# Title Page

**Protocol 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.

**Protocol Number:** MDS-21NRFit001

**Version Number:** 2.0

**Study Device:** BD Spinal NRFit™ Needles
BD Spinal Introducer NRFit™ Needle
BD Spinal NRFit™ Needle Sets
BD Syringes NRFit™

**Study Type:** Post-market Clinical Follow-up Study

**Short Title:** Prospective Clinical Evaluation of BD NRFit™ devices and accessories

**Sponsor Name:** Becton, Dickinson and Company

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**Regulatory Agency Identifier Number(s):** N/A

**Version History**

| Version Number | Date | Type |
|---|---|---|
| 2.0 | 10-Jan-2023 | Amendment |
| 1.0 | 11-Nov-2022 | Initial release |

## Sponsor Protocol Approval

| Signature below indicates approval of the protocol as written. | | |
|---|---|---|
| **Individual or function** | **Name** | **Signature Date** |
| Medical Affairs Team Representative | Edward A. Maratea, Jr | *This document is signed electronically in the eTMF system* |
| Study Statistician | Shuangshuang Fu | *This document is signed electronically in the eTMF system* |
| Regulatory Affairs | John Roberts | *This document is signed electronically in the eTMF system* |
| Project Manager | Gloria Viti | *This document is signed electronically in the eTMF system* |

## Protocol Signature Page

### Investigator Responsibilities

1. Prior to participation in this study, the Investigator or Institution must sign the Clinical Study Agreement (CSA) and obtain written approval from the appropriate Institutional Review Board (IRB)/Ethics Committee (EC).
2. The Investigator must receive BD-sponsored training prior to site activation. The Investigator is responsible for ensuring that all Sub-Investigators and clinical staff are adequately trained prior to performing any data collection or study-related procedures.
3. The Principal Investigator shall ensure that the study is conducted in accordance with the study protocol, any modifications as requested by the IRB/EC, the signed CSA, the ethical principles of the Declaration of Helsinki, Good Clinical Practice (ICH E6) / ISO 14155), and applicable national/regional regulations and laws.
4. If applicable, ensure that written informed consent is obtained from each participant prior to the conduct of any study procedure, using the current IRB/EC approved Informed Consent Form.

I have read and understand the contents of this study protocol. I agree to follow and abide by the requirements set forth in this document. I agree to conduct the trial in accordance with the study protocol, the signed Clinical Study Agreement, and Good Clinical Practice (GCP) as well as Ethical principles that have their origin in the Declaration of Helsinki, EU MDR (Council Regulation 2017/745 of 5 April 2017), applicable FDA, and ISO regulations (e.g., 21 CFR Parts 812, 50, 54, 56; ISO 14155:2020). I agree to participate in BD-Sponsored training prior to performing any data collection or study-related procedures.

Agreed to by (Investigator):

_____
Printed Name – Investigator

_____
Signature – Investigator

_____
Site Number

_____
Date

## Protocol Amendment Summary of Changes

### Amendment 2.0 (10Jan2023)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

### Overall Rationale for the Amendment:

The rationale for the amendment is to provide clarifications described in the summary of changes table in order to obtain consistency through the entire document.

### Summary of Changes Table

| Location of Original Text | Original Text | New Text | Rationale for Change |
|---|---|---|---|
| Header/Title Page | Version Number: 1.0 | Version Number: 2.0 | Version Control |
| Header/Title Page | Date: 11Nov22 | Date: 10Jan23 | Version Control |
| Header/Title Page | **Legal Registered Address:**<br>1 Becton Drive,<br>Franklin Lakes, New Jersey<br>07417<br>US | **Legal Registered Address:**<br>1 Becton Drive,<br>Franklin Lakes, New Jersey<br>07417<br>USA | Clarification: typo error. |
| Header/Title Page | **European Representative:**<br>Angiomed GmbH & Co<br>Medizintechnik KG<br>Wachhausstr,6<br>76227 Karlsruhe, Germany | **European Representative:**<br>BDI Benelux<br>Hagelberg 2,2250 Olen,<br>Belgium | Clarification/modification: European Representative name change. |
| Section 4.1: Overall Design | Participants will be followed from the time of enrollment for up to 10 days (± 3 days) post spinal procedure to assess for any adverse events/complications. | 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. | Clarification/modification: spinal procedure in replacement of enrollment in order to be consistent with the schedule of activities. |
| Section 1.1 Synopsis: intervention(s) /procedure(s)<br><br>Section 5.7: Participant duration | The duration of study participation for an individual subject is expected to be 10 days, ± 3 days, (from procedure through last visit). | The duration of study participation for an individual subject is expected to be 11 days, ± 3 days, (from procedure through last visit). | Clarification/modification: 11 days instead of 10 days in order to include in the participant study duration the day of the spinal procedure. |

| Location of Original Text | Original Text | New Text | Rationale for Change |
|---|---|---|---|
| Section 1.1 Synopsis: intervention(s) /procedure(s)<br><br>Section 7.2: Medical History/Demography/Baseline assessments | Sex assigned at birth | Sex assigned at birth and ethnic origin | Added "ethnic origin" as data that will be documented. |
| Section 7.3.1: Spinal procedure data | • Spinal NRFit™ Needle type, gauge, length, catalog number, and lot number<br>• Spinal NRFit™ Introducer, gauge, length, catalog number, and lot number (if used)<br><br>• Syringes NRFit™ type, size, catalog number, and lot number<br><br>• Spinal NRFit™ set type, gauge, length, catalog number, and lot number | • Spinal NRFit™ Needle type, gauge, length, catalog number, expire date and lot number<br>• Spinal NRFit™ Introducer, gauge, length, catalog number, expire date and lot number (if used)<br>• Syringes NRFit™ type, size, catalog number, expire date and lot number<br>• Spinal NRFit™ set type, gauge, length, catalog number, expire date and lot number | Added "expire date" as data that will be documented. |
| Section 9.4: Reporting of Events | All SAEs, SADEs, and/or UADEs/USADEs must be reported to the Sponsor via electronic CRF without unjustified delay and within three (3) working days of the site/investigator becoming aware of the event. | All SAEs, SADEs, and/or UADEs/USADEs must be reported to the Sponsor via electronic CRF without unjustified delay and within three (3) calendar days of the site/investigator becoming aware of the event. | Clarification/modification: three working days replaced with three calendar days in order to be in compliance with MDGC 2020-10/1 Rev.1 guidelines. |
| Section 9.6: Device Deficiencies | All mechanical failures, malfunctions, missing components, and defects of the study devices will be recorded on the appropriate Case Report Form and will be promptly reported to the Sponsor. | All device deficiencies will be recorded on the appropriate Case Report Form and will be promptly reported to the Sponsor. | Clarification/modification: "all mechanical failures, malfunctions, missing components, and defects of the study devices" sentence has been replaced with "all device deficiencies" in order to not duplicate the same information and to express clearly that all device deficiencies have to be recorded in the case report form. |

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# Abbreviations

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse event |
| ASADE | Anticipated Serious Adverse Device Effect |
| BD | Becton Dickinson and Company |
| BMI | Body Mass Index |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CIP | Clinical Investigation Plan |
| CRF | Case Report/Record Form |
| CRO | Contract Research Organization |
| CSA | Clinical Study Agreement |
| CSF | Cerebrospinal Fluid |
| CV | Curriculum Vitae |
| DMP | Data Management Plan |
| EDC | Electronic Data Capture |
| EMEA | Europe, the Middle East and Africa |
| EU | European Union |
| FDA | Food and Drug Administration |
| FDAAA | FDA Amendments Act of 2007 |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Conference on Harmonization |
| ICF | Informed Consent Form |
| IFU | Instructions for Use |
| IRB/EC | Institutional or Independent Review Board/Ethics Committee |
| ISO | International Organization for Standardization |
| LAR | Legal Authorized Representative |
| MDCG | Medical Device Coordination Group |
| PDPH | Post-Dural Puncture Headache |
| PI | Principal Investigator |
| RMV | Routine Monitoring Visit |
| SAE | Serious Adverse Event |
| SADE | Serious Adverse Device Effect |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SoA | Schedule of Activities |
| SOP | Standard Operating Procedure |
| ™ | Trademark |
| TMF | Trial Master File |
| USADE | Unanticipated Serious Adverse Device Effect |
| WHO | World Health Organization |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

| | | |
|---|---|---|
| Protocol 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. | |
| Short Title | Prospective Clinical Evaluation of BD NRFit™ devices and accessories | |
| Rationale | 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. | |
| Objectives and Endpoints | **Objectives** | **Endpoints** |
| | **Primary Performance Objectives** | **Primary Performance Endpoints** |
| | • 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.<br>• 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.<br>• Percentage of participants with BD NRFit™ Syringes that do not leak at the connection point during medication administration. |

| | | |
|---|---|---|
| | **Primary Safety Objectives** | **Primary Safety Endpoints** |
| | • 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 any device/procedure related adverse events.<br>*The time window of ± 3 days must be used when the 10-day post-procedure occurs during the weekends or holidays. |
| Design and Overview | 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. Participants will be followed from the time of enrollment for up to 10 days (± 3 days) post spinal anesthesia procedure for evidence of adverse events including PDPH. This can be done via phone if the participant is discharged from the hospital. The site staff must take advantage of the time window of ± 3 days only when the 10-day post-procedure occurs during the weekends or holidays. Any adverse event or complication must be diagnosed and confirmed by a study physician.<br>A minimum of 50 participants for each of the two needle tip types (Quincke and Whitacre tip) will be enrolled in the study.<br>The spinal anesthesia procedure may be performed by clinicians trained in the use of Spinal Needles. Specialized training is required for operation of the Spinal Needle. | |

| | |
|---|---|
| Study Devices | The full range of CE-marked devices marketed in the EU will be available for use in this study. These devices include:<br>• BD Spinal NRFit™ Needles: BD Quincke Spinal NRFit™ Needle and BD Whitacre Spinal NRFit™ Needle<br>• BD Spinal Introducer NRFit™ Needle<br>• BD Spinal NRFit™ Needle Sets: BD Quincke Spinal NRFit™ Needle Set and BD Whitacre Spinal NRFit™ Needle Set<br>• BD Syringes NRFit™: BD Syringes NRFit™ Lok and BD Syringes NRFit™ Slip<br>• Ancillary devices: BD Blunt Fill NRFit™ needle and BD Blunt Filter NRFit™ needle<br><br>The BD Quincke Spinal NRFit™ Needle and BD Whitacre Spinal NRFit™ Needle, hereinafter referred to as the BD Spinal NRFit™ Needles, are intended to gain entry into or puncture the spinal cavity permitting injection (including anesthesia)/withdrawal of fluids for purposes of diagnostic lumbar puncture and myelography procedures.<br><br>The BD Spinal Introducer NRFit™ Needle is intended for placement or introduction of spinal needles.<br><br>BD Quincke Spinal NRFit™ Needle Set and BD Whitacre Spinal NRFit™ Needle Set consist of either a BD Quincke Spinal NRFit™ Needle or a BD Whitacre Spinal NRFit™ Needle and a BD Spinal Introducer NRFit™ Needle, hereinafter referred to as the BD Spinal NRFit™ Needle Sets.<br><br>BD Syringes NRFit™ Lok and BD Syringes NRFit™ Slip, hereinafter referred to as the BD Syringes NRFit™, are intended for neuraxial use by healthcare professionals for aspiration/injection of fluids.<br><br>The choice of the specific BD Spinal NRFit™ Needle, gauge, length, tip, type, and size of a BD Syringes NRFit as well as the option of using a BD Spinal NRFit™ Needle set and BD Spinal Introducer NRFit™ Needle, required for an individual participant is left to the discretion of the clinician. BD Spinal Introducer NRFit™ Needle sizes paired to selected BD Spinal NRFit™ Needles may be used.<br><br>The BD Blunt Fill NRFit™ needle is used for aspiration of fluids from vials and ampoules. The BD Blunt Filter NRFit™ needle is used for aspiration and filtration of fluids from vials and ampoules. The BD Blunt Fill NRFit™ and BD Blunt Filter NRFit™ Needles are not for skin injections.<br><br>All devices used in this study will be used in a manner consistent with their labelled indications. |

