Cover Page

Protocol Title:	A randomized controlled post-market study to assess the impact of peripheral intravenous catheter length and gauge on catheter indwell duration and haemolysis in human participants using a bilateral, cephalic vein cannulation model.
Document Type:	Clinical Study Protocol
Document Date:	02-Oct-2020
NCT number:	NCT04344314

TITLE PAGE

Protocol Title:
A randomized controlled post-market study to assess the impact of peripheral intravenous catheter length and gauge on catheter indwell duration and haemolysis in human participants using a bilateral, cephalic vein cannulation model.

Protocol Number: BDT-19PIVCAU001
Version Number: Version 4.0

Study Device:

BD Nexiva™ (20G x 1); single port
BD Nexiva™ (20G x 1.75”); single port
BD Nexiva™ (22G x 1); single port
BD Nexiva™ (22G x 1.75”); single port

Study Type: Feasibility
Short Title: Impact of PIVC Length and Gauge on Catheter Indwell Time.

Sponsor Name: Becton Dickinson Pty Ltd

Legal Registered Address:
66 Waterloo Road
Macquarie Park, NSW 2113
Australia

Sponsor Contact:
David Maggs, MD
david.maggs@bd.com

Principal Investigator:
Andrew Bulmer, PhD
Associate Professor of Pathophysiology
a.bulmer@griffith.edu.au

Regulatory Agency Identifier Number(s)
Registered with Australian TGA: ARTG 243114

Approval Date: 22 May 2020
Version History

Version Number	Date	Type
1.0	11 Mar 2020	Original
2.0	15 May 2020	Revision
3.0	28 Aug 2020	Revision
4.0	02 Oct 2020	Revision

SPONSOR PROTOCOL APPROVAL

Signature below indicates approval of the protocol as written.

Individual or function	Name	Signature	Date
Medical Affairs Team Representative	Vincent Hugo, Director, Medical Affairs	*This document is signed electronically in the eTMF system*	
R&D Study Lead	Christopher Rini	*This document is signed electronically in the eTMF system*	
Study Statistician	Didier Morel	*This document is signed electronically in the eTMF system*	
Regulatory Affairs	Kim Geisler	*This document is signed electronically in the eTMF system*	
Project Manager	Erin White	*This document is signed electronically in the eTMF system*	
Medical Safety and Governance / Medical Monitor	David Maggs, M.D.	*This document is signed electronically in the eTMF system*	
Legal Team Representative	Elise Masiee	*This document is signed electronically in the eTMF system*	

PRINCIPAL INVESTIGATOR AGREEMENT 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 Human Research Ethics Committee (HREC).
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 HREC, 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 HREC 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 applicable TGA guidelines and ISO 14155:2011). 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

