BD Protocol #: **DBC-18PENDL01**

Protocol Title: **Comparative User Experiences with BD Nano™ PRO 32G Extra Thin Wall Pen Needle vs the Terumo Nanopass® 34G Pen Needle**

Current Version	Version 4.0 25Feb2019
Version History	Version 1.0 05Dec2018 (Original) Version 2.0 19Dec2018 Version 3.0 06Feb2019 (Site specific amendment)
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Sponsor Medical Monitor	Stanislav Glezer, MD, Worldwide VP, Medical Affairs BD Diabetes Care Office #: 201.847.5214 Mobile #: 609.454.7955
Sponsor Risk Assessment	☐ Significant Risk (SR) ☒ Non-significant Risk (NSR) ☐ Minimal Risk

This study will be performed in accordance with all stipulations of the protocol and in compliance with all applicable BD Policies and Procedures. This study will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and the Belmont Report. Study conduct will comply with US FDA Regulations, applicable state and local regulations, and the Good Clinical Practice guidelines set forth by the International Conference on Harmonization (ICH-E6) and ISO14155.

SPONSOR PROTOCOL APPROVAL

Signature below indicates approval of the protocol as written.			
Individual or function	**Name**	**Signature**	**Date**
Medical Affairs Team Representative	Shahista Whooley, PharmD	*This document is signed electronically in the eTMF system*	
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INVESTIGATOR SIGNATURE PAGE

Principal Investigator	
Investigational Site	

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in compliance with all applicable Good Clinical Practices and regulations.

Signature of Principal Investigator

Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AUC	Area Under Curve
BD	Becton, Dickinson and Company
BG	Blood Glucose
BMI	Body Mass Index
cat	Catalog
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report/Record Form
cm	Centimeter
DFSP	Defective or Failed Study Product
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007
GCP	Good Clinical Practice
G	Gauge
HIPAA	Health Insurance Portability and Accountability Act
HCP	Healthcare Practitioner
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
INJ	Injection
IRB/EC	Institutional or Independent Review Board/Ethics Committee
lpf	Injection Peak Forces
mm	Millimeter
NDC	National Drug Code
NI	Non-inferiority
PHI	Protected Health Information
PI	Principal Investigator
PN	Pen Needle
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analog Scale
XTW	Extra Thin Wall

1.0 INTRODUCTION

Pen needles are a component of pen-based injection systems routinely utilized for parenteral administration of medications such as insulin. In 2010, BD introduced a 4mm x 32G pen needle. At that time, it was the shortest and thinnest pen needle available. In addition to lowering the risk for intramuscular injections, this pen needle was demonstrated to be preferred by patients vs. their current pen needles. Since its introduction, competitors have launched similar length pen needles with thinner gauge needles, such as 33G and 34G.

Previous studies reported ethnic differences in pain perception (primary study outcome).[1] More specifically, Asian subjects compared to other ethnicities demonstrated lower pain thresholds and greater pain sensitivity.[2, 3, 4, 5] The continuous development of thinner needles is focused on the improvement of the injection comfort through the reduction in pain sensation. It is not clear if the difference in needle gauge beyond 32G, is associated with clinically meaningful changes in pain sensation. BD is conducting several studies in different ethnic and geographic populations to address this question. Data from this study is intended to support appropriate clinical decision making in choosing insulin pen needles in the USA, Japan and other countries.

The comparative pen needle – Terumo Nanopass – although not commercially available in the US, presents the most relevant opportunity for comparison of needles of different gauge. The availability of such device in Japan, makes the choice of Japanese American patients logical from the perspective of eventual results generalizability, not only in the USA, but also in Japan and other countries. Differences in user experience and clinical outcomes may not be limited to pain sensation, but also by the hypothesis that thinner gauge Terumo needle will require more force to deliver the same dose compared to the wider BD needle. If a patient does not change force, dose delivery with the thinner needle will require more time. Besides a potential negative user experience (more force) this may lead to more insulin leakage from both needle tip and insertion site (more time) resulting in incomplete insulin dose delivery. This may directly impact glycemic control.

The intent of this comparative use study is to determine whether Japanese American patients' experiences are different when using the BD Nano™ PRO 4mm x 32G extra thin wall, 5-bevel pen needle (herein referred to as BD Nano™ PRO) vs the Terumo Nanopass® 4mm x 34G (thinner gauge) pen needle (herein referred to as Terumo Nanopass®). These experiences include the perceived force to deliver dose, the ability to deliver the full dose (measured by leakage), injection pain and bending.

2.0 OBJECTIVES

2.1 Primary Objective

Demonstrate non-inferiority of the BD Nano™ PRO pen needle compared to the Terumo Nanopass® pen needle for injection pain.

2.2 Secondary Objectives

Demonstrate superiority of BD Nano™ PRO vs Terumo Nanopass® pen needle for the following:

- Leakage from the needle tip and the injection site (measurements combined) after removal from body
- Subject perceived force required to deliver dose
- Patient end needle bending after removal from body
- If primary outcome demonstrates non-inferiority, then evaluate for superiority of Nano™ PRO vs Terumo Nanopass®

2.3 Exploratory Objectives

Compare BD Nano™ PRO vs Terumo Nanopass® for the following:

- Injection time
- Patient end needle breaking at any time
- Survey responses pertaining to subjective assessments of pen needle characteristics

3.0 STUDY DESIGN

3.1 Overall Study Design

This is a subject partially blinded, block randomized, prospective, single-visit, multi-center study to compare user experiences with BD Nano™ PRO pen needle vs. the thinner commercially available Terumo Nanopass® pen needle. The study will include a minimum of 55 Japanese American study subjects having Type 1 or Type 2 diabetes.

Study conduct will consist of one 60 to 120 minute Site visit in which pre-set doses of saline will be abdominally delivered by Subjects via a reusable insulin pen device. All pen needles will be attached by Study Staff and pen needle outer cover and inner shield will be removed for subjects. Subjects are to perform 12 injections into the abdomen (6 pairs of injections). Pairs of injections will be evaluated and each pair will contain one BD Nano™ PRO and one Terumo Nanopass® pen needle.

Subjects will not see pen needle labels or be informed which pen needle is being used to inject. The BD Nano™ PRO has a distinct configuration and subjects will most likely notice the difference vs the Terumo Nanopass®. Subjects will not be informed of the Terumo Nanopass® brand, length or gauge.

The pen needle order within the pairs of injections will be randomized for each subject and the pairs will be randomized to various abdominal injection sites within each subject.

Besides being informed of the requirement to insert the pen needles ‘straight-in’ (perpendicular), subjects will be instructed to use their usual injection technique.

3.2 Specification of Study Endpoints

3.2.1 Primary Endpoints

- Injection Pain
  - Each Subject will evaluate pain after completion of each pair of injections using a 15 cm relative Visual Analog Scale (VAS).