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|---|---|
| Participants | Approximately 180 participants will be enrolled in order to have a minimum of 150 treated participants. A minimum of 50 participants for each of the two needle tip types (BD Quincke Spinal NRFit™ Needle and BD Whitacre Spinal NRFit™ Needle) will be treated in the study.<br><br>In order to be eligible to participate in this study, an individual must meet all of the following criteria:<br><br>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.<br>2. Expected to be available for observation through the study period (10 days, ± 3 days*, post procedure).<br>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).<br><br>*The time window of ± 3 days must be used when the 10-day post-procedure occurs during the weekends or holidays.<br><br>Participants are excluded from the study if any of the following criteria apply:<br><br>1. Coagulopathy or bleeding disorder, where it is in the opinion of the investigator makes regional anesthetic of increased risk.<br>2. Subjects with a history of neurological impairment of the trunk or lower extremities.<br>3. Infection at the site of needle insertion.<br>4. Previous spine surgery at the level involved in the study procedure. |

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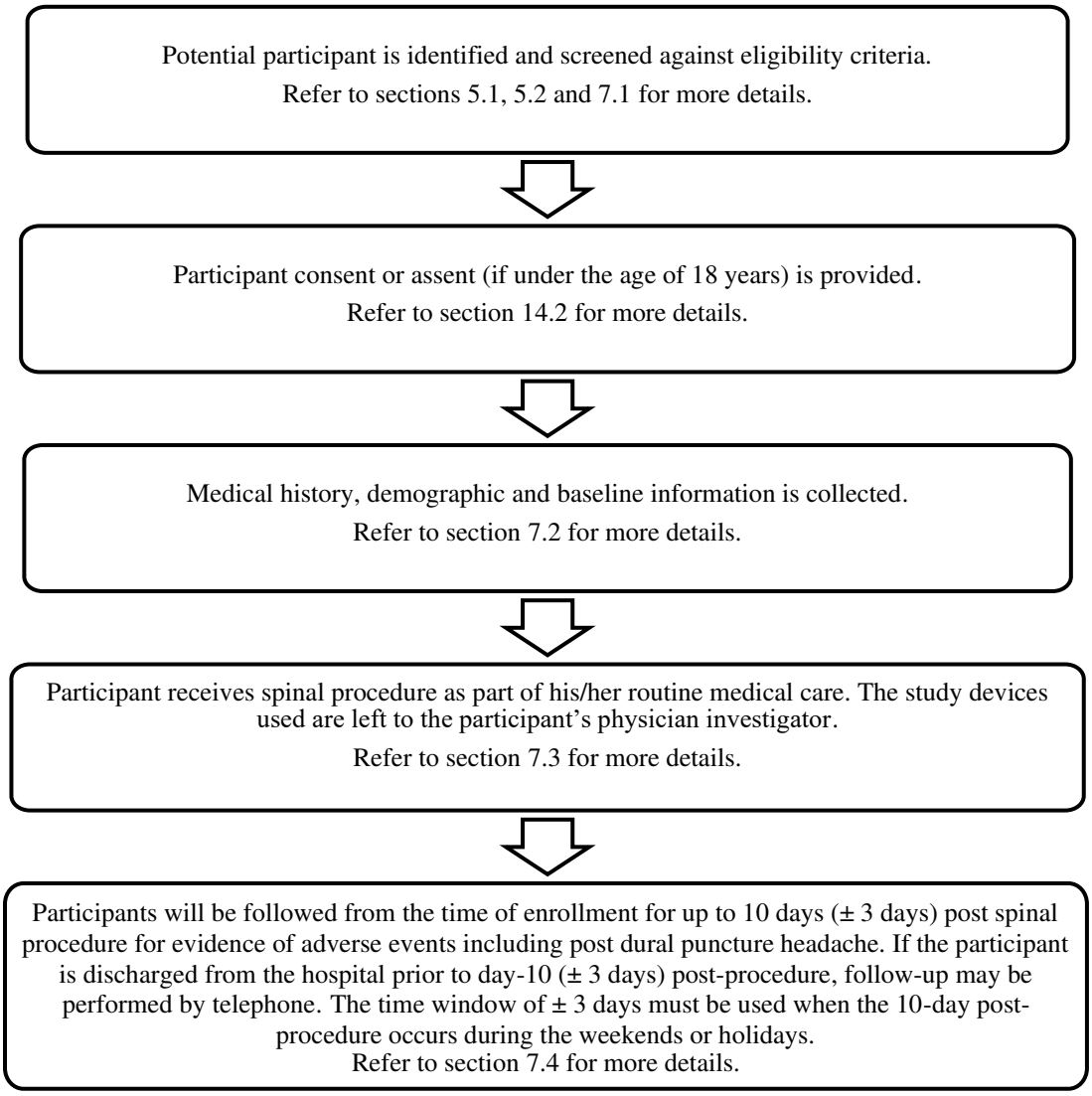
|---|---|
| Intervention(s)/Procedure(s) | After general screening against inclusion/exclusion criteria, potential participants will be provided with detailed information about the study. If the potential participant, or legal authorized representative (LAR) authorized to give consent on behalf of the participant, or parent/guardian and potential participant in the case of those under 18 years of age, provides written informed consent/assent, respectively, he/she will be enrolled in the study. Participant baseline and demographic information will be documented including, but not limited to: age, sex assigned at birth, ethnic origin, reason for surgery/intervention, limited medical history, and reason for spinal anesthesia procedure.<br><br>At the time of the spinal anesthesia procedure, information about the study devices and insertion procedure will be documented including, but not limited to: date and time of insertion, NRFit spinal needle, tip, gauge, and length, introducer NRFit™ gauge and length (if used), syringe NRFit™ type and size, dose medication preparation procedure (type of ancillary device used), participant position, use of local anesthesia, number of spinal needles, lumbar interspace, medications/agents injected. Additionally, to assess overall ease of spinal procedure, the clinician performing the procedure will complete a brief survey describing their experience with the procedure.<br><br>The procedure will be performed using the devices and specific methods selected by the investigator. Details of the procedure will be documented to ensure study endpoints are documented in the appropriate case report form. Device deficiencies/failures will be also collected.<br><br>The participants will be accurately monitored as required for their routine medical care and according to site policy. Complications or adverse events (e.g., PDPH) will be monitored for 10 days (± 3 days) after the procedure. If the participant is 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 site staff must take advantage of the time window of ± 3 days only when the 10-day post-procedure occurs during the weekends or holidays. However, any adverse event or complication must be diagnosed and confirmed by a study physician.<br><br>It is expected to take approximately 47 weeks to complete participant enrollment. The total duration of the investigation is expected to be approximately 49-51 weeks from the first participant enrolled up to last participant having last visit.<br><br>The duration of study participation for an individual subject is expected to be 11 days, ± 3 days, (from procedure through last visit). |
| Investigational Sites | Up to 10 sites within Europe will participate in this study. No more than 25% of participants may be enrolled at any one site. |

| | |
|---|---|
| Data Monitoring Committee | A Data Monitoring Committee will not be used in this study. |
| Regulatory Status | The BD Spinal NRFit™ Needles, BD Spinal Introducer NRFit™ Needle, BD Spinal NRFit™ Needle Sets, BD Syringes NRFit™, BD Blunt Fill NRFit™ needle and BD Blunt Filter NRFit™ needle are currently CE marked and marketed in the EU. |

## 1.2 Schema


Potential participant is identified and screened against eligibility criteria.
Refer to sections 5.1, 5.2 and 7.1 for more details.
Participant consent or assent (if under the age of 18 years) is provided.
Refer to section 14.2 for more details.
Medical history, demographic and baseline information is collected.
Refer to section 7.2 for more details.
Participant receives spinal procedure as part of his/her routine medical care. The study devices used are left to the participant's physician investigator.
Refer to section 7.3 for more details.
Participants will be followed from the time of enrollment for up to 10 days (± 3 days) post spinal procedure for evidence of adverse events including post dural puncture headache. If the participant is discharged from the hospital prior to day-10 (± 3 days) post-procedure, follow-up may be performed by telephone. The time window of ± 3 days must be used when the 10-day post-procedure occurs during the weekends or holidays.
Refer to section 7.4 for more details.

## 1.3 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.

# 2 INTRODUCTION

Becton, Dickinson & Company manufactures a variety of devices used in neuraxial procedures, from medication preparation to delivery. These devices are used in medical procedures utilizing well-established methods.

Neuraxial anesthesia is the administration of medication into the subarachnoid or epidural space to produce anesthesia and analgesia. It can lead to the complete absence of sensory and/or motor function at or below the site of injection. Depending on the dose and concentration of the anesthetic used, neuraxial anesthesia doesn't always result in a complete absence of motor function [1].

Neuraxial anesthesia is performed by placing a needle between vertebrae and injecting medication into the epidural space (for epidural anesthesia) or the subarachnoid space (for spinal anesthesia) [2].

Spinal anesthesia is a type of neuraxial anesthesia; local anesthetic (LA) is injected into cerebrospinal fluid (CSF) in the lumbar spine to anesthetize nerves that exit the spinal cord. Spinal anesthesia is most commonly used for anesthesia and/or analgesia for a variety of lower extremity, lower abdominal, pelvic, and perineal procedures. Spinal anesthesia is also occasionally used for spine surgery [3].

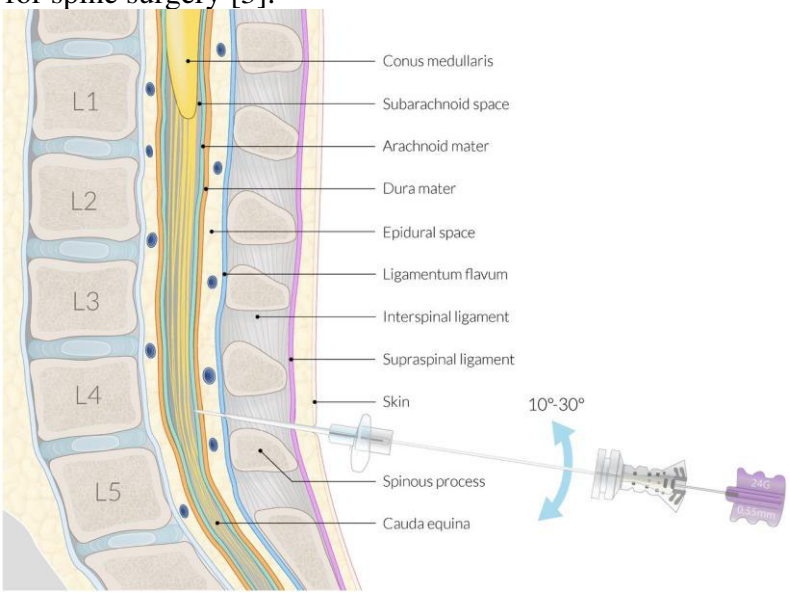



Figure 1 Spinal anesthesia [4]

The BD Quincke Spinal NRFit™ Needle and BD Whitacre Spinal NRFit™ Needle, hereinafter referred to as the BD Spinal NRFit™ Needles, are intended to gain entry into or puncture the spinal cavity permitting injection (including anesthesia) / withdrawal of fluids for purposes of diagnostic lumbar puncture and myelography procedures.

The BD Spinal Introducer NRFit™ Needle is intended for placement or introduction of spinal needles.

The BD Quincke Spinal NRFit™ Needle Set and BD Whitacre Spinal NRFit™ Needle Set consist of either a BD Quincke Spinal NRFit™ Needle or a BD Whitacre Spinal NRFit™ Needle

and a BD Spinal Introducer NRFit™ Needle, hereinafter referred to as the BD Spinal NRFit™ Needle Sets. The indications for use remain the same of those for the BD Spinal NRFit™ Needles and the BD Spinal Introducer NRFit™ Needle.