Abbreviations

ADP	Adenosine diphosphate
AE	Adverse event
aPTT	Activated partial thromboplastin time
BD	Becton Dickinson and Company
BMI	Body Mass Index
CF	Color flow
cfHb	Cell-free haemoglobin
CRF	Case Report Form
CTU	Clinical Trials Unit
C/V	Catheter:vein
EDTA	Ethylenediaminetetraacetic acid
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
IFU	Instructions For Use
INS	Intravenous Nursing Standards
HREC	Human Research Ethics Committee
LLAD	Luer-Lok™ Access Device
MHz	Megahertz
mL	Milliliter
mm	Millimeter
PI	Principal Investigator
PIVC	Peripheral intravenous catheter
PT	Prothrombin
PWD	Pulse wave doppler
RBC	Red blood cell
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SP	Sterile path
TRAP	Thrombin receptor activating peptide
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td>Protocol Title</td><td colspan="2">A randomized controlled post-market study to assess the impact of peripheral intravenous catheter length and gauge on catheter indwell duration and haemolysis in human participants using a bilateral, cephalic vein cannulation model</td></tr>
<tr><td>Short Title</td><td colspan="2">Impact of PIVC Length and Gauge on Catheter Indwell Time</td></tr>
<tr><td>Rationale</td><td colspan="2">Identifying device design factors that increase PIVC indwell time and reduce incidence of haemolysis would minimize patient discomfort (pain, anxiety due to multiple venipuncture) during the course of treatment and reduce associated workload costs (e.g., recollection of haemoglobin-free serum samples, PIVC reinsertion, needlestick injuries) for healthcare institutions.</td></tr>
<tr><td rowspan="3">Objectives and Endpoints</td><td>Objective(s)</td><td>Endpoint(s)</td></tr>
<tr><td>Primary
• Assess patent indwell time between PIVCs of different length and gauge.</td><td>Primary
• Catheter indwell time</td></tr>
<tr><td>Secondary
• Assess haemolysis occurrence based on blood collection device, catheter device configuration
• Blood draw fill time
• Determine the relationship, if any, between catheter blood draw patency indwell time and presence of intra/extravenous thrombi, catheter angle/tip location in situ, catheter length in vessel, vein depth from skin surface, C/V ratio, and vessel anatomy</td><td>Secondary
• Haemolysis: Quantification and frequency of occurrence
• Blood draw fill time
• Incidence of
o Intravenous thrombus (mural, at tip), sheath, vein collapse, presence / location of a valve relative to catheter tip, side branches relative to catheter tip detected via ultrasound
o Extravenous thrombus within catheter hub, needleless connector,</td></tr>
</table>

<table>
<tr><td>Protocol Title</td><td colspan="2">A randomized controlled post-market study to assess the impact of peripheral intravenous catheter length and gauge on catheter indwell duration and haemolysis in human participants using a bilateral, cephalic vein cannulation model</td></tr>
<tr><td></td><td></td><td>extension tubing via visual observation</td></tr>
<tr><td></td><td>• Evaluate changes in vessel dimensions, PIVC position (insertion angle and in situ tip position), and hemodynamics from baseline throughout indwell time</td><td>• Vessel dimensions, blood flow velocity (color and PWD), vessel depth from skin surface, catheter length in vessel, catheter insertion angle, in situ tip position/length</td></tr>
<tr><td></td><td>Exploratory
• Assess incidence of complications prompting device removal
• Evaluate manual flush variability (as applicable) using in-line pressure measurements</td><td>Exploratory
• PIVC Complications: Frequency of occurrence (vein collapse, phlebitis, dislodgement, extravasation, accidental removal)
• Flush pressure profile and duration of flush</td></tr>
<tr><td>Design and Overview</td><td colspan="2">This is a single-centre, open-label, multi-visit, self-controlled study design, in ~40 healthy participants, randomized by gauge of peripheral intravenous catheter (PIVC) device into the lower arm cephalic vein of both arms.

The purpose of this feasibility study is to assess impact of catheter length and gauge on PIVC indwell time over a multi-day (72 hour) period. This study will also evaluate the incidence of haemolysis from PIVC using a LLAD and vacutainer tube (2mL, 6mL) blood collection method compared to venipuncture from the antecubital fossa.