3.2.2 Secondary Endpoints

- After each injection:
  - Leakage
    - After saline delivery equivalent to 30U of U100 insulin (0.3mL) and Subject removal of pen needle from body, Study Staff will use the provided materials and scale to absorb leakage from the pen needle tip and injection site to measure the amount of leakage.
    - Leakage will be considered to be present if measurement is equivalent to or greater than 5% of dose (equivalent to or greater than 1.5U of U100 insulin – equivalent to ≥0.015g)
  - Bending – patient-end cannula
    - Study Staff will use a provided needle bend scale and visually inspect pen needles to determine the presence of bending. If present, study staff will determine and document degree of bend with the provided scale. For the purpose of answering the study objective, needle bend will be considered ≥2 on the bend rating scale.
- After each pair of injections:
  - Injection force
    - Each Subject will evaluate perceived injection force after each pair of injections using a 5-point Likert scale (from 1st injection required much less force to deliver medication to 2nd injection required much less force to deliver medication).

Which pen needle required less force or effort to deliver the dose?				
1st injection significantly less force or effort	1st injection slightly less force or effort	Both injections about the same	2nd injection slightly less force or effort	2nd injection significantly less force or effort

3.2.3 Exploratory Endpoints

- During each injection:

  Injection time – includes the following time periods for each injection

1) Time from when subject 1st pushes injection button to time button fully depressed
2) Time from when injection button fully depressed to when pen needle removed from body
3) Total injection time – the 2 time periods above combined

- After each injection:
  - Breaking
    - Study Staff will record any patient end needle breakage. Breakage is defined as the patient-end metal cannula separated into two pieces.
- After all injections completed:
  - Survey responses
    - Subject completes the following 5-point Likert scale survey (from Disagree to Agree). Subject will be instructed to respond to the questions based on their usual (in-home use) injection experience. Subject responses to survey questions will be tallied.

Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree

- Injection pain affects my level of satisfaction with my treatment.
- Injection pressure needed to deliver the dose affects my level of satisfaction with my treatment.
- Post injection leakage increases my level of concern that I may not be receiving my full dose of medication.
- A bent needle increases my level of concern about the reliability of my injection.

3.2.4 Safety Endpoints

- Occurrence of adverse events will be evaluated, recorded, and followed up as required.

3.3 Acceptance Criteria

Primary Objective:

- BD Nano™ PRO non-inferior to Terumo Nanopass® for injection pain with partially blinded injections based on relative VAS, where -75mm indicates

worse pain for BD Nano™ PRO and +75mm indicates worse pain for Terumo Nanopass® with a non-inferiority criterion of -10mm.

Secondary Objective:

- The BD Nano™ PRO will be evaluated for superiority vs Terumo Nanopass® for leakage, injection force, and bending.
- If the BD Nano™ PRO demonstrates non-inferiority for injection pain for the Primary Objective, compare the BD Nano™ PRO vs Terumo Nanopass® for superiority.

Exploratory Objectives:

- No formal acceptance criterion has been established for the following objectives: time to deliver dose, dwell time, and survey responses after all injections completed.

3.4 Treatment Allocation and Methods to Reduce Bias

3.4.1 Randomization

The order of the pen needles within the pairs and abdominal injection sites for each pair will be randomized across each Subject. Injection site diagram will be provided to assist in complying with site randomization.

3.4.2 Masking/Blinding

Subjects will be blinded to pen needle randomization, order of pairing, and will not be informed of needle type. Since the BD Nano™ PRO and the Terumo Nanopass® are designed differently, subjects will be aware which pen needle type is being used, but not the brand or needle gauge.

3.4.3 Skill and Behavior of Persons Interacting with the Device

Before study participation, without any verbal or written support, all Subjects must demonstrate to the Study Staff proficiency injecting with an insulin pen into an injection model. All subjects will be given up to 10 attempts to demonstrate proficiency. Based on the proficiency checklist, subjects will be required to perform three ‘straight in’ (perpendicular) injections in addition to other required tasks in order to take part in the study injections.

3.5 Stopping Rules

No stopping rules for the study have been developed by the Sponsor. The Principal Investigator is responsible for suspending study enrollment for reasons of Subject/Clinician safety and well-being.

4.0 STUDY POPULATION

This study will enroll a minimum of 55 Japanese American subjects with Type 1 or Type 2 diabetes who use an injection pen system to deliver their insulin and/or Victoza. A minimum of 35 subjects must self-attest to either being born in Japan or having at least one parent or one grandparent born in Japan.

4.1 Inclusion Criteria

Male and female patients will be considered for participation in the study if they fulfill the following conditions:

a. Self-attesting Japanese American adults 18 to 75 years of age (inclusive)
b. Self-attest to Japanese descent
c. Diagnosed with Type 1 or Type 2 diabetes
d. Self-injecting using an injection pen for ≥3 months with any pen needle
e. Injecting a minimum of ≥10 units of insulin and/or Victoza at least once per day
f. Able to demonstrate proficiency using an injection pen into an injection model
f. Able and willing to provide informed consent
g. Able and willing to complete all study procedures

4.2 Exclusion Criteria

Subjects with any one of the following characteristics will be excluded from participation in this study:

a. Not self-injecting (for example injections completed by a family member)
b. Self-injecting with a pen injector for less than 3 months
c. Unwilling to inject into abdomen
d. Unwilling to have hair at the injection area reduced with an electric razor if it is determined the hair will interfere with leakage evaluation
e. Failure to confirm which pen needle (gauge and needle length) subject is currently using. To confirm, subject may be asked to bring their pen and pen needles to the site or site staff may confirm via medical record or pharmacy.
f. Pregnant (self-attestation)
g. Currently taking anti-platelet or anticoagulant therapy (up to 162 mg per day of aspirin is permitted).
h. History of a bleeding disorder
i. History of recurrent dermatological conditions or skin disorder (e.g., psoriasis, eczema)
j. Gross skin anomalies and abnormalities located at or very close to the injection sites that would significantly limit available injection space.
k. History of symptomatic low blood pressure or history of fainting (syncope) during hypodermic injections
l. Use of any analgesic medications within 24 hours of first study injection, and during the study (up to 162 mg per day of aspirin is permitted).

m. A current or previous medical or physical condition that, in the opinion of the investigator, would place the patient at risk or make them unable to perform study procedures or has the potential to confound interpretation of the study results

n. Currently participating in another pen needle study

o. Employed by, or currently serving as a contractor or consultant to BD or any diabetes injectable medication, injection pen, or pen needle manufacturer

5.0 DESCRIPTION OF STUDY PRODUCTS

Pen needles are a component of pen-based injection systems routinely utilized for parenteral administration of medications such as insulin. A pen needle consists of a doubled ended cannula that is assembled into an injection-molded plastic hub using adhesive. The hub has threads, which allow it to be screwed onto the pen-injector device. This allows the Non-Patient (NP) end of the needle to penetrate through the rubber septum of the pen cartridge to create the fluid flow path. The pen needle device interfaces with the delivery site providing a conduit for delivery into the subcutaneous tissue space. Pen needles will be attached and primed per manufacturer's instructions with 0.9% sterile saline. A new pen needle will be utilized for each injection.

5.1 Test Product

- BD Nano™ PRO 4mm x 32G XTW 5-bevel pen needle
  - The BD pen needle to be used in this study has a 32G extra-thin walled cannula with a nominal length of 4mm, and a 5-bevel tip

5.2 Reference Product

- Terumo Nanopass® 4mm x 34G
  - The Terumo Nanopass will be labeled "For Investigational Use Only" as this product is not currently available for sale in the US.