The BD Spinal NRFit™ Needles, BD Spinal NRFit™ Needle Sets and BD Spinal Introducer NRFit™ Needle were launched in 2020 and they are currently marketed in the European Union (EU) and in other countries around the world. The BD Spinal NRFit™ Needles and BD Spinal NRFit™ Needle Sets are classified as class III medical devices and BD Spinal Introducer NRFit™ Needle is classified as a class IIa medical device.

The BD Syringe NRFit™ Lok and BD Syringe NRFit™ Slip, hereinafter referred to as the BD Syringes NRFit™, are syringes with ISO 80369-6 (NRFit™) compliant lock or slip connectors. The BD Syringes NRFit™ devices are class IIa medical devices, as defined in the MDR (EU) 2017/745. The BD Syringes NRFit™ devices are intended for neuraxial use by healthcare professionals for aspiration/injection of fluids. These devices are currently sold in the European Union (EU) and other countries.

The ancillary devices as the BD Blunt Fill NRFit™ Needles and the BD Blunt Filter NRFit™ Needles are classified as class I medical devices and they are used for aspiration of fluids and for aspiration and filtration of fluids from vials and ampoules, respectively.

## 2.1 Background

A 2009 study of obstetric anesthesia practice found four deaths due to administration of tranexamic acid into the neuraxis [5]. 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 [6], [7] have concluded that the mortality and morbidity associated with such errors is secondary to the universal adoption of Luer lock equipment [8].

Furthermore, sentinel interest groups in the US and the EU have issued warnings about the risk of universal Luer connectors, that allow these misconnections [9]. Therefore, implementation of devices with non-Luer connectors could improve patient safety and decrease the risk of misconnections [6].

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.

## 2.2 Rationale

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.

## 2.3 Risk/Benefit Assessment

Since only participants requiring use of one of the study devices as part of their standard medical care, there are no anticipated risks and benefits associated with participation in the study other than those associated with device usage and with the neuraxial procedure. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BD Spinal NRFit™ Needles, the BD Spinal Introducer NRFit™ Needles, BD Spinal NRFit™ Needle Sets, and the BD Syringes NRFit™ devices may be found in their respective Instructions for Use (IFUs).

### 2.3.1 Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention (s): BD Spinal NRFit™ Needles and BD Spinal NRFit™ Sets** | | |
| Complications vary based upon anatomic site and clinician experience and may include:<br>•localized/systemic infection,<br>•exposure to bodily fluids and/or bloodborne pathogens,<br>•subarachnoid/subdural/epidural (spinal) hematoma,<br>•herniation,<br>•low back pain,<br>•paresthesia,<br>•accidental puncture of the dura,<br>•post dural puncture headache,<br>•total subarachnoid block,<br>•seizures,<br>•pneumocephalus,<br>•nerve injury,<br>•cerebral ischemia or hemorrhage,<br>•bladder dysfunction from prolonged blockade,<br>•cauda equine syndrome,<br>•transient neurologic symptoms,<br>•adhesive arachnoiditis, | A benefit-risk assessment for the overall medical device is documented in the Risk Management Report.<br>All risks and combinations of risks were reviewed, and it has been determined that all are within acceptable limits. The benefits of the device outweigh each risk individually as well as any combination of risk and are consistent with the use of the devices. Therefore, the devices are considered safe for their intended use. These risks are identified as residual risks and are disclosed to the end user. | Only participants requiring a Spinal needle device as part of their standard medical care will receive a device. The treating physician will select the most appropriate device for the participants based on their specific needs.<br>The general guidelines “aseptic technique and proper preparation are essential” and “observe universal precautions with all patients” are included in the BD Spinal NRFit™ needles and in the BD Spinal NRFit™ Sets IFUs.<br><br>Only physicians experienced in performing procedures using Spinal Needles and Spinal Needle Sets should perform neuraxial anesthesia procedures. A caution statement, “To be used by properly qualified and trained healthcare professionals”, is included in the BD Spinal |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| • anterior spinal artery syndrome,<br>• acute neuropathic pain,<br>• damage to CNS blood vessels,<br>• AV fistula formation,<br>• spinal cord ischemia,<br>• permanent neurological injury,<br>• paraplegia,<br>• hypotension,<br>• cardiovascular collapse,<br>• death. | | NRFit™ needles and in the BD Spinal NRFit™ Sets IFUs.<br>See device specific IFU for additional information. |
| **Study Intervention (s): BD Spinal Introducer NRFit™ Needle** | | |
| Complications vary based upon anatomic site and clinician experience and may include:<br>• localized/systemic infection,<br>• exposure to bodily fluids and/or bloodborne pathogens,<br>• low back pain,<br>• accidental puncture of the dura,<br>• post dural puncture headache. | A benefit-risk assessment for the overall medical device is documented in the Risk Management Report.<br>All risks and combinations of risks were reviewed, and it has been determined that all are within acceptable limits. The benefits of the device outweigh each risk individually as well as any combination of risk and are consistent with the use of the devices. Therefore, the devices are considered safe for their intended use. These risks are identified as residual risks and are disclosed to the end user. | Only physicians experienced in performing procedures using Spinal Introducer Needles should perform neuraxial anesthesia procedures. A caution statement, "To be used by properly qualified and trained healthcare professionals", is included in the BD Spinal Introducer NRFit™ needle IFU.<br>See device specific IFU for additional information. |
| **Study Intervention (s): BD Syringes NRFit™** | | |
| Potential Procedure Related Complications:<br>• Pain,<br>• exposure to bloodborne pathogens,<br>• potential for infiltration/extravasation, particulate embolism,<br>• air embolism,<br>• localized/systemic infection,<br>• death. | A benefit-risk assessment for the overall medical device is documented in the Risk Management Report.<br>All risks and combinations of risks were reviewed, and it has been determined that all are within acceptable limits. The benefits of the device outweigh each risk individually as well as any combination of risk and are consistent with the use of the devices. Therefore, the devices considered safe for their intended use. These risks are identified as residual risks and are disclosed to the end user. | The IFUs report that Syringes are intended for neuraxial use by healthcare professional.<br>The caution statements, "Observe syringe carefully during procedures" and "Always inspect the package before opening" are included in the BD Syringes NRFit™ IFUs.<br>The general guidelines "aseptic technique and proper preparation are essential" and "observe universal precautions with all patients" are included in the BD Syringes NRFit™ IFUs. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Leakage resulting in an inaccurate dose or exposure to medicine and bodily fluids. | | A general guideline "An ISO 80369-6 compliant syringe tip cap can be used to prevent leakage of fluids or medications from the syringe" is included in the BD Syringes NRFit™ IFUs. See device specific IFU for additional information. |
| **Study Procedures** | | |
| No study-specific risks identified, compared to any neuraxial procedure as part of standard medical care. Neuraxial procedures maybe associated with the following risks:<br>•Inadequate or failed anesthesia<br>•Hemodynamic changes, most commonly hypotension<br>•Post-dural puncture headache<br>•Localized pain<br>•Localized skin irritation<br>•Urinary retention (temporary)<br>•Nerve injury (rare)<br>•Spinal-epidural hematoma (rare)<br>•Infection | See Clinical literature [10]; [11]; [12]; [13]; [14] for additional information. | •Physicians should select the smallest diameter needle sufficient to support the specific procedure<br>•Patient blood pressure and heart rate should be closely monitored throughout the procedure and after medication administration<br>•Only physicians with sufficient training and experience should perform neuraxial anesthesia procedures |
| Potential procedure complications with the ancillary devices:<br>•Redness<br>•Irritation<br>•Pain<br>•Bleeding<br>•Anxiety<br>•Syncopal episode<br>•Granuloma<br>•Hematoma<br>•Paresthesia<br>•Exposure to bloodborne pathogens<br>•Potential for infiltration/extravasation<br>•Particulate embolism<br>•Localized/systemic infection<br>•Floaters | | The warning statements, "Aseptic technique and proper preparation are essential" and "Percutaneous puncture with a contaminated needle may lead to serious illness, or other infectious diseases" are included in the Blunt Fill NRFit™ Needles and Blunt Filter NRFit™ Needles IFUs. See device specific IFU for additional information. |

### 2.3.2 Benefit Assessment

There is no direct benefit for study participation for an individual patient other than the placement of one of the study devices.

### 2.3.3 Overall Benefit: Risk Conclusion

There is no anticipated additional risk associated with the device use or any study procedure due to participation in this study compared to any BD Spinal NRFit™ Needles, the BD Spinal Introducer NRFit™ Needles, BD Spinal NRFit™ Needle Sets, and the BD Syringes NRFit™ use as part of standard medical care.

## 3 OBJECTIVES AND ENDPOINTS

| 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.<br>• 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.<br>• Percentage of participants with BD NRFit™ Syringes that do not leak at the connection point during medication administration. |

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

### 3.1 Acceptance Criteria

Acceptance criteria are anticipated for the following objectives:

- Relevant literature for the state-of-the-art generic device group- spinal needle and spinal introducer needle supports the predefined clinical performance objectives, success rate in placing the needle in the subarachnoid space and obtaining CSF. Confirmation of the spontaneous appearance of cerebrospinal fluid (CSF) emerging from the spinal needle hub. The Primary efficacy endpoint is the spontaneous appearance of CSF with the expected rate ranging ≥ 90% [15], [16], [17], [18], [19] and [20].
- Relevant literature for the state-of-the-art generic device group- spinal needle and spinal introducer needle supports the predefined clinical safety objectives, incidence of Post Dural Puncture Headache (PDPH) ≤ 3% within 7 days following spinal procedure. In the state-of-the-art literature several studies investigated incidence of PDPH, it ranges from 0% to 28.12%. All cases occurred within 7 days following the procedure [15], [16], [17], [18], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44].
- Relevant literature for the state-of-the-art generic device group- spinal needle and spinal introducer needle supports the predefined clinical safety objectives, preventing misconnection and wrong route medication delivery misconnections or wrong route administration of medication has prompted the introduction of ISO 80369, NRFit needles [45], [46], [47], [48], [49], [50], [51], [52], [53].

Other acceptance criteria are:

- Incidence of misconnection 0%
- Incidence of medication leak at BD NRFit™ syringe connection point < 2%
- Incidence of aspiration/injection through a BD NRFit™ syringe > 80%

# 4 STUDY DESIGN

## 4.1 Overall 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. 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 site staff must take advantage of the time window of ± 3 days only when the 10-day post-procedure occurs during the weekends or holidays. However, any adverse event or complication must be diagnosed and confirmed by a study physician.

Additionally, to assess overall ease of spinal procedure, the clinician performing the procedure will complete a brief survey describing their experience with the procedure.

The total duration of the study is expected to be approximately 49-51 weeks from first participant enrolled up to last participant having last visit.

## 4.2 Scientific Rationale for Study Design

This study is designed to collect clinical data on the safety and performance of the BD Spinal NRFit™ Needles, the BD Spinal Introducer NRFit™ Needles, the BD Spinal NRFit™ Needle Sets, and the BD Syringes NRFit™ devices. The usage of the study and ancillary devices, according to its intended use will ensure that study activities have no direct impact on the endpoints being assessed and that they represent outcomes typically associated with the intended medical use of the study devices in clinical practice.

### 4.2.1 Participant Input into Design

Not applicable. Participant input was not sought while designing the study.

## 4.3 End of Study Definition

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.

# 5 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.

## 5.1 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.

## 5.2 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.

## 5.3 Lifestyle Considerations

Not applicable. There are no study-specific restrictions other than those typically associated with use of a study devices (e.g., keeping the insertion area clean and dry).

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but have not subsequently met the eligibility criteria. Data on informed consent, age, sex assigned at birth, and reason of screening failure will be collected. Additional information may also be collected if appropriate.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

### 5.5 Vulnerable Population

As the instruction for use of the BD NRFit™ Spinal Needles, BD Spinal NRFit™ Needle Sets, BD NRFit™ Spinal Introducer Needles, and BD NRFit™ Syringes does not foresee any limitations in terms of subject age or status and the study aims to collect data on clinical use, the study will also consider participants under 18 years of age, or participants requiring a legal authorized representative. In addition, pregnant and breastfeeding subjects are not excluded from study participation. As the study devices will be used as intended, this population is considered to be not exposed to any additional risk due to study participation.