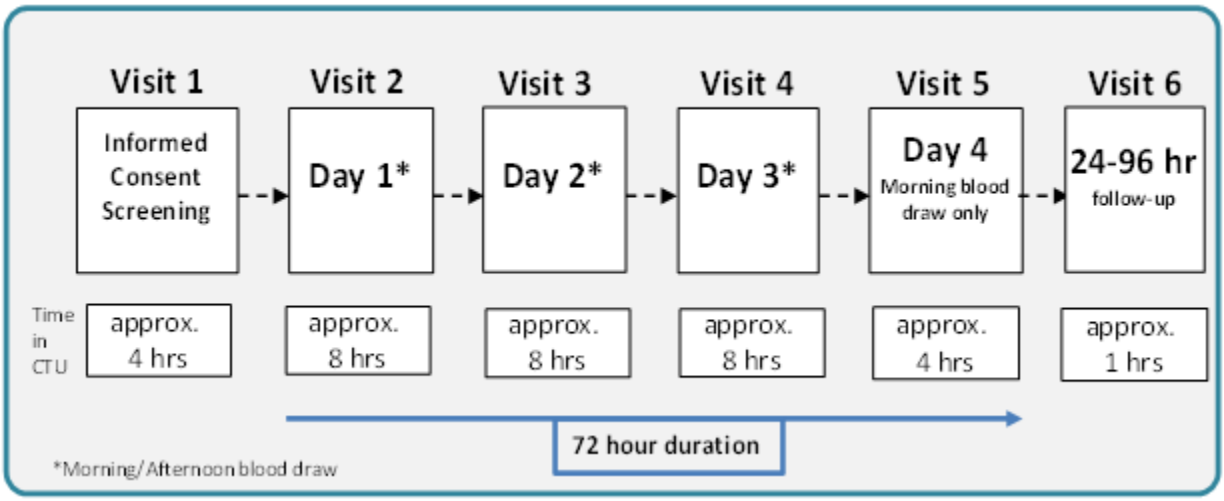
The visit schedule is outlined in the section 1.3.</td></tr>
</table>

<table>
<tr><td>Protocol Title</td><td>A randomized controlled post-market study to assess the impact of peripheral intravenous catheter length and gauge on catheter indwell duration and haemolysis in human participants using a bilateral, cephalic vein cannulation model</td></tr>
<tr><td>Study Device</td><td><table>
<tr><th>Description</th><th>Part Number</th><th>Manufacturer</th></tr>
<tr><td>BD Nexiva™ (20G x 1); single port</td><td>383516</td><td>BD</td></tr>
<tr><td>BD Nexiva™ (20G x 1.75”); single port</td><td>383518</td><td>BD</td></tr>
<tr><td>BD Nexiva™ (22G x 1); single port</td><td>383512</td><td>BD</td></tr>
<tr><td>BD Nexiva™ (22G x 1.75”); single port</td><td>383513</td><td>BD</td></tr>
</table></td></tr>
<tr><td>Participants</td><td>Recruitment and screening of approximately forty healthy (18-65 years old) male or female participants after ethics approval and provision of their informed consent to participate.</td></tr>
<tr><td>Intervention(s)/Procedure(s)</td><td>After screening and enrollment, participants will be randomized in order of their enrollment to either 20 or 22G of the BD Nexiva™ PIVC and order of placement location (left or right arm first). The participant will have both the 1 inch and 1.75 inch PIVCs inserted on Study Day 1 (Visit 2), one into each arm. After successful insertion into the lower cephalic vein of the selected arm, the site will be regularly accessed (twice daily) for phlebotomy and then flushed. The site will be assessed visually for tissue effects, skin reactivity, and pain, and using ultrasound for vessel anatomy/dimensions, catheter tip location in the vessel, color, and PWD. After catheter removal there will be a final inspection of the insertion site and securement dressing, assessing for tissue effect, skin reactivity, and pain.</td></tr>
<tr><td>Investigational Sites</td><td>This study is a single-center study that will be conducted at Griffith University Gold Coast Campus, Clinical Trials Unit in Queensland, Australia.</td></tr>
<tr><td>Data Monitoring Committee</td><td>Not applicable.</td></tr>
<tr><td>Regulatory Status</td><td>Registered with Australian TGA: ARTG 243114</td></tr>
</table>

1.2 Schedule of Activities

Procedure	Screening (up to 30 days before Day 1)	Study Visits (Days, Weeks, etc.)					Notes
		Index Procedure (Day 1)	Day 2	Day 3	Day 4	Follow-up	
Informed consent	X						
Inclusion and exclusion criteria	X						Recheck clinical status before randomization/ study intervention
Demography	X						
Physical Exam (including vital signs)	X						
Medical history	X						
Drug Screening (Urine)	X	X*					*Testing required prior (up to 48 hrs) to Day 1 procedures
Venipunture	X	X					
Platelet Aggregometry	X						
Blood Glucose / Cholesterol, Lipids	X						Fasted blood samples
Complete Blood Count	X						
Ultrasound (cephalic vessels)	X	X	X	X	X		
Randomization		X					
PIVC Insertion		X					
Injection Site Assessment		X	X	X	X	X	
PIVC Securement Dressing Assessment		X	X	X	X		
PIVC Blood Draw/Flush		X	X	X	X		
Flush Pressure Monitoring		X	X	X	X		
AE review		←==========→					
SAE review		←==========→					