5.3 Ancillary Products

- Sanofi ClikSTAR® Insulin Reusable Pen
  Note: Either a new or cleaned ClikSTAR® Insulin Reusable Pen will be used for each subject depending on site preference. See Appendix 18.3 for Pen Cleaning Procedure).
- Pen needles (for pen/pen needle proficiency evaluation)
- Pen needle removal fixtures
- Electric shaver/razor (if injection area has excessive hair that will interfere with leakage evaluation)
- Antiseptic pads
- Bandages
- Analytical Scale and required ancillary scale supplies (e.g. marble slab, calibrated weight)
- Injection Pads
- Cellulose Spears
- Plastic Falcon Tubes
- 3mL 0.9% Sodium Chloride Injection Cartridges

0.9% Sodium Chloride Injection, (Mfd for Becton Dickinson by Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA).

Placebo Injection Solution: 0.9% Sodium Chloride Injection, 3cc Cartridge. The sterile 0.9% saline cartridges were aseptically manufactured and filled by Baxter Pharmaceutical Solutions LLC using cGMP for Becton Dickinson. The cartridges met all performance requirements, including toxicology and sterility acceptance criteria, outlined in the BD Standardized Cartridge Specification. The sterile 0.9% saline cartridges will be inserted into commercially available pen systems to provide the necessary placebo reservoir.

Note: New pen cartridges will be utilized for each subject and will not be reused between subjects.

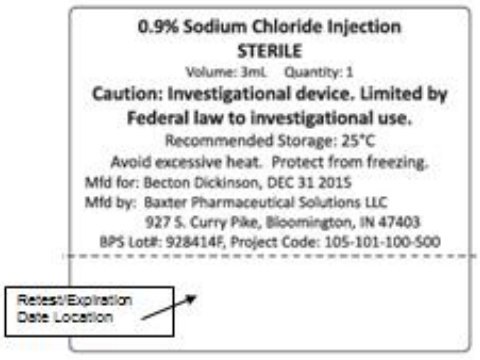
5.4 Product Labeling

Investigational devices (or the immediate packaging) shall be labeled in accordance with regulatory requirements, including the following statement: “CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use.” The BD Nano™ PRO unit label, at minimum on its immediate package, must indicate “For Investigational Use only”, with full statement on the outer packaging. The Terumo Nanopass®, must also indicate “For Investigational Use only”, with full statement on the outer packaging. Refer to Study Supply Plan for further details on labeling requirements and saline cartridges process/certification.

For BD Nano™ PRO investigational products, box labeling will also include at a minimum:

- Product Identification
- Manufacture name and location
- EWO/Batch#
- Use by/expiration date
- Sterility Claim (sterile or non-sterile)
- “For Investigational Use only”

Saline Cartridge Label Content



All other ancillary products will be supplied as labeled by the manufacturer.

5.5 Maintenance and Storage of Study Products

All study products will be stored according to the manufacturer's instructions. Refer to section 11.0 of the protocol for additional instructions regarding product disposition during the study and upon study completion (e.g., disposal, return or destruction, defective products).

6.0 STUDY METHODS

6.1 Screening and Enrollment

Before study start, investigational Site will ensure the following:

1. Analytical scales for leakage assessment are set up and calibrated by trained personnel.
2. All Study Staff assigned to the following specific tasks will be trained and demonstrate proficiency with procedure:
    a. Set up pen/pen needle system
    b. Timing injection duration
    c. Leakage measurements
    d. Measure needle bend
    e. Needle removal

If site cannot confirm which pen and pen needle (gauge and length) the subject is currently using, the subject must bring their injection delivery system(s) (pen and pen needle) with them to the Site. Subjects will also be asked to wear comfortable clothes to the Site on study day to enable easy accessibility to injection site area.

Prior to study participation, every potential Subject must provide written informed consent and will be assigned a Subject number. After being presented with an overview of the study procedures, each Subject will be given ample time to review the consent form and ask any questions about the procedures. If the Subject agrees to participate in the study he or she will sign the Informed Consent.

This study requires one subject visit of approximately 60-120 minutes. Once consent has been obtained the following information will be collected and procedures will be performed to determine whether the subject meets the eligibility requirements.

6.1.1 **Demographics/Diabetes History**

Subjects will be asked a number of background and demographic questions to ensure they meet the study-specific eligibility criteria. The PI or Investigator will review the medical history information self-reported by the Subject; this information will be recorded in the source documents. Information collected will include, but is not limited to age, gender, ethnicity and diabetes history (Type 1 or Type 2 diabetes, current injection therapy, current pen needle, typical injection site(s)).

6.1.2 **Visual Inspection of Injection Site**

A visual assessment of the injection site area will be performed to determine if any obvious skin anomalies or imperfections that would significantly limit available injection sites, (e.g. redness, swelling, moles, marks, bruises, cuts, abrasions, discoloration, tattoos, masses,

lipohypertrophy and or any other abnormalities). Study Staff will determine if the hair at the injection sites will need to be removed (with provided electric shaver) prior to injections. Note: excessive hair must be removed to allow measurements of leakage.

6.1.3 **Proficiency**

Subjects will be asked to perform up to 10 mock injections into an injection pad with a provided saline pen to demonstrate proficiency in performing pen injections. A subject will be considered proficient once they have achieved 3 proper injections (e.g. injection 'straight in' (perpendicular)) in addition to other tasks listed in the proficiency checklist. With a pen needle pre-attached and primed by Study Staff, the Study Staff will use a checklist to determine successful proficiency of the Subject to perform an injection using the ClikSTAR Pen. If the Subject is unable to demonstrate proficiency, s/he will be discontinued from the study.

6.1.4 **Randomization**

Upon successful completion of proficiency, each Subject will be assigned a randomization number.

6.2 Study Procedures

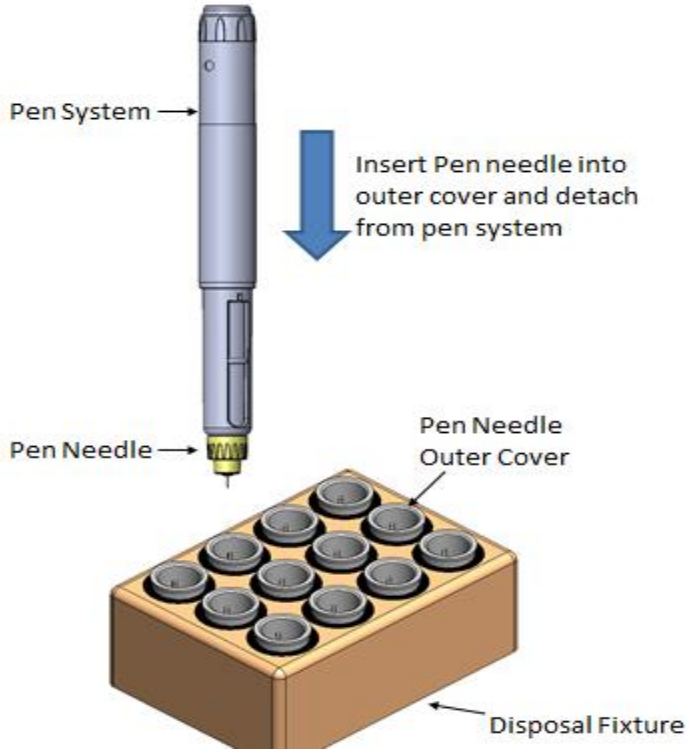
6.2.1 Injections

- Subjects will be informed that "these pen needles are to be inserted 'straight-in" (perpendicular)Subjects will be provided with an Insulin Reusable Pen with saline cartridges in place and the pen needles attached, primed, and set to 30U. (A new ClikSTAR® Insulin Reusable Pen will be used for each subject at specific sites; subjects at remaining sites may use a new or cleaned ClikSTAR® Insulin Reusable Pen).
- Each injection pair will include:
    - 1 pen with the BD Nano™ PRO pen needle
    - 1 pen with the Terumo Nanopass® pen needle
        - Using their usual injection technique, Subjects will inject saline with the pair of pens into their abdomen per Study Staff instruction and according to the randomization schedule.
        - *If subject inserts at an acute angle or uses a skin pinch up, it is allowable under this study protocol but should documented on the study source.*
    - The location of the injection sites will be randomized
    - Each injection will be at least 1 inch from the previous injection