Some participating clinical sites may decide to not include vulnerable subjects as per their hospital policy or may not include minors as the participating department treats only adults.

### 5.6 Point of Enrolment

The time at which, following recruitment and before any study-related procedures are undertaken, a participant signs and dates the informed consent form.

### 5.7 Participation duration

It is expected to take approximately 47 weeks to complete participant enrollment. The total duration of the study is expected to be approximately 49-51 weeks from first participant enrolled up to last participant having last visit.

The duration of study participation for an individual subject is expected to be 11 days, ± 3 days, (from procedure through last visit).

## 6 STUDY INTERVENTIONS

### 6.1 Investigational/Test Device

The BD Spinal NRFit™ Needles (BD Quincke Spinal NRFit™ Needle and BD Whitacre

Spinal NRFit™ Needle) are intended to gain entry into or puncture the spinal cavity permitting injection (including anesthesia) / withdrawal of fluids for purposes of diagnostic lumbar puncture and myelography procedures. They consist of a needle, stylet, and needle shield and are available in various gauges and needle lengths. The needle consists of a hollow needle (cannula) bonded to a translucent hub at one end and a specific needle point type (Quincke or Whitacre) at the other end. The stylet has a handle which is color coded and correlates to the gauge size.

The BD Spinal Introducer NRFit™ Needle is intended for placement or introduction of spinal needles. The BD Spinal Introducer NRFit™ Needle consists of a needle, needle hub and needle shield and is available in various gauges. The needle consists of a hollow needle (cannula) bonded to a translucent colored hub (per gauge) at one end and a specific needle point type at the other end. The introducer needle is an optional aid through which a spinal needle can be inserted.

The needle hub of the BD Spinal NRFit™ Needles and the BD Spinal Introducer NRFit™ Needle incorporates ISO 80369-6 compliant connectors. The needle shields are yellow to

indicate that the devices are intended to only connect to ISO 80369-6 (NRFit™) compatible devices such as syringes.

The BD Spinal NRFit™ Needles and the BD Spinal Introducer NRFit™ Needle are sterile, non-toxic and non-pyrogenic. These products are not made with natural rubber latex, Bisphenol A (BPA) or Di-ethylhexyl Phthalate (DEHP).

The BD Spinal NRFit™ Needles and the BD Spinal Introducer NRFit™ Needle are to be used by properly qualified and trained healthcare professionals.

The BD Spinal NRFit™ Needle Sets (BD Quincke Spinal NRFit™ Needle Set and BD Whitacre Spinal NRFit™ Needle Set) consist of either a BD Quincke Spinal NRFit™ Needle or a BD Whitacre Spinal NRFit™ Needle and a BD Spinal Introducer NRFit™ Needle. The indications for use, populations for which the devices are intended, and materials remain the same of those for the BD Spinal NRFit™ Needles and the BD Spinal Introducers NRFit™ Needles.

The BD Syringes NRFit™ (BD Syringe NRFit™ Lok and BD Syringe NRFit™ Slip) are intended for transient use, intended for neuraxial use by healthcare professionals for aspiration/injection of fluids.

They are sterile, single use syringes with ISO 80369-6 (NRFit™) compliant lock or slip connectors. The syringe plunger rod is yellow to designate a device intended to only connect to ISO 80369-6 compatible devices such as spinal needles. These syringes are non-toxic, non-pyrogenic and are not made with natural rubber latex, butylated hydroxytoluene (BHT) or Di-ethylhexyl Phthalate (DEHP).

The BD Spinal NRFit™ Needles, BD Spinal Introducer NRFit™ Needle and BD Syringes NRFit™ are intended for adult and pediatric patients.

Appendix 16.1 provides an overview of the study device variants available for use.

The BD Spinal NRFit™ Needles, BD Spinal Introducer NRFit™ Needle, the BD Spinal NRFit™ Needle Sets, and BD Syringes NRFit™ will be provided by the Sponsor. Devices will either be disposed of at the site according to the site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation.

Accurate records of all devices received at, dispensed, returned to, and disposed of by the site should be recorded on Study Product Accountability Log.

Aseptic technique and proper preparation are essential for the neuraxial procedure, requiring the physician to wear cap, mask, sterile gloves, and sterile gown. The participant will be covered with a sterile drape and prepped with an appropriate antiseptic agent per procedures guidelines. If a BD Spinal Introducer NRFit™ Needle is used, it is placed between the lumbar vertebrae at the desired interspace and angle. The BD Spinal NRFit™ needle (Quincke or Whitacre) is then inserted through the Introducer NRFit™ needle. The stylet is removed to check for the appearance of CerebroSpinal Fluid (CSF), and then replaced if further advancement of the spinal needle is needed. Once the CSF appears to a satisfactory degree, the medication is delivered through the BD Syringes NRFit™ (Lok or Slip) into the CSF, and the NRFit™ spinal and introducer needles are removed. Site staff may monitor the participant for physiologic and medication effects as part of their routine medical care.

### 6.2 Control Device/Standard of Care

Not applicable. This is a single-arm study.

### 6.3 Ancillary Devices/Products

Neuraxial procedures are conducted under strict aseptic technique and require the physician to wear cap, mask, sterile gloves, and sterile gown. The participant will be covered with a sterile drape and prepped with an appropriate antiseptic agent. Materials used to comply with aseptic technique, including the medication for local skin anesthesia, will be provided by the site according to their site-specific requirements. These products will be used as part of the standard of care of each site. Selected information regarding these products will be collected (See Section 7.3).

Ancillary devices BD Blunt Fill NRFit™ Needles and the BD Blunt Filter NRFit™ Needles are used to aspirate desired medication from an ampule or vial and dose into a BD Syringes NRFit™. They consist of a hollow needle with a blunt needle point, a needle shield and an ISO 80369-6 (NRFit™) compliant, yellow-colored needle hub. The needle hub of the Blunt Filter NRFit™ Needle also has a translucent purple/pink colored portion to indicate that the device contains a filter, while the Blunt Fill NRFit™ Needle has an opaque, red portion. Selected information regarding these devices will be collected (See Section 7.3).

The BD Blunt Fill NRFit™ Needles and the BD Blunt Filter NRFit™ Needles will be provided by the Sponsor. Devices will either be disposed of at the site according to the site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation.

Accurate records of all devices received at, dispensed, returned to, and disposed of by the site will be recorded on Study Product Accountability Log.

### 6.4 Device Labeling

This study will utilize marketed products. As such, no special labelling is required. However, to ensure that the study devices will be used at the study sites only on behalf of the study, the device packaging will be labeled as "For clinical trial use only" and in the translated format in local languages. Additional details may be found in the Study Supply Plan.

### 6.5 Treatment Allocation and Measures to Minimize Bias

This is a post-market study in which study devices are used as intended. The choice of the specific device is left to the discretion of the clinician.

All the participants will be proposed the study in chronological order when they attend a regular clinic visit, this rule will allow to avoid any selection bias.

All participants potentially fulfilling the inclusion/exclusion criteria will be sequentially

offered participation in this study when they attend for a clinical visit prior to performance of neuraxial procedure.

# 7 STUDY PROCEDURES AND ASSESSMENTS

- Study procedures and their timing are summarized in the Schedule of Activities (SoA, Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All inclusion/exclusion criteria must be reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. The investigator will maintain a subject identification log of all the participants enrolled in the study, assigning an identification code linked to their names, alternative subject identification or contact information.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

## 7.1 Screening and Enrollment

After general screening against inclusion/exclusion criteria, potential participants will be provided with detailed information about the study. For details on the Informed Consent process, please refer to section 14.2. A participant will be considered enrolled once informed consent (or assent as applicable) is signed. Enrolled patients will be assigned a unique participant number.

## 7.2 Medical History / Demography / Baseline Assessments

After enrollment, participant baseline and demographic information will be documented, including, but not limited to:

- Age
- Sex assigned at birth and ethnic origin
- Height and weight (for calculated body mass index)
- Limited Medical history including, but not limited to:
  - Coagulopathy or bleeding disorder
  - History of neurological impairment of the trunk or lower extremities
  - Infection at the site of needle insertion
  - Previous spine surgery at the level involved in the spinal procedure
  - History of chronic or recurring headaches
  - Spine deformity (kyphosis/scoliosis)
- Reason for surgery/intervention (e.g., surgery of lower extremities, surgery of lower abdomen)
- Reason for neuraxial procedure (e.g., analgesia or anesthesia)

- American Society of Anesthesiologists (ASA) physical status (PS) classification. See appendix 16.2 for the definitions and ASA-approved examples [54].

## 7.3 Spinal procedure

Choice of the specific BD Spinal NRFit™ Needle, gauge, length, tip, type and size of a BD Syringes NRFit as well as the option of using a BD Spinal NRFit™ Needle set and BD Spinal Introducer NRFit™ Needle, required for an individual participant is left to the discretion of the clinician. BD Spinal Introducer NRFit™ Needle sizes paired to selected BD Spinal NRFit™ Needles may be used. The devices, participant, aseptic technique, and insertion site will be prepared according to standard medical practices and site-specific procedures.

Ancillary devices are the BD Blunt Fill NRFit™ Needles and the BD Blunt Filter NRFit™ Needles, and they are used to aspirate desired medication from an ampule or vial by connecting the needle hub to a NRFit™ syringe, and to dose into a BD Syringes NRFit™.

If a BD Spinal Introducer NRFit™ Needle is used, it is placed between the lumbar vertebrae at the desired interspace and angle. The BD Spinal NRFit™ needle (Quincke or Whitacre) is then inserted through the Introducer NRFit™ needle. The stylet is removed to check for the appearance of Cerebrospinal Fluid (CSF), and then replaced if further advancement of the spinal needle is needed.

Once the BD Spinal NRFit™ Needle and BD Spinal Introducer NRFit™ Needle, if the latter is used, is successfully placed, the procedure will be completed, injecting the medication through a BD Syringes NRFit™ into the CSF, and removing the NRFit™ spinal and introducer needles.

The devices will be utilized according to the specific medical needs of the participant and site-specific protocols and procedures.

Residents in training program in anesthesia cannot perform the spinal procedure within the study.

### 7.3.1 Spinal procedure data

Information about the spinal procedure will be documented, including, but not limited to:

- Date and time of NRFit™ Introducer/spinal needle insertion
- Participant position (e.g., lateral position, sitting position)
- Aseptic technique
- Preparation anesthetic medication procedure (e.g., accessories used, including Blunt Fill and Blunt Filter NRFit™ Needles)
- Local anesthetic medication used for local skin anesthesia
- Lumbar Interspace selected for the procedure*
- Spinal NRFit™ Needle type, gauge, length, catalog number, expire date and lot number

- Spinal NRFit™ Introducer, gauge, length, catalog number, expire date and lot number (if used)
- Syringes NRFit™ type, size, catalog number, expire date and lot number
- Spinal NRFit™ set type, gauge, length, catalog number, expire date and lot number
- Number of spinal needles*
- Lumbar level at which spinal needle placement was successful
- Medications/agents injected (type, dose, volume)
- Maximum spinal block level measured (left and right) (if performed)
- Adverse events/complications (including but not limited to study endpoints)
- Device deficiencies/failures

* Physicians performing the spinal procedure may use more than one spinal NRFit™ needle. One reason could be a failure with the device, but frequently it is due to the fact that another spinal NRFit™ needle with a different size may be more suitable for that particular participant, due to an individual participant anatomy for example. In this second case, there is no device failure, just the clinician's preference to use a different needle to achieve procedural success.

Information about the different spinal NRFit™ needles (type, gauge, and length) utilized with the corresponding different interspace levels used during the spinal procedure will be also collected with the reason of failure.

### 7.3.2 Ease of Use Procedure Survey

After the spinal procedure has been performed and related data is recorded, the clinician performing the procedure will complete a brief survey describing their experience with the procedure to assess the performance of the study / ancillary devices used in the procedure.