1.3 Schema



2 INTRODUCTION

Peripheral intravenous catheters (PIVCs) are key tools required for the management of patient care worldwide. Indeed, more than 80% of patients admitted to hospital will have a PIVC inserted during their stay[1] largely due to their widespread application including drug/fluid administration, monitor blood pressure, blood transfusion, and blood sampling for analytical assays[2,3]. Clinical research has reported early PIVC removal and replacement due to multiple, and complex failure modes encompassing device placement/maintenance, device design, infusate properties, biological response, and patient factors[4]. Further development efforts to identify device and technique factors affecting PIVC function are needed to improve patient outcomes and reduce healthcare costs.

2.1 Background

The rate and prevalence of PIVC failure remains unnecessarily high[5-7] despite the significant advances in PIVC design and a renewed focus on improving clinical techniques. Multiple failure modes (phlebitis, infiltration, occlusion (biological/mechanical/infusate precipitate), dislodgement, and infection) have been identified through review of PIVC failure in clinical research[4]. Recently, using a Computational Fluid Dynamic (CFD) research model, Piper et al.[8] identified multiple variables including PIVC dimensions, PIVC in situ position, and infusion rate could influence catheter survival. Delineating the complex interactions between clinical practice (e.g., infusion rate, PIVC angle of insertion, PIVC tip positioning relative to vessel wall, blood collection equipment, site maintenance), device design (e.g., PIVC gauge and length, biomaterial), and physiology (e.g., vessel diameter, vasospasm, phlebitis, blood flow velocity, RBC fragility) may help to identify the mechanisms that induce thrombosis, haemolysis and, subsequently, PIVC failure.

It has been hypothesized that longer PIVC catheters may extend indwell time based upon catheter tip location within the vessel, increased tip distance from insertion site, and reduced

probability of accidental dislodgement; however there is limited published data investigating the impact of PIVC catheter length on indwell time[9,10]. Identifying device design factors that impact PIVC indwell time and lead to blood damage and/or thrombosis may help to minimize patient discomfort (e.g., multiple needlesticks) and reduce associated costs (e.g., recollection of haemoglobin-free serum samples, PIVC reinsertion) for healthcare institutions – the importance of which should not be underestimated.

An additional related ongoing concern for healthcare institutions is the prevalence of haemolysis (defined as cell membrane leakage or rupture that causes haemoglobin to be released into the plasma) in routine blood samples (3.3%) which can impact patient care and treatment [11-13].

Multiple factors may contribute to increased haemolysis during PIVC blood collection. These include:

- proficiency of the clinician or nurse in phlebotomy techniques [14];
- prolonged application of a tourniquet which can increase red blood cell (RBC) fragility and susceptibility to lysis [15-17];
- the soft biomaterial from which the PIVCs are made (i.e., silicone or polyurethane) which aim to increase indwell time, may collapse (silicone) and increase the negative pressure upon the RBC [18,19];
- the length and gauge of the catheter employed for blood collection [17,20];
- the lubricant (e.g., polydimethylsiloxane) and solvent used for manufacturing that can lead to chemically-induced haemolysis [20];
- increased suction and turbulence during blood draw through a vacutainer which may cause mechanically-induced haemolysis [19,21], although this remains uncertain [22]; and
- the inflammatory status of the patient which can increase the mechanical fragility of RBC making them more susceptible to lysis [23].

