of signature: 08-Aug-2024 17:07:20 GMT+0000

Reason for signing: Finalize	Name: Gloria Viti Role: Clinical Project Management Date of signature: 08-Aug-2024 18:15:12 GMT+0000

Reason for signing: Finalize	Name: Haiqing Tang Role: Clinical Statistical Programmer Date of signature: 08-Aug-2024 18:23:27 GMT+0000

Reason for signing: Finalize	Name: Edward Maratea Role: Medical Affairs Core Team Member Date of signature: 08-Aug-2024 20:33:06 GMT+0000

Reason for signing: Finalize	Name: Yanchang Zhang Role: Clinical Statistician Date of signature: 08-Aug-2024 23:03:19 GMT+0000

Signature Page for VV-TMF-316780 v1.0