## 7.4 Follow-Up

Participants will be followed through 10-days (± 3 days) post procedure to assess for adverse events/complications. Assessments may be performed in a variety of ways, including by telephone, if the participant has been discharged from the hospital prior to day-10 post procedure. The site staff must take advantage of the time window of ± 3 days only when the 10-day post-procedure occurs during the weekends or holidays. Any adverse event or complication must be diagnosed and confirmed by a study physician. Additional information may also be collected if appropriate.

### 7.4.1 Follow-Up data

During the required follow-up period the following data will be collected:

- Adverse events/complications

- Post-dural puncture headache (PDPH)

Since there are many causes of headache, it is important that the physicians make the diagnosis of Post Dural-Puncture Headache after sufficient evaluation and being reasonably certain that is the cause of the headache. Post-dural puncture headache is defined as a headache which occurs in the upright/standing position and is relieved when the participant is lying down, provided no other cause of headache could be identified. PDPH is a headache occurring within 5 days of a lumbar puncture, caused by cerebrospinal fluid (CSF) leakage through the dural puncture. It is usually accompanied by neck stiffness and/or subjective hearing symptoms. It remits spontaneously within 2 weeks, or after sealing of the leak with autologous epidural lumbar patch [55]. Participants will be questioned for the presence, severity, onset, duration, and characteristics of headaches, and any other complications. The severity of the headache will be graded from none to mild, moderate, or severe as following [56]:

- None: No PDPH
- Mild: when PDPH caused no interference with daily activities and was treated with no medication or oral analgesics.
- Moderate: when PDPH caused a patient difficulty in performing daily activities and was treated with oral analgesics.
- Severe: a headache that resulted in the patients being unable to perform his or her daily activities or being confined to bed and requiring oral or IV analgesic and/or epidural blood patch for treatment.

# 8 PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 8.1 Discontinuation/Withdrawal

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, no further data will be collected for the participant.
- If the participant withdraws consent from the study, he/she will inform the study physician who will record the withdrawal in the source documentation and appropriate section of the electronic case report form.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Participants who withdraw or discontinue the study early (e.g., prior to day-10 post procedure follow-up or prior the procedure) may be replaced.

## 8.2 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly is unable to be contacted by the study site.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant, where possible, with two telephone calls, or a message to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record with possible reasons lost to follow-up, if available.

# 9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

## 9.1 Definitions of Events

### 9.1.1 Adverse Events (AEs)

An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the

investigational medical devices or procedure and whether anticipated or unanticipated (ISO 14155:2020).

Pre-existing conditions should be considered as part of the participant's medical history and should not be reported as an AE unless there is a substantial increase in severity or frequency of the condition, which has not been attributed to natural history. Likewise, planned hospital visits and/or hospital stays should not be considered as adverse events. Exacerbation of an existing condition should be reported as an AE if the event meets the protocol definition of an AE.

The clinical course of the event will be followed according to accepted standards of medical practice until the event resolves, stabilizes, or in the opinion of the Investigator, is no longer considered clinically significant. The Investigator must supply the Sponsor with information concerning the follow up and/or resolution of the AE.

### 9.1.2 Serious Adverse Events (SAEs)

A serious adverse event is defined by ISO 14155:2020 as an adverse event that led to any of the following:

a. death;
b. serious deterioration in health of the participant, users, or other persons as defined by one or more of the following:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function including chronic diseases, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c. fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

### 9.1.3 Adverse Device Effect (ADE) / Serious Adverse Device Effect (SADE)

An adverse device effect is defined as any adverse event that is considered to be related to the use of an investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation or operation or any malfunction of the investigational device (study device) and includes any event that is a result of a user error or intentional misuse of the investigational medical device.

A serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

### 9.1.4 Unanticipated (Serious) Adverse Device Effect (UADE/USADE)

An unanticipated (serious) adverse device effect (UADE/USADE) is any (serious) adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a study device, which by its nature, incidence, severity, or outcome has not been identified in the current instructions for use and/or current version of the risk analysis report, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.

UADEs/USADEs will be reported to the appropriate governing body per ISO 14155:2020.

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

## 9.2 Severity of Adverse Events

Each AE shall be assessed for its severity, or the intensity of an event, experienced by the participant according to the criteria below.

| Severity Rating | Description |
|---|---|
| Mild | Event, signs, or symptoms that do not interfere with the participant's daily activity, are usually considered self-limiting, can be treated with non-prescription type medications, and do not require medical intervention |
| Moderate | Event may interfere or cause low level inconvenience with the participant's daily activity. Requires medical intervention and/or treatment; however, unlikely to require hospitalization or be considered potentially life-threatening in nature |
| Severe | Event may cause significant discomfort to the participant and/or interferes with the participant's daily activity. Requires medical intervention and/or treatment to preclude a permanent impairment; may be life threatening and/or require hospitalization |

## 9.3 Relationship of Adverse Event to Device(s)/Procedure

Each AE will be assessed for its relationship to the study device or procedure according to the following guidelines.

A. Assess each AE for its relationship to the device or procedure.
- Device Related: This category should be restricted to AEs directly attributable to the study devices used.
- Procedure: A procedure includes any study-related activity performed during the neuraxial procedure.

B. The following categories shall be used for assigning the certainty of the relatedness.

| Relatedness | Description according to MDCG 2020-10/1 |
|---|---|
| Not Related | Relationship to the device, comparator or procedures can be excluded when:<br>• The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;<br>• The AE/SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;<br>• The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the AE/SAE;<br>• The event involves a body-site or an organ that cannot be affected by the device or procedure;<br>• The AE/SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);<br>• The event does not depend on a false result given by the investigational device used for diagnosis^, when applicable;<br><br>In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.<br><br>^If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer) or might not be diagnosed with the correct disease or condition. |
| Possible | The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible. |

| Relatedness | Description according to MDCG 2020-10/1 |
|---|---|
| Probable | The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause. |
| Causal relationship | The AE/SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:<br>• The event is a known side effect of the product category the device belongs to or of similar devices and procedures;<br>• The event has a temporal relationship with investigational device use/application or procedures;<br>• The event involves a body-site or organ that<br>o the investigational device or procedures are applied to;<br>o the investigational device or procedures have an effect on;<br>• The AE/SAE follows a known response pattern to the medical device (if the response pattern is previously known);<br>• The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the AE/SAE (when clinically feasible);<br>• Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;<br>• Harm to the subject is due to error in use;<br>• The event depends on a false result given by the investigational device used for diagnosis^^, when applicable;<br><br>In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.<br><br>^^If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition. |

## 9.4 Reporting of Events

For all adverse events, all sections of the appropriate Case Report Form (CRF) must be completed, reporting the date of the adverse event, resolution, action taken, assessment of both the seriousness and the relationship to the study devices and the related procedure Additional information may also be collected if appropriate.

- All SAEs, SADEs, and/or UADEs/USADEs must be reported to the Sponsor via electronic CRF without unjustified delay and within three (3) calendar days of the site/investigator becoming aware of the event.

- De-identified copies of all requested relevant documentation should be submitted to the Sponsor within 72 hours of knowledge, as appropriate.
- Only in case the eCRF system is not operational, the SAEs and (U)SADEs can be sent to the Sponsor per e-mail to the e-mail address MDS.ClinicalSafety@bd.com
- Safety related correspondence or questions can be addressed to following contact. BD Trial Safety Team, email: MDS.ClinicalSafety@bd.com

It is the responsibility of the Investigator to report adverse events to individual Institutional Review Boards (IRBs)/Ethics Committees (ECs) and/or regulatory authorities according to the local regulations in each participating country. The Sponsor or their designee is responsible for reporting AEs to regulatory authorities according to the local regulations in each participating country.

## 9.5 Safety Committees

A safety committee will not be used for this study.

## 9.6 Device Deficiencies

The Investigator will record a device deficiency if a device used in the study, which appeared to be inadequate with respect to its identity, quality, durability, reliability, usability, safety or performance whether due to mechanical failure, malfunction, or defect. Device deficiencies also include use errors and inadequate labeling. This applies to: devices used to treat the participant, or devices in which the package was opened, but the device was not used for treatment, or devices with which treatment was attempted, but the device did not remain through the entire study procedure/period.

All device deficiencies will be recorded on the appropriate Case Report Form and will be promptly reported to the Sponsor. The device(s) should be returned to the Sponsor if requested.

If the device deficiency was associated with an AE, the reporting provisions for AEs,

ADEs, SAEs, SADEs and UADEs/USADEs apply.

Reported deficiencies will be investigated and reported under 21 CFR part 803 Medical Device Reporting by the Sponsor if necessary, or as required by appropriate national laws and regulations. The site may be contacted to provide additional information to allow the Sponsor to conduct a thorough investigation.

It is the responsibility of the Investigator to notify the IRB/EC of such device deficiencies in accordance with the IRB/EC and/or the Competent Authority's local regulations.

## 9.7 Serious Health Threat

During the course of the study, device deficiencies or adverse events will be assessed if they constitute a serious health threat. The serious health threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a

serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Serious health threat includes the

possibility of multiple deaths occurring at short intervals, or other significant and unexpected serious adverse events that can be regarded as a potential serious health hazard in subjects, users or other persons and which are possibly related to the investigation device use.

# 10 STATISTICAL METHODS

The statistical analysis plan will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in the following sections. This section includes a summary of the planned statistical analyses of the most important endpoints including primary endpoints.

## 10.1 Overview of Study Design

This is a multi-center, prospective, post-market study to assess the safety and performance of marketed BD NRFit™ Spinal Needles, the BD Spinal Introducer NRFit™ Needles, the BD Spinal NRFit™ Needle Sets, and the BD Syringes NRFit™.

## 10.2 Sample Size Considerations

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 1 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 1: Sample Size and Precision

| Sample Size | Rate | Precision (Half width of 95% CI) |
|---|---|---|
| 150 | 90% | 4.8% |
| 100 | 90% | 6.0% |
| 150 | 80% | 6.4% |
| 150 | 3% | 3.1% |
| 150 | 2% | 2.7% |

## 10.3 Analysis Population

The following populations are defined:

| 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 |

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.

## 10.4 General Considerations

Study endpoints may be missing due to reasons including lost to follow-up visits, procedures not being performed, or participant discontinuation. It is essential to minimize missing data and always record why it is missing. Analyses will be performed using evaluable data, combining all investigational sites. Statistical output will be generated using SAS (SAS Institute, Cary, NC) version 9.4 or above.

## 10.5 Primary Endpoint(s)

### 10.5.1 Primary Performance Endpoints

#### 10.5.1.1 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.

- 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; 95% confidence interval (exact method) will be calculated.

#### 10.5.1.2 Performance of the BD NRFit™ Syringes

- Rate of successful aspiration and injection of anesthetic through BD NRFit™ Syringes
- Rate of BD NRFit™ Syringes that do not leak at the connection point during medication administration

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; 95% confidence interval (exact method) will be calculated.

### 10.5.2 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 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; 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)

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.

### 10.6 Other Analyses

For other data not specifically captured under primary endpoints, summary statistics for categorical variables will include frequency counts and proportions and for continuous variables mean, standard deviation, minimum, median and maximum. Further details will be included in the final Statistical Analysis Plan (SAP).

## 11 DATA COLLECTION AND RECORD MAINTENANCE

### 11.1 Case Report Forms

The Investigator is responsible for ensuring the completeness and accuracy of all study documentation.

All required clinical data will be collected/documented in sponsor-provided electronic Case Report Forms (CRFs). Applicable national and local regulations are followed on the handling of electronic data. Modification of the CRFs will only be made if deemed necessary by the Sponsor and/or the appropriate regulatory body. The site must complete the eCRFs according to the participant's visit on an ongoing basis to allow regular review by the Sponsor or their designee, within approximately three (3) days of the site/investigator is aware of the data.

Site numbers and participant numbers will be used to track participant information throughout the study. Participant personal information will be pseudonymized/de-identified.

### 11.2 Source Documentation

Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical and/or study file of each enrolled participant.