- During needle injection, Study Staff will record two times:
    - From initial pressing of injection button (dose set knob), to button fully depressed
    - From initial pressing of injection button to the removal of the needle from body

Immediately after each injection the following evaluation will be performed:

- Study Staff will use the provided materials and scale to absorb leakage from the pen needle tip and injection site to measure the amount of leakage (refer to Appendix 18.1 for leakage measurement procedure). If any bleeding is observed, this will be noted and leakage measurement will only be collected from the pen needle tip. Leakage measurement amounts will not be discussed in the presence of the Subject.
- Study Staff will visually inspect each needle for the presence of bending and/or breakage. If no bending is visually observed, Site Staff will record a score of "0" and the pen/needle will be placed in the pen needle disposal fixture.



- If bending is visually observed, the pen/pen needle **will be placed on the bend scale** (refer to Appendix 18.2). The degree of bending will be assessed and scoring recorded by Study Staff. Post scoring, the pen/needle will be placed in the pen needle disposal fixture. The pen needle disposal fixtures, along with all used pen needles, will be returned to the Sponsor.
- The Subject will then inject the subsequent pen/pen needles into the site according to randomization schedule for a total of six pairs (total of twelve injections)

After each pair of injections

- Subjects will complete a 15 cm relative VAS for injection pain and Likert-scale assessment for perceived injection force

After all injections completed

- Additional survey questions to be completed

Study staff will follow the same procedures for each pen/pen needle set as noted above.

6.3 End of Visit and Study Completion

- The subjects will be discharged from the Site following completion of the study procedures, when their injection sites show no evidence of bleeding, and when they are comfortable leaving the Site.
- Subjects will be instructed to contact the PI or designee if they experience any new, or worsening signs and symptoms at the injection sites after leaving the Site.
- All adverse events occurring with Subjects during the study will be recorded and followed until resolution as appropriate.

7.0 INTERRUPTION OR DISCONTINUATION OF PARTICIPATION/TESTING

7.1 Discontinuation of Study Subjects

Subjects may request withdrawal from the study at any time or may be withdrawn at the discretion of the Principal Investigator for any of the following reasons:

- Adverse Event/Concurrent Illness
- Noncompliance with study requirements or restrictions
- Failure to meet ongoing inclusion criteria, or development of an excluding condition
- Protocol deviation
- Withdrawal of consent
- Subject is lost to follow up
- Administrative issues
- Any other reason which, in the opinion of the PI, makes the Subject's participation in the study not in his or her best interest.

7.2 Discontinuation Visits and Follow-up Procedures

For Subjects discontinued due to adverse events, 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.

7.3 Replacement of Discontinued Subjects/Specimens

Recruitment of 60 Subjects is anticipated to accommodate potential subject attrition.

7.4 Retention of Data from Discontinued Subjects/Specimens

No data will be collected from Subjects/specimens after the point of discontinuation except as needed to follow ongoing adverse events. All study data collected from the Subject up to the point of discontinuation will be recorded on the Case Report Form, entered into the study database, and included in subsequent analyses, as appropriate.

8.0 RISK / BENEFIT ASSESSMENT

8.1 Potential Risks

The risks to the Subject are non-significant and the findings may reveal information that may improve medical care for persons with diabetes. The potential benefit to medical practice outweighs the non-significant differential risk experienced by the study Subject compared with current standard of care. As a result of inserting a pen needle, Subjects may experience pain, bleeding, or local infection. However, given the size of the investigational pen needles (4mm x 32G or smaller) and the procedures being used in disinfecting the skin and pen devices prior to inserting the pen needle, these risks are negligible.

Risks associated with a pen needle injection may include:

- Discomfort or pain
- Fainting
- Bleeding
- Bruising
- Redness
- Infection

8.2 Potential Benefits

There are no direct benefits to the Subject for participation in this study. The findings may reveal information that will allow for a better understanding of pen needles, and thus may improve medical care for persons with diabetes.

9.0 SAFETY

9.1 Adverse Event Definitions

Adverse Event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease in a Subject that is temporally associated with the use of an investigational product or procedures, even if the event is not considered to be related to the study product or procedures.

This includes events not seen at baseline and events that have worsened if present at baseline. The term AE will refer to all adverse events (serious and non-serious) occurring during participation in a study of either investigational devices and/or drugs.

Serious Adverse Event (SAE): An SAE is any AE occurring during study participation that results in any of the following outcomes:

- Death
- Life Threatening (refers to any event in which the Subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Hospitalization or prolongation of a hospital stay
- Persistent or significant disability or incapacitation (refers to any event which results in a substantial and/or permanent disruption of the Subject's ability to carry out normal life functions)
- Required intervention to prevent permanent impairment/damage

- Congenital anomaly/birth defect
- Important medical event that may require intervention to prevent one of the preceding conditions.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects (21CFR-812.3(s)). Refer to Protocol Section 8.1 (Potential Risks) for a list of *anticipated* adverse events, signs or symptoms.

9.2 Adverse Event (AE) Management

Subjects will be questioned in an open-ended manner throughout the conduct of the study as appropriate for any new or worsening undesirable signs or symptoms they may have experience since being exposed to the study product. Elicited signs and symptoms must be comprehensively documented on the appropriate source documentation.

Each sign, symptom, disease or illness reported must be evaluated by the Investigator or designee to determine if it meets the definition of an Adverse Event.

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.

Some reported or observed signs and symptoms are inherent to subcutaneous injection and are likely to occur transiently for nearly all Subjects in this study. Such signs or symptoms will not be considered AEs as long as they are mild (transient, easily tolerated, no interference with daily activities) and the Principal Investigator agrees. The following will not be not be considered AEs:

- Mild, self-limited pain, swelling at the injection site and presence of wheals
- Mild bruising at the injection site
- Mild self-limited bleeding at the injection site

However, these signs and symptoms ***must be considered AEs and*** documented on the Adverse Event CRF should any of them occur in such a way that the extent or nature of the experience exceeds that normally associated with the procedure, as judged by the Subject to be excessive pain, bruising or bleeding.

All needle breaking that results in a cannula remaining in the body either partially or fully, ***must be considered an AE*** and documented on the Adverse Event CRF.