The prevalence of haemolysis can lead to erroneous biochemical results including creatine kinase, lactate dehydrogenase, potassium, coagulation testing, iron, aspartate aminotransferase and alanine aminotransferase thus necessitating a second blood draw and laboratory analysis [24]. This can present a potential delay in patient care and increase healthcare cost per patient [25].

The current protocol for drawing blood via venipuncture is inefficient for time-poor nursing staff, taking an average of approximately 5-10 minutes [26]. In contrast, the benefits of performing blood collection via PIVC is highlighted by the endorsement of the Infusion Nurses Society guidelines [27] and include: 1) reduced chance of needle stick injuries for health care workers [28]; 2) reduced pain, discomfort and anxiety for patients [28,29]; and 3) reduced cost of care [12,29]. Nevertheless, many institutions [30] continue to perform venipuncture for blood sampling based on recent studies that indicate increased prevalence of haemolysis via PIVC collection [17,19,28,29,31] which itself increases an economical burden for healthcare institutions [25]. Caution should be used, however, when comparing the effect of blood collection device (i.e., venipuncture vs. PIVC) on haemolysis rates. Wollowitz, Bijur, et al. [17], for example, compared PIVC haemolysis rates between PIVCs and butterfly needles in patients from an

emergency department whereby confounding factors such as inflammatory status of patients, or tip position/angle may have independently contributed to differences in haemolysis rates. Moreover, judicious examination of the data reported [17] indicates that haemolysis rates differed between PIVC gauges (20G Nexiva™, 13.9% haemolysis; 22G Nexiva™ 25.5% haemolysis) thus suggesting that the catheter:vein (C/V) ratio may have also impacted the results reported. More recent evidence [28], however, from an alternative population (i.e., gastrointestinal surgery patients) indicates PIVC blood collection does not impact haemolysis rates or indwell time and is preferable for patients to minimize the pain associated with venipuncture. Collectively, the results from these studies suggest that factors *independent* of blood draw device, including aspiration method (syringe versus vacutainer) may have impacted haemolysis rates.

2.2 Rationale

BD Medication Delivery Solutions is investigating a specific PIVC device design factor (length) that may extend indwell time and consequently enable successful PIVC based blood collection throughout treatment. Identifying device design factors that increase PIVC indwell time and reduce incidence of haemolysis would minimize patient discomfort (pain, anxiety due to multiple venipuncture) during the course of treatment and reduce associated workload costs (e.g., recollection of haemoglobin-free serum samples, PIVC reinsertion, needlestick injuries) for healthcare institutions.

2.3 Risk/Benefit Assessment

Before participants choose to volunteer for this study, the possible risks and benefits will be explained by a member of the research team. The risks associated with the current study are listed below.

2.3.1 Risk Assessment

Anticipated risks listed below are based on known risks for study procedures to both the participant and HCP, (i.e. venipuncture, cannulation, and flush pressure monitoring). Other risks listed below for the study devices as described (listed) in the Nexiva and Diffusics IV Catheters (a-EURA).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Venipuncture • Pain • Nerve Damage • Fainting • Bleeding • Haematoma	The risks that are associated with taking a small amount of blood are minor. A small amount of discomfort is possible during blood collection; however, this is rare, short lived and occasionally cannot even be perceived. In accordance	Infection will be minimized by using sterile needles and equipment, clean gloves, cleaning of participant skin with rubbing alcohol around the site, before collection. Bruising is a negligible risk and will be followed-up upon