### 11.3 Data Management

Data management is the responsibility of the Sponsor or their designee. Data from completed CRFs will be managed in a secured, controlled database. A Data Management Plan (DMP) will be developed that outlines the procedures used for recording, data tracking, data review, database cleaning, issuing/resolving data queries and database lock. Procedures

for rectifying errors and omissions, verification, validations and securing of the electronic data system as well as data storage will also be contained within the DMP. The procedure to maintain and protect the participants data privacy and information on data storage upon completion of the study will be detailed in the DMP too.

### 11.4 Record Retention

The Investigator shall retain all study records for a minimum of ten (10) years after the study termination. Study records may be stored longer if required by national law or other local rules. The data for some of these records may be available in computerized form but the final responsibility for maintaining study records remains with the Investigator. No records may be destroyed during the retention period without the written approval of the Sponsor.

The Investigator may withdraw from the responsibility to maintain records for the period

required by transferring custody of the records to any other person who will accept

responsibility for retaining them. Notice of a transfer shall be given to the Sponsor not later than ten (10) working days after the transfer occurs.

## 12 QUALITY CONTROL AND ASSURANCE

### 12.1 Control of Study Products

In this post-market study, marketed devices will be used, provided by the Sponsor. No special controls are required in this study. Study products will be released only for use by Investigators who have obtained written IRB/EC approval (as required) for participation in this study, who have completed all required study documentation, and who have been qualified by the Sponsor. Investigators must maintain control over all study products, and ensure they are used in accordance with this protocol. Failure to do so may result in the Sponsor suspending or terminating the study at the Investigator's site.

The Investigator will ensure that study products are only dispensed to participants properly enrolled in the study. The Investigator must maintain records of receipt, disposition, return and/or destruction of all study products. All study products released to the site must be accounted for at the unit level prior to study close out, regardless of disposition. The Sponsor-Monitor will regularly review all records regarding study product accountability.

The Sponsor will maintain records that document the shipment, receipt, disposition, return and/or destruction of study products. Additional details may be found in the Study Supply Plan.

### 12.2 Monitoring

The Sponsor will designate trained and qualified personnel to monitor the progress of this clinical study in accordance with established standard operating procedures and the study-specific Monitoring Plan.

Prior to study start, a study initiation visit (SIV) will be conducted to review with the Investigator(s) and staff the provisions and proper conduct of this study. This visit will include a detailed review of this protocol, verification that all necessary documents are on file at the investigational site and confirmation of IRB/EC approvals.

During the study, routine monitoring visits (RMVs) will be conducted to assure the site continues to adhere to the protocol, the investigator agreement, and regulations regarding conduct of clinical studies. The Sponsor-Monitor will confirm that the ICF to be used is the version approved by the IRB/EC, confirm the applicable national privacy laws have been followed, verify that all necessary documents are on file at the investigational site and confirm that there are provisions to continue and maintain all documents and records throughout the study as required by applicable regulations. These monitoring visits will assess continued protocol compliance, adequate participant enrollment, accurate data reporting, monitoring of participant safety through identification and/or review of any device-related AEs, UADEs, or SAEs, device accountability, continued maintenance and calibration of study-specific equipment (if applicable), and continued IRB/EC acceptance of the study.

At the completion of the study, the Sponsor-Monitor will conduct a final close-out visit or COV. The purpose of this visit may include but is not limited to collecting all outstanding study data documents, confirming that the Investigator's files are accurate and complete, reviewing the record retention requirements with the Investigator, providing for the return of unused devices to the Sponsor, reviewing records which account for device shipments and ensuring that all applicable requirements for closure of the study are met.

### 12.3 Audits and Inspections

If the study is selected for audit by the Sponsor or if there is an inspection by the appropriate Health Authorities, the Investigator and her/his team will make themselves available during the visit. The Investigator must agree to the inspection of all study related records and give the auditor/inspector direct access to source documents for verification of data on CRFs. The participant's anonymity must be ensured, and data checked during the audit must remain confidential.

As soon as the Investigator is aware of an upcoming inspection/audit by the Health Authorities, he/she will promptly inform the Sponsor. As agreed with the Investigator, Sponsor personnel may be present at the site during the inspection.

### 12.4 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.

Except when necessary to protect the life or physical well-being of a participant, protocol deviations are not permitted. The Sponsor and the investigational site's IRB/EC must be notified immediately if an emergency situation arises in which the safety of a participant may require immediate intervention different than that defined in the protocol. This must be followed by written confirmation that describes the emergency action and outcomes, within five (5) working days from the date of the emergency action in accordance with the governing IRB/EC's requirement.

It is the Investigator's responsibility to ensure that there are no deviations from the Protocol. Except in an emergency, when a protocol deviation is planned or anticipated, the Sponsor should be contacted for approval. All deviations must be recorded on the appropriate CRF regardless of whether medically justifiable or sponsor approved. Upon evaluation by the

Sponsor, actions may be required to prevent additional deviations, such as retraining of the site, implementation of additional site procedures, and more frequent monitoring. If these steps fail, more serious measures, up to and including termination of enrollment at the site, may be implemented.

# 13 ADMINISTRATIVE REQUIREMENTS

## 13.1 Investigator and Site Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of this protocol, including the protection of human participants. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to this protocol and enrollment of sufficient numbers of evaluable participants. The curriculum vitae (CV) of the Investigator(s), Sub-Investigator(s) and Study Coordinator(s) will be maintained in the Sponsor's files as documentation of qualification by training and experience.

The Principal Investigator will sign the Investigator Agreement pages of this protocol, agreeing to comply with all applicable regulations and the requirements of this study as per the clinical study agreement.

Any site that is deactivated prior to initial enrollment, either by the Sponsor or by the individual site itself, may be replaced.

## 13.2 Training

Each Investigator and appropriate site personnel will be trained on this protocol and study procedures during the Site Initiation Visit and on the study device, if needed.

All training will be documented and filed at the investigational site and with the Sponsor.

## 13.3 Required Documents

An Investigator may not screen or enroll participants until authorized to do so by the Sponsor. At a minimum, the following documentation should be received by the Sponsor prior to the commencement of study activities:

- Fully executed Non-disclosure Agreement (NDA) between PI/site and Sponsor;
- CVs, signed and dated within 2 years of study start for the PI and Sub-Investigator(s);
- CVs for Study Coordinator(s);
- Signed Clinical Study Agreement (CSA) by PI/site (or designee);
- Signed Investigator Agreement Page by PI and Sub-Investigator(s);
- Signed Financial Disclosure Statement by PI and Sub-Investigator(s);
- Completed and Signed Training Log by PI and Sub-Investigator(s);
- Study Personnel Identification list;
- Written approval from the IRB/EC of both the protocol and ICF, and any other applicable protocol specific material; and

- IRB/EC Membership List, Assurance of Compliance Form, or equivalent.

### 13.4 Insurance

Where required by local regulation, insurance coverage will be provided by BD for study participants.

### 13.5 Publication Policy

The sponsor believes that results of applicable clinical studies should be published in peer-reviewed literature in a timely, accurate, complete and balanced manner, regardless of study outcomes, whenever possible. As such, at the conclusion of this study, an article may be prepared for publication in a reputable scientific journal. Formal presentation(s) or publication(s) of data collected from this study will be considered as a joint publication by the investigator(s) and the appropriate personnel of the Sponsor. Authorship will be based on generally accepted criteria of the ICMJE (International Committee of Medical Journal Editors) and determined by mutual agreement.

The publication of the principal results from any single-center experience within the study is not allowed until the preparation and publication of the multicenter results. Exceptions to this rule require the prior approval of the Sponsor. The analysis of other pre-specified and non-pre-specified endpoints will be performed by the Sponsor or its designee. Such analyses, as well as other proposed investigations or manuscripts will require the approval of the Sponsor.

### 13.6 Study Registration

While this is a not an Applicable Clinical Trial and does not meet the FDA Amendments Act of 2007 (FDAAA) criteria for clinical study registration, the study will be registered on www.clinicaltrials.gov to ensure transparency. The study will also be registered on additional local registries, if applicable. The content of the publicly accessible database(s) will be updated throughout the conduct of the clinical study and the results will be entered after study completion.

### 13.7 Termination of Study

The Sponsor reserves the right to suspend enrollment or terminate the study at any time

for any reason. If suspicion of an unacceptable risk, including serious health threat to subjects, arises during the study, the Sponsor may suspend the study while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.

Additionally, the Sponsor may suspend enrollment or terminate the study at a specific investigational site for reasons including, but not limited to, inadequate data collection, low participant enrollment rate, achievement of the total enrollment, conditions imposed by the reviewing IRB/EC and/or non-compliance with this protocol or other clinical research requirements. Written notice will be submitted to the Investigator in advance of such termination.

In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the IRB/EC, and all Investigators and Regulatory Authorities as required by regulation.

# 14 ETHICAL AND REGULATORY CONSIDERATIONS

## 14.1 IRB/EC Approval

Sponsor or designees must submit the study protocol, Informed Consent Form (if applicable), and all other locally required documentation to an appropriate IRB/EC and obtain study-specific written approval (favorable opinion) before Investigators being allowed to participate in the study. Before commencement of the study, the Investigator or designee must provide the Sponsor with written documentation of such approval. The IRB/EC must give written renewal of the original approval at least annually to continue the study, if applicable per local regulation. In this case, a copy of the written renewal must be provided to the Sponsor.

The IRB/EC will be notified of any amendments to the protocol, as well as possible associated information and consent form changes, where applicable, and written approval (favorable opinion) will be obtained prior to implementation, as applicable.

The Investigator or designee is responsible for fulfilling any conditions of approval imposed by the IRB/EC, such as regular safety reporting, study timing, etc. The Investigator or designee will provide the Sponsor with copies of such reports.

## 14.2 Informed Consent and Confidentiality

Prior to any study procedure, the Investigator (or designee) must explain to each participant in layman's terms, the nature of the study, its purpose, expected duration, and the risks and benefits of study participation. For participants under the age of 18, participants' parent(s)/guardian must provide their informed consent and the child must provide assent, depending on local EC requirements, by personally signing and dating the respective consent form prior to begin of this study. For adult participants, where the participant is not able to or not capable to give informed consent, the legal representative will be asked to give consent on behalf of the participant. However, the participant will also be informed about the study within his/her ability to understand.

Also, participant will be informed of uses and disclosures of their medical information for research purposes, and their rights to access information about them. All applicable national privacy laws (e.g., General Data Protection Regulation [GDPR] requirements in the EU) will be followed in this study. The participants must be informed of their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care. Participants will be informed of their right to new information and/or findings relating to the clinical study, and the process by which this information is made available. After this explanation, given sufficient time to decide whether to participate, before any study procedure is conducted, and before entering the study, the participant must voluntarily provide consent by signing, dating and timing the form personally in accordance with ISO 14155:2020(E). The participant will receive a copy of his/her signed ICF. The

Informed Consent process has to be documented in the participant's medical records. If new information becomes available that may significantly affect the subject's health status, then this information will be provided in written form. Re-consent will be obtained if this is considered as necessary.

The above requirements also apply with respect to informed consent obtained from participant's legally authorized representative.

### 14.2.1 Confidentiality

Participant confidentiality must be strictly held in trust by the Investigator, study staff, and the Sponsor. Participant confidentiality and anonymity will be maintained by removal of identifiers from any data, documentation, or clinical samples submitted to the Sponsor.

Any data collected meeting the definition of protected/confidential health information or personal identifying information will be collected and maintained using the designated authorizations and following privacy procedures as specified in the applicable health authority regulations including the European Union General Data Protection Regulation (GDPR).

The Sponsor-Monitor, authorized representatives of the sponsor, and/or applicable Health Authorities may inspect all documents and records required to be maintained by the Investigator. The Investigator/Site will permit access to such records.

## 14.3 Regulatory Status

The study devices are CE marked and will be studied in a post-market fashion in Europe.

## 14.4 Statement of Compliance

This clinical investigation will be conducted in compliance with the protocol and following regulatory requirements:

- ISO 14155:2020 (Good Clinical Practice);
- EU MDR (Council Regulation 2017/745 of 5 April 2017);
- Ethical principles that have their origin in the Declaration of Helsinki; and
- Applicable sections of the national laws and regulations.