9.3 Assessment of Adverse Events (AEs)

All AEs must be assessed for Seriousness, Severity, and Relationship. All AEs, regardless of classification, must be comprehensively documented in the CRF and on the SAE form, if applicable, and reported to BD. This includes AEs related to marketed study products. The following information about the event is to be reported on the AE CRF:

- Seriousness, classified as: Non-Serious or Serious
- Severity, classified as:
  - Mild: Transient symptoms, easily tolerated, no interference with daily activities
  - Moderate: Marked symptoms, moderate interference with daily activities, tolerable
  - Severe: Considerable interference with daily activities, intolerable
- Relationship to the study product or study procedures:
  - Not Related: Evidence suggests absolutely no possible causal relationship between the event and the investigational study device (or procedures).
  - Unlikely Related: Evidence suggests that other possible causes or contributing etiological factors may have caused the event other than the investigational study device (or procedures).
  - Possibly Related: Evidence suggests a causal relationship between the event and the investigational study device (or procedures) cannot be ruled out
  - Related: Evidence suggests a reasonable causal relationship between the event and the device (or procedures) is likely

In addition, the following should be recorded for each AE:

- Action(s) taken to remedy the AE, including change in study treatment or participation, or medical/surgical treatments
- Duration of the AE from onset through resolution, as applicable
- Cause (including suspected product/procedure and/or other cause)
- Outcome of the event, including resolution and sequelae, as applicable

9.4 Additional Procedures for Assessing & Reporting Serious Adverse Events (SAE)

SAE criteria are specified in Section 9.1. All SAEs must also be assessed by the Investigator and Sponsor Medical Monitor to determine whether an SAE is expected or unexpected. An adverse event will be considered unexpected or unanticipated if the nature, severity or frequency of the event is not consistent with the risk information previously described in the protocol, Informed Consent, or Investigator's Brochure (if applicable).

Any adverse event meeting the criteria for 'Serious', regardless of the Investigator's opinion of expectedness or relationship to the study product, must be reported to BD within 24 hours. The Investigator or designee must report the event by telephone or email to the Study Monitor. In addition to reporting the SAE to the Study Monitor, the Investigator must also submit a completed SAE form to the BD Trial Safety Dept. via fax or email listed below within 24 hours of receipt of the information.

- Safety Email: BD_Trial_Safety@BD.com
- Safety Fax Line: (US) 1-201-847-5688

Medical questions about study safety issues and serious adverse events can be directed to the Sponsor Medical Monitor.

9.4.1 Reporting Obligations to IRB/EC and Health Authorities

The Investigator must report any adverse events which are serious, unanticipated/unexpected and probably or possibly related to the study product or procedures to the reviewing IRB/EC.

This report must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event.

The Investigator may also have additional responsibilities for AE reporting to their governing Health Authority which they are responsible for identifying and fulfilling.

The Sponsor will provide results of any evaluation of an unanticipated/unexpected adverse device effect to appropriate Health Authorities, to all Investigators, and to all reviewing IRB/ECs within 10 working days after the Sponsor is notified of the event. If the Investigator wishes to assume responsibility for filing reports of evaluation results to their own IRB/EC in lieu of the Sponsor, they must notify the Sponsor in writing of this preference and must retain evidence of their compliance with this requirement.

BD will comply with all other Sponsor safety reporting requirements and timelines for other entities (e.g., Data Safety Monitoring Boards) and local health authorities in other countries where this study or other studies with the same product are being conducted, in compliance with study procedures and applicable local regulatory requirements and BD Standard Operating Procedures.

10.0 INCIDENTS

A Clinical Study Incident is defined as any problem or issue involving the investigational product(s), reference methods, associated procedures or equipment, or represents a product-related injury (or potential for injury) to study Subjects or personnel as a result of execution of this protocol. Clinical Study Incidents may adversely (or potentially adversely) affect human safety, the integrity of the evaluation data, or the operation of devices or systems, and warrant prompt attention.

Incidents involving injury to study Subjects will also be reported as Adverse Events (refer to Section 9). Examples of Clinical Study Incidents that are not Adverse Events might be **mislabeling or adulteration of the investigational device, equipment or device malfunctions, and errors in the device instructions, damage to devices caused by shipping or handling or improper storage, or injury to study personnel due to execution of the protocol**. If appropriate, an Incident may also be documented and reported as a protocol deviation.

Study-specific procedures for reporting Incidents, as well as adverse events and protocol deviations, will be provided to the study Site prior to study execution. The Monitor should be contacted immediately when the Site becomes aware of or suspects any defective or malfunctioning product. This includes:

- Products that are involved in Study Incidents,
- Products that are found to be expired, damaged or defective,
- Products that are possibly the cause of an adverse effect, regardless of whether the product was believed to be damaged, defective or malfunctioning.

Such products (whether investigational or marketed) should be segregated and returned with appropriate documentation to the BD address below, unless instructed otherwise by BD. The Study Monitor should be contacted with any questions regarding return of study products. BD will supply mailing kits specifically intended for product contaminated with potentially bio-hazardous material.

11.0 RETURN OR DESTRUCTION OF STUDY PRODUCT

Unless instructed otherwise by BD, the Investigator will return all used pen needles (secured in the provided system), unused or unopened test, reference, and ancillary study products to BD. At the conclusion of the study, and as appropriate during the course of the study, any products, supplies or BD equipment that are required to be returned will be shipped to BD at the address below, unless instructed otherwise:

Falguni Patel
Becton, Dickinson and Company
1 Becton Drive, G334L
Franklin Lakes, NJ 07417
201-847-4688

11.1 Defective or Failed Study Products

DFSP: The term DFSP generally refers to any damaged, malfunctioning, or failed product (confirmed or suspected) identified at the investigational Site. DFSP includes:

- Products that are involved in Study Incidents,
- Products that are found to be damaged or defective,
- Products that fail or malfunction during the study,
- Study products rendered unusable due to Subject/patient/Site Staff mis-use or improper storage conditions,
- Products that are possibly the cause of an adverse effect, regardless of whether the product was believed to be damaged, defective or malfunctioning.

The Monitor must be contacted immediately when the Site becomes aware of any DFSP. All DFSP (whether investigational or marketed) should be segregated and returned with appropriate documentation to the BD address above, unless instructed otherwise by BD. The Study Monitor should be contacted with any questions regarding return of study products. BD will supply mailing kits specifically intended for product contaminated with potentially bio-hazardous material.

Depending on the intended use of the study products in the study (e.g., if assessing failure modes), there may be exceptions or additions to the requirements for DFSP/Incident documentation; these will be described in this protocol or the study-specific Monitoring Plan.

12.0 DATA COLLECTION AND MANAGEMENT

12.1 Source Documents

Source data includes all information in original records (and certified copies of original records) of clinical findings, observations, or other activities (in a clinical study) used for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies) and are used to verify the authenticity of information recorded on the Case Report Form (CRF). Typical source documents include the hospital chart, medical office file, laboratory report, clinician notes, patient record, recorded data from automated instruments or other documentation prepared and maintained by the investigator/staff or ancillary services which contains a record of all observations and other data pertinent to the investigation on a study Subject.

The investigator is required to maintain original source documents at the Site. Should an original source document (e.g., an instrument printout, direct entry CRF) need to be forwarded to BD for data entry, the Site must retain a clearly designated certified copy. The Study Monitor will confirm that procedures for copy certification have been established at the Site prior to transmittal of any original source documents.