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Infection at insertion site • Exposure to blood to either participant or HCP • Needle stick injury to either participant or HCP	with the collection of blood, there is a minor chance of infection at the puncture site. There is also a minor chance of developing a haematoma (bruising) at the site. There is also a possibility of fainting, light-headedness (due to nervous anxiety) after taking blood.	in the days after blood collection by the research team. If the participant is nervous about blood collection, they will be asked about this prior to collection so and necessary precautions taken (i.e., take blood lying down, provide water etc.). Participants will be asked to inform the team of other conditions (e.g. cold/flu, blood clotting abnormalities), so that we can minimize any risk.
Cannulation • Pain • Psychological distress, nervousness/anxiety • Nerve Damage • Fainting • Bleeding • Haematoma • Systemic infection (bacteremia) • Infiltration • Extravasation • Thrombophlebitis • Thrombosis • Local infection/inflammation • Swelling/oedema • Fever/chills • Allergic reaction (adhesive) • Exposure to blood to either participant or HCP • Needle stick injury to either participant or HCP • Pulmonary embolism • Abuse/use of catheter by participant	The risks associated with cannulation include: thrombophlebitis (blood clot and inflammation in/around the vein cannulated), infection, extravasation and can occur and range from 63% in patients receiving IV therapy through a peripheral intravenous catheter[32]. Blood stream infection is a serious but very infrequent complication in PIVCs which occurs in approximately 0.2% of intravenous catheters[4]. Thrombophlebitis is characterized by pain, swelling, redness, or palpable venous mass beyond the catheter tip. There is a minor amount of discomfort associated with catheter insertion of an indwelling catheter. Statistics regarding cannulation risks and adverse reactions are obtained from a hospital environment in patients receiving drug/intravenous fluid therapy who at risk of clotting/infection etc. The size of any thrombus will be assessed using sonography, recorded, and the participant referred to general practitioner for	Pain, nerve damage, and extravasation will be mitigated as an experienced nurse (or equivalent such as a trained phlebotomist) will catheterize the participants according to Infusion Therapy Standards of Practice guidelines[27], and under ultrasound guidance. Infection will be minimized by using an aseptic non-sterile, non-touch technique (ANTT) approach. This includes use of sterile needles and equipment, clean gloves, cleaning of participant's skin with rubbing alcohol around the site, before cannulation. Bruising is a negligible risk and will be followed-up upon in the days after cannulation by the research team. The presence and growth of a blood clot can be influenced by inter-individual susceptibility to clotting/thrombotic risk, in addition to the cannula maintenance protocol. Risks associated with local thrombosis are negligible, however, if the clot enlarges (i.e., to beyond 5 cm in length) it can pose a significant risk to patient health[47], and if that occurs the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	clinical decision. A smaller risk exists that any clot may dislodge and move into the pulmonary circulation, causing a potentially serious and life-threatening pulmonary embolism. The degree of risk is related to the presence of peripheral venous thrombosis and the size of this thrombus, which will be actively monitored in this study. A fibrin sheath may also form around the PIVC, which if dislodged could move to the pulmonary circulation. The risk is minimal, however, as the duration of the study and length of the PIVC is short, limiting the size of any fibrin sheath over the period of investigation. A risk of device dislodgement and therefore, bleeding exists, if the device catches or is intentionally removed. A risk also exists of the participant using the device to access the circulation.	participant will be referred to local health practitioners (i.e. on campus), for appropriate clinical decision. If the participant is nervous about cannulation, they will be asked about this prior to participating so necessary precautions may be taken (i.e., provide water etc.). Risk of dislodgement will be reduced by the use of an adhesive dressing and additional bandage over the site to prevent catching and inadvertent removal of the device. Participants will be provided with care instructions. A tamper evident device will be attached to each catheter and the device tested daily to assess whether deliberate and unauthorized access to the device has been made. Unauthorized access to the device will result in the participant being de-enrolled from the study and devices removed.
Flush Pressure Monitoring • Electrical shock	A real-time, battery-operated data logger device is connected to the pressure transducer, saline within it, and the participant's body. Although the current delivered to this device is minimal (i.e., it is battery operated), a very small risk of electrocution exists from this device.	In order to mitigate these risks, the charger for the monitoring device will be electrically tested and tagged with a safety compliance label confirming accordance with AUS/NZS 3760 standard as per University requirements. Clinically approved pressure transducers will also be used thus minimizing electrical risk to the participant.
Study Product		
• Pain (more than anticipated upon insertion) • Blood loss (minimal, no intervention required/more	There is a potential that the clinician does not fully reseat after breaking system adhesion and the	To mitigate this from occurring, IFU instructs clinicians to push the finger grip and tip shield back snuggly together prior to accessing vessel.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
than minimal, intervention required) • Infection (localized-cellulitis-abscess • Infection (Systemic-Sepsis)	catheter remains over the bevel of the needle during insertion. If IV components fall off or are not tightened properly, could lead to leakage of blood or infusate. There is always a chance that the IV catheter package may be compromised. Mishandling of the product to the extent that exceeds the design intent (e.g., exposure to wet surfaces, sharp implements).	IFU instructs clinicians to carefully check that components are tightened appropriately and secure. In order to mitigate the risk of infection(s), IFU instructs clinicians to check package integrity and not use product if package is damaged, opened, or expiration date has passed.