The clinical investigation will not commence at a clinical site until approval (favorable opinion) from the respective IRB/EC has been received. All additional requirements imposed by the IRB/EC(s) will be followed. Involvement of the national competent authorities (e.g. by notification, seeking authorization) will be accomplished as required by national laws and regulations.

Where required by local or national regulation, the Sponsor will provide product liability insurance for the participants included in the study. The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator

responsibilities in relation to the study. Financial remuneration will cover the cost per included participant, and the specified terms of payments will be described in the contract.

# 15 REFERENCES

[1] H. Vo and D. Berkery, "An overview of neuraxial anesthesia," American Nurses Association (ANA), 2019. [Online]. Available: https://www.myamericannurse.com/an-overview-of-neuraxial-anesthesia/. [Accessed September 2022].

[2] U. Ituk and C. A. Wong, "Overview of neuraxial anesthesia," [Online]. Available: https://www.uptodate.com/contents/overview-of-neuraxial-anesthesia?search=neuraxial%20anesthesia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. [Accessed February 2021].

[3] A. M. DeLeon and C. A. Wong, "Spinal anesthesia: Technique," [Online]. Available: https://www.uptodate.com/contents/spinal-anesthesia-technique?search=neuraxial%20anesthesia&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=5. [Accessed February 2021].

[4] AMBOSS, "Local and regional anesthesia," 29 September 2022. [Online]. Available: https://www.amboss.com/us/knowledge/Local_and_regional_anesthesia/. [Accessed 03 October 2022].

[5] P. Santosh and R. Loveridge, "Obstetric Neuraxial Drug Administration Errors: A Quantitative and Qualitative Analytical Review," *Anesthesia&Analgesia,* vol. 121, no. 6, pp. 1570-7, December 2015.

[6] N. Calthorpe, "The history of spinal needles: getting to the point," *Anaesthesia,* vol. 59, no. 12, pp. 1231-1241, 2004.

[7] R. Litman, V. Smith and P. Mainland, "New solutions to reduce wrong route medication errors.," *Paediatric Anaesthesia,* vol. 28, no. 1, pp. 8-12, 17 Nov 2017.

[8] R. Lawton, P. Gardner, B. Green, C. Davey, P. Chamberlain, P. Phillips and C. Hughes, "An engineered solution to the maladministration of spinal injections," *Quality and Safety in Health Care,* vol. 18, no. 6, pp. 492-5, Dec 2009.

[9] T. C. K. Brown, "History of pediatric regional anesthesia," *Pediatric Anesthesia,* vol. 22, no. 1, pp. 3-9, Jan 2012.

[10] Z. Tekgül , S. Pektaş, M. Turan, Y. Karaman, M. Çakmak and M. Gönüllü, "Acute Back Pain Following Surgery under Spinal Anesthesia," *Pain Practice,* vol. 15, no. 8, pp. 706-11, Nov 2015.

[11] D. Prakash, L. Heskin , S. Doherty and R. Galvin, "Local anaesthesia versus spinal anaesthesia in inguinal hernia repair: A systematic review and meta-analysis," *Surgeon,* vol. 15, no. 1, pp. 47-57, Feb 2017.

[12] "Local infiltration analgesia adds no clinical benefit in pain control to peripheral nerve blocks after total knee arthroplasty," *Knee Surg Sports Traumatol Arthrosc,* vol. 24, no. 10, pp. 3299-3305, Oct 2016.

[13] M. Moradi, S. Shami, F. Farhadifar and K. Nesseri, "Cerebral Subdural Hematoma Following Spinal Anesthesia: Report of Two Cases," *Case Reports in Medicine,* vol. 2012, no. Article ID 352028, 2012.

[14] E. M. E. Bos, J. Haumann, M. de Quelerij, W. P. Vandertop, C. J. Kalkman, M. W. Hollmann and P. Lirk, "Haematoma and abscess after neuraxial," *British Journal of Anaesthesia,* vol. 120, no. 4, pp. 693-704, 2018.

[15] B. Fredman, E. Zohar, U. Rislick, O. Sheffer and R. Jedeikin, "Intrathecal anaesthesia for the elderly patient: the influence of the induction position on perioperative haemodynamic stability and patient comfort," *Anaesthesia and intensive care,* vol. 29, no. 4, pp. 377-82, Aug 2001.

[16] T. Standl, A. Stanek, M. Burmeister, S. Grüschow, B. Wahlen, K. Müller, J. Biscoping and H. Adams, "Spinal anesthesia performance conditions and side effects are comparable between the newly designed Ballpen and the Sprotte needle: results of a prospective comparative randomized multicenter study," *Anesthesia & Analgesia,* vol. 98, no. 2, pp. 512-517, Feb 2004.

[17] L. Shutt, S. Valentine, M. Wee , R. Page , A. Prosser and T. Thomas , "Spinal anaesthesia for caesarean section: comparison of 22-gauge and 25-gauge Whitacre needles with 26-gauge Quincke needles," *British journal of anaesthesia,* vol. 69, no. 6, pp. 589-94, Dec 1992.

[18] M. Schmittner, T. Terboven, M. Dluzak, A. Janke, M. Limmer, C. Weiss, D. Bussen, M. Burmeister and G. Beck, "High incidence of post-dural puncture headache in patients with spinal saddle block induced with Quincke needles for anorectal surgery: a randomised clinical trial," *International Journal of Colorectal Disease,* vol. 25, no. 6, pp. 775-81, Jun 2010.

[19] H. Randriamizao, A. Rakotondrainibe, L. Razafindrabekoto, P. Ravoaviarivelo, A. Rajaoner and M. Andriamanarivo , "Use of spinal anaesthesia in neonates and infants in Antananarivo, Madagascar: a retrospective descriptive study," *BMC research notes,* vol. 13, no. 1, pp. 1-6, Oct 2020.

[20] R. Abdullayev, O. Küçükebe, B. Çelik, N. Kirman, H. Hatipoğlu and F. Akaltun Hatipoğlu, "Does Atraucan cause more postdural puncture backache?," *Turk J Med Sci,* vol. 45, no. 4, pp. 877-81, 2015.

[21] H. Kokki and H. Hendolin, "Comparison of 25 G and 29 G Quincke spinal needles in paediatric day case surgery. A prospective randomized study of the puncture characteristics, success rate and postoperative complaints.," *Pediatric Anesthesia,* vol. 6, no. 2, pp. 115-119, 1996.

[22] J. Shaikh and et al., "Post dural puncture headache after spinal anaesthesia for Caesarean section: A comparison of 25G Quincke, 27G Quincke and 27G Whitacre spinal needles.," *J Ayub Med Coll Abbottabad,* vol. 20, no. 3, pp. 11-3, 2008.

[23] J. Buettner, K. Wresch and R. Klose, "Postdural Puncture Headache: Comparison of 25-Gauge Whitacre and Quincke Needles.," *Regional Anesthesia: The Journal of Neural Blockade in Obstetrics, Surgery, & Pain Control,* vol. 18, no. 3, pp. 166-169, 1993.

[24] A. Erol and et al., "Auditory function after spinal anaesthesia: the effect of differently designed spinal needles.," *Eur J Anaesthesiol,* vol. 26, no. 5, pp. 416-420, 2009.

[25] A. Castrillo and et al., "Postdural puncture headache: impact of needle type, a randomized trial.," *The Spine Journal,* vol. 15, no. 7, pp. 1571-1576, 2015.

[26] M. Schmittner and et al., "Influence of the pre-operative time in upright sitting position and the needle type on the incidence of post-dural puncture headache (PDPH) in patients receiving a spinal saddle block for anorectal surgery.," *International journal of colorectal disease,* vol. 26, no. 1, pp. 97-102, 2011.

[27] R. Batova and S. Georgiev, "Impact of spinal needle design and approach to postdural puncture headache and spinal anesthesia failure in obstetrics.," *Anestezjologia Intensywna Terapia,* vol. 51, no. 2, pp. 81-86, 2019.

[28] E. Gisore, V. Mung'ayi and T. Sharif, "Incidence of post dural puncture headache following caesarean section under spinal anaesthesia at the Aga Khan University Hospital, Nairobi," *East African medical journal,* vol. 87, no. 6, pp. 227-230, 2010.

[29] S. Malhotra and et al., "Spinal analgesia and auditory functions: a comparison of two sizes of Quincke needle," *Minerva anestesiologica,* vol. 73, no. 7-8, pp. 395-399, 2006.

[30] P. Pan and et al., "Incidence of postdural puncture headache and backache, and success rate of dural puncture: comparison of two spinal needle designs," *South Med J,* vol. 97, no. 4, pp. 359-63, 2004.

[31] H. Flaatten and et al., "Postural post-dural puncture headache. A prospective randomised study and a meta-analysis comparing two different 0.40 mm OD (27 g) spinal needles," *Acta anaesthesiologica scandinavica,* vol. 44, no. 6, pp. 643-647, 2000.

[32] S. Lee and et al., "Impact of spinal needle type on postdural puncture headache among women undergoing Cesarean section surgery under spinal anesthesia: A meta-analysis.," *Journal of Evidence-Based Medicine,* vol. 11, no. 3, pp. 136-144, 2018.

[33] D. Zhang and et al., "Lower incidence of postdural puncture headache using whitacre spinal needles after spinal anesthesia: A meta-analysis.," *Headache: The Journal of Head and Face Pain,* vol. 56, no. 3, pp. 501-510, 2016.

[34] M. Alam and et al., "Headache following spinal anaesthesia: a review on recent update.," *Journal of Bangladesh College of Physicians & Surgeons,* vol. 29, no. 1, p. 32, 2011.

[35] F. Ayub and et al., "Frequency of headache with 25G or 27G quincke needles after spinal anesthesia in patients undergoing elective cesarean section.," *Anaesthesia, Pain & Intensive Care,* vol. 21, no. 2, pp. 170-173, 2017.

[36] A. Zorrilla-Vaca, R. Healy and C. Zorrilla-Vaca, "Finer gauge of cutting but not pencil-point needles correlate with lower incidence of post-dural puncture headache: a meta-regression analysis," *Journal of Anesthesia,* vol. 30, no. 5, pp. 855-863, 2016.

[37] B. Sohail and et al., "Postdural Puncture Headache; Comparison Between Lumbar Puncture Needle No. 25 G and 27 G.," *Professional Medical Journal,* vol. 18, no. 1, pp. 51-56, 2011.

[38] A. Pal and et al., "Do pencil-point spinal needles decrease the incidence of postdural puncture headache in reality? A comparative study between pencil-point 25G Whitacre and cutting-beveled 25G Quincke spinal needles in 320 obstetric patients.," *Anesthesia: Essays & Researches,* vol. 5, no. 2, pp. 162-166, 2011.

[39] R. Abdullayev and et al., "Incidence of postdural puncture headache: Two different fine gauge spinal needles of the same diameter," *Journal of Obstetric Anaesthesia and Critical Care,* vol. 4, no. 2, pp. 64-68, 2014.

[40] S. Apiliogullari and et al., "Spinal needle design and size affect the incidence of postdural puncture headache in children," *Pediatric Anesthesia,* vol. 20, no. 2, pp. 177-182, 2010.

[41] H. Özdemir and et al., "The effects of needle deformation during lumbar puncture," *Journal of Neurosciences in Rural Practice,* vol. 6, no. 2, pp. 198-201, 2015.

[42] S. Nath and et al., "Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis," *The Lancet,* vol. 391, no. 10126, pp. 1197-1204, 2018.

[43] A. Zorrilla-Vaca and et al., "The Impact of Spinal Needle Selection on Postdural Puncture Headache: A Meta-Analysis and Metaregression of Randomized Studies," *Regional Anesthesia and Pain Medicine,* vol. 43, no. 5, pp. 502-508, 2018.

[44] S. Lomax and A. Qureshi, "Unusually early onset of post-dural puncture headache after spinal anaesthesia using a 27G Whittacre needle," *BJA: The British Journal of Anaesthesia,* vol. 100, no. 5, pp. 707-708, 2008.

[45] R. Onia and et al., "Simulated evaluation of a non-Luer safety connector system for use in neuraxial procedures," *Br J Anaesth,* vol. 108, no. 1, pp. 134-9, 2012.