12.2 Case Report Forms (CRF)

The case report forms (CRF) will be provided by the Sponsor. The term "CRF" as used in this protocol may refer to traditional paper CRFs, or electronic case report forms for electronic data capture (EDC), as determined by the Sponsor.

The Investigator may delegate CRF completion to study personnel. However, the Sponsor must be apprised in writing of the name of such persons and the scope of their authority. The Principal Investigator or designee is obligated to review each CRF page and sign or initial the indicated pages using ink or for EDC, an electronic signature. An individual record will be kept for each Subject that provided informed consent.

All entries to a paper CRF should be made clearly in black or dark blue indelible ballpoint pen to ensure the legibility of self-copying or photocopied pages. Corrections are made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

CRF entries will be compared to source documents by the study monitor or designated personnel. Unless specified otherwise, all information on the CRFs must be traceable to original source documents.

12.2.1 CRF as Source Document

In this study, the following CRFs may serve as original source documents:

- Visual Analog Scale for pain
- 5-Point Likert for injection force
- Demographics/Diabetes History
- Subject Questionnaire(s)

12.2.2 CRF/Data Transmittal

Instructions for CRF Transmittal will be provided to the Site at Study Initiation. Specific procedures may be described in a study-specific Monitoring Plan.

12.3 Data Management and Storage

Data Management will be performed by the Sponsor. Data from completed CRFs will be entered into a controlled database and the database verified for accuracy against the CRFs, when applicable. If electronic data capture is utilized, the electronic records entered at the Site will be entered directly into the controlled database. Data security is ensured through password protection, limited access, audit trails, and regular backups of the data. Upon completion of the

study and verification of data, data will be screened for accuracy and completeness, after which the database will be locked from any additional changes. A copy of the locked database will be provided to the GCD Statistics Department for statistical analysis.

13.0 STATISTICAL METHODS

Statistical methods will be detailed in a Statistical Analysis Plan. Any deviations from the original statistical plan will be justified and described in an amended statistical analysis plan and/or the protocol, or in the final statistical report and clinical study report.

13.1 Sample Size Determination

Leakage data is currently being used to calculate sample size.

Based on previous study data (BDT-2P00116) where leakage ≥1.5U was observed in 20/298 (6.7%) of injections performed with Terumo Nanopass® and in 3/297 (1%) of injections performed with BD Nano™ PRO, a simulation was performed (code found in SVN repository under DBC-18PENDL01\Stat\Sample Size\ Bayesian prior proportion R) indicating that 292 injections per each pen needle type would provide 90% power to show BD Nano™ PRO superiority to Terumo Nanopass®. If each Subject tests 6 pairs of pen needles, 292 injections per each pen needle requires 49 subjects (rounded to 50 subjects). 50 Subjects will generate data for 600 pen needles: 300 pen needle pairs; 300 BD Nano™ PRO and 300 Terumo Nanopass®. A 10% buffer was added (to compensate for subject attrition or unusable data), leading to a planned enrollment number of 55 subjects.

Pain: Assuming the SD for relative VAS is ~50mm (based on DBC-17NUCLS07), a sample size of 300 pairs (50 Subjects × 6 pairs) has >90% power of passing a -10mm NI criteria, assuming a true average of -0.5mm in favor of Terumo Nanopass® (based on a 2-sided 95% CI for the mean).

13.2 Data Evaluability

All data collected will be analyzed and reviewed for possible exclusion based on significant outliers or protocol deviations.

Analyses of relative data will only include pairs where both injections were completed.

13.3 Statistical Methods

Descriptive statistics (number of observations, mean, and standard deviation, minimum and maximum) will be calculated and presented for all quantitative responses. Frequency tables with number of observations, percentage of total and 95% confidence interval (score method) for the percentage (as applicable) will be created for discrete responses.

Analysis for relative VAS pain: a two-sided 95% confidence interval will be calculated for the average rating. A modeling approach may be used to adjust for the pair order effect, BD order effect within pair (due to the often-observed bias towards favoring the last pen needle used in a pair), abdomen site effect and random subject effect. Results will be tested for non-inferiority, followed by superiority:

If the lower bound of the CI is > -10mm, we can conclude in non-inferiority
If the lower bound of the CI is > 0mm, we can conclude in superiority

Analysis for injection force via 5-point Likert scale: the responses will be converted to ratings of -2 – 2 (where positive ratings favor BD) and a two-sided 95% confidence interval will be calculated for the average rating. A modeling approach may be used to adjust for the pair order effect, BD order effect within pair, abdomen site effect and random subject effect. Results will be tested for superiority:

If the lower bound of the CI is > 0, we can conclude in superiority

Responses will also be converted to 3 categories: favoring Terumo Nanopass® (negative ratings), no difference (0 ratings) and favoring BD Nano™ PRO (positive ratings) and the difference in percentage of responses with a preference for BD vs Terumo needle calculated, adjusting for the "no preference" category.

Analysis for needle bending and leaking: analysis will be performed using a binary logistic regression with random subject effect and fixed pen needle effect, pair order effect, PN order effect within pair and abdomen site effect. The average difference in percentage of occurrence with BD PN and Terumo PN will be calculated with 95% confidence interval and assessed for statistical significance. The upper bound of the confidence interval will be compared to 0: superiority will be concluded given that the upper bound of the 95% confidence interval for the difference in proportions is < 0%.

Analysis for time to deliver and dwell time: A mixed effect model will be used (fixed effects of pen needle type, abdomen site, order of pair, order of pen needle within pair and random Subject effect) to estimate average difference (BD PN – Terumo PN) in time to deliver and dwell time. The upper bound of the confidence interval will be compared to 0: superiority will be concluded given that the upper bound of the 95% interval for the average difference is < 0 seconds.

Other exploratory endpoints will be summarized.

13.4 Demographics/Other descriptive information

Demographic variables will be summarized for all subjects in each study group. Count, mean, standard deviation, median, min, and max values will be calculated for all continuous variables. Count and percentage will be calculated for the categorical variables. Subject disposition will be tabulated.

13.5 Safety Analysis

Data listings will be provided for any adverse event and serious adverse event. Adverse events will be summarized descriptively by pen needle and study subgroup.

13.6 Interim analysis

No interim analysis is planned under this protocol.

13.7 Additional analyses

No additional analyses planned under this protocol.

14.0 QUALITY CONTROL AND ASSURANCE

14.1 Accountability of Study Products

Investigational 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 Subjects (or used for specimens) properly enrolled in the study. The Investigator must maintain records of receipt, disposition, return and/or destruction of all study products. All investigational study products released to the Site must be accounted for at the unit level prior to study close out, regardless of disposition. The Study 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.

14.2 Monitoring

BD, the study sponsor, will designate trained and qualified personnel to monitor the progress of this clinical study in accordance with BD Monitoring SOPs and the study-specific Monitoring Plan. A pre-study Site qualification visit will be conducted to assess the adequacy of the Site facilities and staff with respect to study requirements.