2.3.2 Benefit Assessment

There are no direct benefits to the participant for participation in this study. The findings may reveal information that will allow for a better understanding of the effects of catheter length/gauge on indwell time and incidence of haemolysis from blood collection, and thus may minimize venipuncture and improve medical care for persons with an indwelling PIVC.

2.3.3 Overall Benefit: Risk Conclusion

Taking into consideration the measures to minimize risk to participants in this study, the potential risks identified in association with the proposed study are justified by the anticipated benefits that may be afforded to participants with the need for an indwelling PIVC. Furthermore, the BD Nexiva catheter is registered with the Australian Therapeutic Good Administration, and in this study, is being used within its approved indication for use. In addition, risks will be minimized through selection of investigators who are qualified and skilled in the performance of venipuncture.

3 OBJECTIVES AND ENDPOINTS

3.1 Brief Description of Objectives and Endpoints

Objectives	Endpoints
Primary	
• Assess patent indwell time for PIVCs of different length and gauge	• Catheter indwell time

Secondary	
• To assess haemolysis occurrence based on blood collection device, catheter device configuration	• Haemolysis: Quantification and frequency of occurrence
• To evaluate blood draw fill time	• Blood draw fill time
• To determine the relationship, if any, between catheter blood draw patency indwell time and presence of intra/extravenous thrombi, catheter angle/tip location in situ, catheter length in vessel, vein depth from skin surface, C/V ratio, and vessel anatomy	• Incidence of: o Intravenous thrombus (mural, at tip), vein collapse, presence / location of a valve relative to catheter tip, side branches relative to catheter tip detected via ultrasound
• To evaluate changes in vessel dimensions, PIVC position (insertion angle and in situ tip position), and hemodynamics from baseline throughout indwell time	• Vessel diameter, blood flow velocity, in situ tip position, extravenous thrombus within catheter hub, needleless connector, extension tubing via visual observation
Tertiary/Exploratory	
• To assess incidence of complications prompting device removal	• PIVC Complications: Frequency of occurrence (vein collapse, phlebitis, venous thrombosis, dislodgement, extravasation, accidental removal)
• To evaluate manual flush variability (as applicable) using in-line pressure measurements	• Flush pressure profile and duration of flush

3.2 Hypotheses for Specific Outcomes

3.2.1 Indwell time

1) The duration of PIVC indwell time will be greater in duration for longer catheters.
2) The duration of PIVC indwell time will be greater for catheters of smaller gauge (larger bore).

3.2.2 Cell free haemoglobin

1) The cfHb concentrations observed in blood samples (all vacutainers) collected from shorter catheters will be greater than that observed in longer catheters over time.
2) The cfHb observed in blood samples (all vacutainers) collected from catheters with a larger gauge (smaller bore) will be greater than blood collected from smaller gauge (larger bore) over time.
3) The cfHb observed in blood samples (all catheters) collected into greater volume vacutainers will be greater than blood collected into smaller volume vacutainers.
4) The duration of PIVC indwell time will be associated with impairments in other secondary and exploratory endpoints