[46] T. Cook and et al., "Multicentre clinical simulation evaluation of the ISO 80369-6 neuraxial non-Luer connector," *Anaesthesia,* vol. 74, no. 5, pp. 619-629, 2019.

[47] R. Litman, V. Smith and P. Mainland, "New solutions to reduce wrong route medication errors," *Paediatr Anaesth,* vol. 28, no. 1, pp. 8-12, 2018.

[48] T. Cook, "Non-Luer connectors: are we nearly there yet?," *Anaesthesia,* vol. 67, no. 7, pp. 784-792, 2012.

[49] S. Patel and R. Loveridge, "Obstetric Neuraxial Drug Administration Errors: A Quantitative and Qualitative Analytical Review," *Anesth Analg,* vol. 121, no. 6, pp. 1570-7, 2015.

[50] R. Lawton and et al., "An engineered solution to the maladministration of spinal injections," *Quality and Safety in Health Care,* vol. 18, no. 6, pp. 492-5, 2009.

[51] K. Cannons and I. Shaw, "Changing practice for neuraxial applications using NRFit™ small-bore connectors to improve patient safety," *British Journal of Nursing,* vol. 30, no. 4, pp. S22-S27, 2021.

[52] V. Smith and R. Litman, "Staying Connected: How to Prevent Wrong Route Medication Errors in the Operating Room," *Current Anesthesiology Reports,* vol. 7, no. 2, pp. 119-124, 2017.

[53] I. f. S. M. P. ISMP, "Death And Neurological Devastation From Intrathecal Vinca Alkaloids: Prepared In Syringes = 120; Prepared In Minibags = 0," 05 Sep 2013. [Online]. Available: https://www.ismp.org/resources/death-and-neurological-devastation-intrathecal-vinca-alkaloids-prepared-syringes-120. [Accessed 10 Oct 2022].

[54] ASA, "https://www.asahq.org," 13 Dec 2020. [Online]. Available: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. [Accessed Oct 2022].

[55] International Headache Society (IHS), "https://ichd-3.org," International Headache Society, 2021. [Online]. Available: https://ichd-3.org/7-headache-attributed-to-non-vascular-intracranial-disorder/7-2-headache-attributed-to-low-cerebrospinal-fluid-pressure/7-2-1-post-dural-puncture-headache/. [Accessed 18 October 2022].

[56] P. H. Pan, R. Fragneto, C. Moore and V. Ross, "Incidence of Postdural Puncture Headache and backacke, and success rate of dural puncture: comparison of two spinal needle designs," *Southern Medical Journal,* vol. 97, no. 4, pp. 359-63, April 2004.

# 16 APPENDICES

## 16.1 Study devices

| Catalog number | Product Type | Product Description |
|---|---|---|
| 400220 | BD Whitacre Spinal NRFit™ Needle | 25G × 4.06″ (0.50 × 103.2 mm) |
| 400221 | BD Whitacre Spinal NRFit™ Needle | 25G × 4.70″ (0.50 × 119.1 mm) |
| 400222 | BD Whitacre Spinal NRFit™ Needle | 27G × 4.06″ (0.40 × 103.2 mm) |
| 400223 | BD Whitacre Spinal NRFit™ Needle | 27G × 4.70″ (0.40 × 119.1 mm) |
| 400978 | BD Whitacre Spinal NRFit™ Needle | 22G × 3.50″ (0.70 × 88.9 mm) |
| 400979 | BD Whitacre Spinal NRFit™ Needle | 24G × 3.50″ (0.55 × 88.9 mm) |
| 400980 | BD Whitacre Spinal NRFit™ Needle | 25G × 3.50″ (0.50 × 88.9 mm) |
| 400982 | BD Whitacre Spinal NRFit™ Needle | 27G × 3.50″ (0.40 × 88.9 mm) |
| 400063 | BD Quincke Spinal NRFit™ Needle | 25G × 3.00″ (0.5 × 76.2 mm) |
| 400065 | BD Quincke Spinal NRFit™ Needle | 18G × 3.00″ (1.2 × 76.2 mm) |
| 400070 | BD Quincke Spinal NRFit™ Needle | 18G × 3.50″ (1.2 × 88.9 mm) |
| 400072 | BD Quincke Spinal NRFit™ Needle | 22G × 1.50″ (0.7 × 38.1 mm) |
| 400073 | BD Quincke Spinal NRFit™ Needle | 22G × 2.50″ (0.7 × 63.5 mm) |
| 400077 | BD Quincke Spinal NRFit™ Needle | 22G × 3.00″ (0.7 × 76.2 mm) |
| 400079 | BD Quincke Spinal NRFit™ Needle | 22G × 3.50″ (0.7 × 88.9 mm) |
| 400086 | BD Quincke Spinal NRFit™ Needle | 25G × 2.00″ (0.5 × 50.8 mm) |
| 400089 | BD Quincke Spinal NRFit™ Needle | 25G × 3.50″ (0.5 × 88.9 mm) |
| 400215 | BD Quincke Spinal NRFit™ Needle | 18G × 6.00″ (1.20 × 152.4 mm) |
| 400216 | BD Quincke Spinal NRFit™ Needle | 20G × 6.00″ (0.90 × 152.4 mm) |
| 400217 | BD Quincke Spinal NRFit™ Needle | 22G × 5.00″ (0.70 × 127 mm) |
| 400218 | BD Quincke Spinal NRFit™ Needle | 22G × 7.00″ (0.70 × 177.8 mm) |
| 400219 | BD Quincke Spinal NRFit™ Needle | 25G × 4.70″ (0.50 × 119.1 mm) |
| 400925 | BD Quincke Spinal NRFit™ Needle | 19G × 3.00″ (1.1 × 76.2 mm) |
| 400926 | BD Quincke Spinal NRFit™ Needle | 19G × 3.50″ (1.1 × 88.9 mm) |
| 400927 | BD Quincke Spinal NRFit™ Needle | 20G × 1.50″ (0.9 × 38.1 mm) |
| 400928 | BD Quincke Spinal NRFit™ Needle | 20G × 3.00″ (0.9 × 76.2 mm) |
| 400929 | BD Quincke Spinal NRFit™ Needle | 20G × 3.50″ (0.9 × 88.9 mm) |
| 400930 | BD Quincke Spinal NRFit™ Needle | 23G × 3.50″ (0.6 × 88.9 mm) |
| 400931 | BD Quincke Spinal NRFit™ Needle | 26G × 3.50″ (0.45 × 88.9 mm) |
| 400932 | BD Quincke Spinal NRFit™ Needle | 27G × 3.50″ (0.4 × 88.9 mm) |
| 400177 | BD Spinal Needle Introducer NRFit™ | 20G × 1.25" (0.90 × 31.8 mm) |
| 400919 | BD Spinal Needle Introducer NRFit™ | 22G × 1.25" (0.70 × 31.8 mm) |
| 400227 | BD Whitacre Spinal NRFit™ Needle with introducer set | 27G × 3.50″ (0.40 × 88.9 mm) + 22G x 1.25” (0.70mm x 31.8mm) |
| 400228 | BD Whitacre Spinal NRFit™ Needle with introducer set | 25G × 3.50" (0.50 × 88.9 mm) + 20G x 1.25” (0.90mm x 31.8mm) |

| | | |
|---|---|---|
| 400229 | BD Whitacre Spinal NRFit™ Needle with introducer set | 25G × 4.06" (0.50 × 103.2 mm) + 20G x 1.25" (0.90mm x 31.8mm) |
| 400230 | BD Whitacre Spinal NRFit™ Needle with introducer set | 27G × 4.06" (0.40 × 103.2 mm) + 22G x 1.25" (0.70mm x 31.8mm) |
| 400224 | BD Quincke Spinal NRFit™ Needle with introducer set | 25G × 3.50″ (0.50 × 88.9 mm) + 20G x 1.25" (0.90 × 31.8 mm) |
| 400225 | BD Quincke Spinal NRFit™ Needle with introducer set | 26G × 3.50″ (0.45 × 88.9 mm) + 20G x 1.25" (0.90 × 31.8 mm) |
| 400226 | BD Quincke Spinal NRFit™ Needle with introducer set | 27G × 3.50″ (0.40 × 88.9 mm) + 22G x 1.25" (0.70 × 31.8 mm) |
| 400050 | BD Syringe NRFit™ Lok | 3mL |
| 400172 | BD Syringe NRFit™ Slip | 3mL |
| 400173 | BD Syringe NRFit™ Lok | 5mL |
| 400051 | BD Syringe NRFit™ Slip | 5mL |
| 400174 | BD Syringe NRFit™ Lok | 10mL |
| 400175 | BD Syringe NRFit™ Slip | 10mL |
| 400182 | BD Syringe NRFit™ Lok | 20mL |
| 400183 | BD Syringe NRFit™ Lok | 50mL |
| **Ancillary devices** | | |
| 400066 | BD Blunt Filter NRFit™ Needle | 18G x 1 ½ (1.2 mm x 40 mm) |
| 400067 | BD Blunt Fill NRFit™ Needle | 18G x 1 ½ (1.2 mm x 40 mm) |

## 16.2 ASA physical status (PS) classification - Current Definitions and ASA-Approved Examples [54]

| ASA PS Classification | Definition | Adult examples, including, but not limited to: | Pediatric examples, including but not limited to: | Obstetric examples, including but not limited to: |
|---|---|---|---|---|
| **ASA I** | A normal healthy patient | Healthy, non-smoking, no or minimal alcohol use | Healthy (no acute or chronic disease), normal BMI percentile for age | |
| **ASA II** | A patient with mild systemic disease | Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease. | Asymptomatic congenital cardiac disease, well controlled dysrhythmias, asthma without exacerbation, well controlled epilepsy, non-insulin dependent diabetes mellitus, abnormal BMI percentile for age, mild/moderate OSA, oncologic state in remission, autism with mild limitations. | Normal pregnancy*, well controlled gestational HTN, controlled preeclampsia without severe features, diet-controlled gestational DM. |
| **ASA III** | A patient with severe systemic disease | Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents. | Uncorrected stable congenital cardiac abnormality, asthma with exacerbation, poorly controlled epilepsy, insulin dependent diabetes mellitus, morbid obesity, malnutrition, severe OSA, oncologic state, renal failure, muscular dystrophy, cystic fibrosis, history of organ transplantation, brain/spinal cord malformation, symptomatic hydrocephalus, premature infant PCA <60 weeks, autism with severe limitations, metabolic disease, difficult airway, long term parenteral nutrition. Full term infants <6 weeks of age. | Preeclampsia with severe features, gestational DM with complications or high insulin requirements, a thrombophilic disease requiring anticoagulation. |

| ASA PS Classification | Definition | Adult examples, including, but not limited to: | Pediatric examples, including but not limited to: | Obstetric examples, including but not limited to: |
|---|---|---|---|---|
| **ASA IV** | A patient with severe systemic disease that is a constant threat to life | Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis. | Symptomatic congenital cardiac abnormality, congestive heart failure, active sequelae of prematurity, acute hypoxic-ischemic encephalopathy, shock, sepsis, disseminated intravascular coagulation, automatic implantable cardioverter-defibrillator, ventilator dependence, endocrinopathy, severe trauma, severe respiratory distress, advanced oncologic state. | Preeclampsia with severe features complicated by HELLP or other adverse event, peripartum cardiomyopathy with EF <40, uncorrected/decompensated heart disease, acquired or congenital. |
| **ASA V** | A moribund patient who is not expected to survive without the operation | Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction. | Massive trauma, intracranial hemorrhage with mass effect, patient requiring ECMO, respiratory failure or arrest, malignant hypertension, decompensated congestive heart failure, hepatic encephalopathy, ischemic bowel or multiple organ/system dysfunction. | Uterine rupture. |
| **ASA VI** | A declared brain-dead patient whose organs are being removed for donor purposes | | | |

** Although pregnancy is not a disease, the parturient' s physiologic state is significantly altered from when the woman is not pregnant, hence the assignment of ASA 2 for a woman with uncomplicated pregnancy.*
*The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part).*

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