Prior to study start, a study initiation visit will be conducted to provide training to Site Staff with regard to the protocol, the completion of study documentation and Case Report Forms (CRFs), the monitoring schedule, and all regulatory requirements. During the study, routine monitoring visits will be conducted to assure the Site continues to adhere to the protocol, the investigator agreement, and regulations regarding conduct of clinical studies. Assessments will be made regarding the Subjects' protection and safety, when relevant, as well as the quality, completeness, and integrity of the data. The Study Monitor will assist the investigative Site with query resolution and will perform Site close-out activities once all queries have been resolved.

Additional visits may be carried out depending upon Site activity and performance. The Investigator must agree to the inspection of all study related records and give direct access to source documents for verification of data on CRFs.

The Investigator is responsible for ensuring that any Site-owned equipment required for use in the study is properly installed and maintained (e.g., inspected, calibrated, alarmed). Documentation of equipment maintenance procedures must be available for review by the Monitor.

14.3 Audits and Inspections

If the study is selected for audit by the Sponsor or if there is an inspection by the appropriate Health Authorities, then the Investigator and 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 Subject's anonymity must be safeguarded and data checked during the audit remain confidential.

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

14.4 Protocol Deviations

Protocol deviations are not permitted and should be implemented prospectively as a protocol amendment whenever practical or appropriate, unless required to protect the safety and well-being of the Subject. The Investigator must notify the Sponsor immediately of any such deviation resulting from the need to protect a Subject.

Protocol deviations (other than those required to protect the safety and well-being of a Subject) may impact the evaluability of study data, and may place Subjects at risk. If the Investigator or their staff inadvertently deviates from the study plan, the Investigator should implement appropriate corrective and preventive procedures, and should notify the Sponsor at their earliest convenience. Significant deviations may also need to be reported to the IRB/EC and local health authority.

The Study Monitor will evaluate records of study conduct at the Site to identify any deviations, and will also report them to the Sponsor. 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 the Site and withdrawal of study product may be necessary.

15.0 ETHICAL AND REGULATORY STANDARDS

15.1 IRB/EC

An appropriate IRB/EC must review this protocol, the Informed Consent Form (if applicable), and any other supporting study documents which affect Subject or study personnel safety, prior to study initiation at an investigational Site. No investigational Site may begin the study until the IRB/EC has given its written approval, signed by the IRB/EC chairperson or authorized personnel, and a copy of the approval letter and the approved Informed Consent Form (if applicable) has been provided to the Sponsor.

15.2 Informed Consent

Prior to giving informed consent, each candidate will have the opportunity to review the study procedures, risks and benefits and ask any questions he or she may have regarding the study. Before enrollment, each Subject must give informed consent, documented by signing a written form, created and approved in compliance with 21 CFR Part 50.25 and 21 CFR Part 56. Each Subject should be given a copy of the signed informed consent document.

15.3 Confidentiality of Data

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and BD and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating Subjects. Subject confidentiality and anonymity

will be maintained at all times by removal of all identifiers from any data, clinical samples or documentation submitted for this study.

Any data collected meeting the definition of PHI will be collected and maintained using the designated authorizations and following all privacy procedures as specified in the applicable health authority regulations.

BD will maintain the security and confidentiality of all clinical study data sent to BD. BD clinical study databases will not be shared with any third party without the express written consent of the Principal Investigator and/or Site.

The Study Monitor or other authorized representatives of BD may inspect all documents and records required to be maintained by the Investigator. The Site will permit access to such records. BD and the Site may be required to provide regulatory agencies access to clinical study data and records, as well as source documents.

All other agreements as to confidentiality by BD, the Principal Investigator, and the Site may be found in the Confidential Disclosure Agreement and the Clinical Trial Agreement.

15.4 Protocol Modifications

Amendments to the protocol will not be implemented without agreement from the Sponsor and prior submission to and written approval from the governing IRB/EC, except when necessary to eliminate an immediate hazard to the Subject. Notice of an emergency modification shall be given to the Sponsor and the reviewing IRB/EC as soon as possible, but in no event later than 5 working days after the emergency occurred. Protocol amendments may affect Informed Consent Forms for current and future Subjects.

Minor changes to the protocol, such as correction of typographical errors or changes in personnel names (other than the PI) or contact information will be processed as administrative changes. Administrative changes will be submitted to the governing IRB/EC but implementation of the administrative change may proceed without prior IRB/EC approval, unless so required by the IRB/EC or Site SOPs.

15.5 Study Discontinuation

BD reserves the right to temporarily suspend or prematurely discontinue the study at a single Site or at all Sites at any time and for any reason. If such action is taken, BD will discuss the reasons with all Investigators (the Investigator). If the study is terminated or suspended due to safety reasons, the Sponsor will inform the health authorities as required, and provide the reason(s) for the action. Investigator(s) must inform their IRB/EC promptly and provide the reason(s) for the suspension or termination.

15.6 Clinical Study Registration

In compliance with Title VIII of Public Law 110-85, known as FDA Amendments Act of 2007 (FDAAA), BD will register all applicable studies and disclose study results in a publicly accessible database, e.g. the ClinicalTrials.gov web site. Applicable studies will be registered no later than 21 days after commencing enrollment. Study results for applicable studies will be posted to the website within 12 months of the last Subject visit for collection of primary outcome data, or after health authority approval for previously unapproved devices. BD has responsibility for determining whether this study qualifies as an “applicable” study under the law, and if so, will take responsibility for registration and disclosure as required by law.

15.7 Publication of Results

BD believes that results of applicable clinical studies of our products should be published in peer-reviewed literature in a timely, accurate, complete and balanced manner, regardless of study outcomes. BD is committed to making information public whenever it relates to the safety and efficacy of its marketed products.

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the investigator(s) and the appropriate personnel of BD. Authorship will be based on generally accepted criteria of the ICMJE (International Committee of Medical Journal Editors) and determined by mutual agreement. For multi-center studies, the first publication will be based on data from all centers, analyzed as stipulated in the protocol by BD statisticians, and not based on data from a single Site or a subset of Sites. Investigators participating in multi-center studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other investigators and BD (the sole exception being an unanticipated adverse event that is product-related and which might have clinically significant safety implications for a marketed product or a class of products).

BD must receive copies of any intended communication in advance of publication as specified in the Clinical Trial Agreement. In a timely manner, BD will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and to provide any relevant supplementary information to the investigators.

15.8 Record Retention

If the Principal Investigator or Clinical Center withdraws from the responsibility of keeping the study records, custody must be transferred to a person or entity who will accept the responsibility. BD must be notified in writing of the name and address of the new custodian.

Federal regulations require that a copy of all essential study documents (e.g., IRB/EC approvals, signed informed consent forms, source documents, CRF copies, safety reports, test article dispensing records, etc.), must be retained in the files of the responsible Investigator for a minimum of 2 years following notification by BD that all investigations are completed, terminated, or discontinued, or that the FDA has approved the application (21 CFR 812.140).

16.0 BIBLIOGRAPHY/REFERENCES

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2. Watson PJ, Latif RK, Rowbotham DJ. Ethnic differences in thermal pain responses: a comparison of South Asian and White British healthy males. *Pain.* 2005;118:194-200
3. Palmer B, Macfarlane G, Afzal C, et al. Acculturation and the prevalence of pain amongst South Asian minority ethnic groups in the UK. *Rheumatology.* 2007; 46:1009-1014
4. O Komiyama, M Kawara, A De Laat. Ethnic differences regarding tactile and pain thresholds in the trigeminal region. *The Journal of Pain*. 2007; 8(4): 363-369.
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17.0 PROTOCOL REVISION HISTORY

Version #	Rationale for Change	Section or Page affected	Description of change
1.0	New Protocol		
2.0	Clarified Leakage collection when blood is at the injection site Corrected typo of TM in title	Section 6.2.1 Section 13.2 Section 18.6	Updated language to insure leakage was collected from PN tip, if there was blood at injection site Removed that if blood was observed that the sample would not be included in the data analysis Updated leakage procedure
3.0	Sutter Health has safety concerns on re-using the ClikSTAR® Insulin Reusable Pen for more than one subject.	Section 5.0 and Section 6.2.1	A new ClikSTAR® Insulin Reusable Pen will be used for each subject.
4.0	Revised protocol introduction to justify use of study population Clarified exclusion criteria for subject PN Give sites the option provide each subject with either a new or cleaned ClikSTAR® Insulin Reusable Pen	Section 1.0 Section 4.2e Section 5.3	Revised protocol introduction to include justification for study population and inclusion criterion Updated exclusion to allow site staff to confirm the pen needle the subject is currently using via medical record or pharmacy. Either a new or cleaned ClikSTAR® Insulin Reusable Pen will be used for each subject depending on site preference. See Appendix 18.3 for Pen Cleaning Procedure)

Version #	Rationale for Change	Section or Page affected	Description of change
	Clarified the two times that Site Staff will record during needle injection	Section 6.2.1	Total injection time will be recorded by Site Staff. The time from injection button fully depressed to the removal of needle from body will be calculated by Sponsor
		Section 16.0	References added
	Updated introduction to cleaning procedure section	Section 16.3	Added more detail on steps involved in pen cleaning procedure
	Update Medical Affairs signature and remove Marketing signature	Sponsor Approval Section	Changed MA representative to Shahista Whooley and deleted Marketing approval which is no longer needed.

18.0 APPENDICES

18.1: Gravimetric Leakage Quantification Procedure

Quantification of Liquid from Pen Needle and Skin Surface after Administration

Study Staff preparing and handling plastic tubes and eye spears must do so with gloved hands to prevent transfer of oils from hands to the assembly. Tubes are to be pre-weighed in the morning of the day of use.

Materials:

- Cellulose Spears
- Analytical Balance minimally accurate to 0.000 gm
- Plastic Falcon tubes (to hold spears)

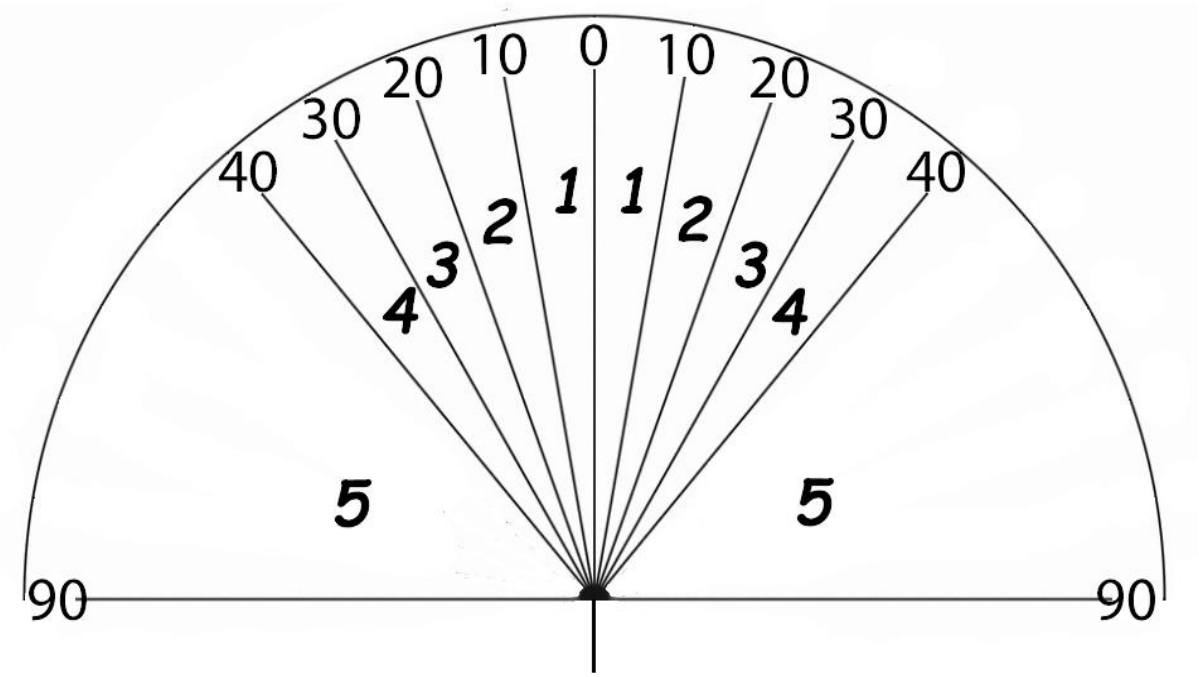
Procedure:

1. Label (number) a set of plastic tubes.
2. Arrange empty, uncapped tubes in test-tube rack and place one spear in each tube, replace caps securely on tubes.
3. Zero the Balance. Balance should be placed in an area with limited activity to avoid vibration.
4. Pre-weigh tube with spear by placing on the scale vertically (resting on its cap). Tubes will be pre-weighed in the morning of the day of use.
5. Record the dry weight on the appropriate data collection form (pre (dry)-weight).
6. Collect fluid from skin and needle tip using the pre-weighed absorbent spear. Do not collect fluid from skin if bleeding
7. Immediately replace spear into tube, replace cap securely and as soon as possible weigh the tube by placing on the scale vertically (resting on its cap) or place in pre-weighed beaker.
8. Record wet weight on the data collection form (post (wet)-weight).
9. Discard tube with eye spear.

18.2 Needle Bending Evaluation

The Study Staff will visually determine if the pen needle is bent. If bent, staff will measure and document needle bending using the provided scale. Post bend scoring, pen needle will be disposed of as appropriate.

Cannula bend scale (example):



Degree of Bend	Score
0° (no bend)	0
> 0° to 10°	1
>10° to 20°	2
> 20° to 30°	3
> 30° to 40°	4
> 40°	5

18.3 Pen Cleaning Procedure

In this study there is minimal risk of transmission of any pathogens through skin contact, as the pen is only in contact with the patient's hands. The pens will be cleaned using the procedure described below after each use using hospital grade bleach-based disinfectant wipes. Any pens contaminated with blood will not be re-used and will be discarded in the appropriate container for destruction.

- The following cleaning procedure will be performed by Study Staff between each Subject use:
- Cleaning the pens is to be completed using hospital grade disinfectant wipes
- **Gloves should be worn while completing this cleaning procedure**
- Clean the pens by wiping all surfaces of the pen with disinfectant wipe. Care is to be exerted that no lint or other particles are left behind during the process.
    - **Use fresh disinfectant wipe for each pen.** Discard wipe after each use.
    - **Air dry the pens for about <u>one minute</u>.**