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, single-center, open-label feasibility trial to provide preliminary signals of performance to help make decisions about whether to continue with the development of product enhancements. Four variations of the BD Nexiva PIVC (20G x 1, 20G x 1.75, 22G x 1, or 22G x 1.75) will be placed in the lower cephalic vein of both arms in approximately 40 healthy volunteers; 20 participants with 20G x 1 inch and 20G x 1.75 inch catheters, and second group of 20 participants with 22G x 1inch and 22G x 1.75 inch catheters. PIVC indwell time will be monitored (removal at 72 hrs or upon inability to flush/aspirate) with blood collected by venipuncture (Day 1 only) and via the devices using 2 and 6mL vacutainers throughout the remainder of indwell time.

After 5 participants have completed their final visit, the in-situ catheter positions will be compared to the expected tip position based on the catheter lengths (1 inch versus 1.75 inch for either gauge). Tip position of the longer catheter is expected to reside more horizontally within the vessel. In the event catheter tip position differences are not distinct between catheter device lengths study conduct may be stopped. Additionally, this analysis will be used to refine study logistics associated with device placement, securement, sonographic measurements, and blood sample acquisition/testing over the 72-hour study duration.

Each participant will complete 6 visits: a Screening Visit (V1), followed by 4 Visits (V2-V5) to be started within 30 days after screening, and a 24-96 hour follow-up post catheter removal (V6).

The duration of the study execution is expected to be 5 months.

4.2 Scientific Rationale for Study Design

Given that participant variability (e.g., coagulation and platelet function) may impact study endpoints (e.g., device indwell time and haemolysis)[23], the current study utilizes a simultaneous paired experimental design to assess whether differences in device design (i.e., lengths of 1 inch and 1.75 inch) impact PIVC indwell time; unpaired analysis will be employed to investigate the effects of catheter gauge on PIVC indwell time. PIVC length was selected for paired analysis as it is hypothesized that longer PIVC catheters may extend indwell time based upon catheter tip location within the vessel, increased tip distance from insertion site, and reduced probability of accidental dislodgement. Although gauge is a factor that may impact indwell time, participant screening is conducted to only enroll those with catheter-to-vessel (C/V) ratios no greater than 45%; thus it is anticipated that gauge will have an effect less susceptible to participant variability and was selected for the unpaired analysis. As both device length and gauge are expected to influence haemolysis[17,20] the study design enables evaluation of both design features.

Identification of device design factors that improve PIVC indwell time and decrease incidence of haemolysis during PIVC-based blood collection is of clinical significance due to the associated benefits for the patient (e.g., uninterrupted medical treatment, and decreased discomfort, pain and anxiety)[28,29,33], for the health care worker (e.g., reduced chance of needle stick injuries)[28], and for the healthcare institution (i.e., reduced cost of care)[12,29].

4.2.1 Participant Input into Design

Not applicable

4.3 End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities. N.B. the number of phases completed can vary depending on the longevity of the devices placed.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5 STUDY POPULATION

Participants of clinical trials at the Clinical Trials Unit (CTU) based at the Griffith University Gold Coast campus are recruited through two primary mechanisms: 1) local advertising via digital and paper flyers; and 2) identification of suitable participants in the CTU volunteer registry (database). All advertising in the printed and audio-visual medial has prior approval of the Griffith University Human Research Ethics Committee (HREC). The CTU volunteer registry has been maintained since 2015 and currently contains more than 700 volunteers.

5.1 Inclusion Criteria

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

a. Female or Male
b. 18-65 years of age
c. Not pregnant at time of recruitment within 48 hrs Day 1 procedures (self-reported)
d. Normal coagulation results (prothrombin time 13-17 sec; activated partial thromboplastin time 27-37 sec)
e. Normal platelet aggregation results for ADP, TRAP, and collagen induced maximal amplitude (>70% amplitude over 6 mins)
f. Target cephalic veins readily cannulatable (i.e., ≥ ~2.55 mm to obtain C/V ratio less than 45% as indicated by standard 52 of the INS guidelines[27]
g. Able and willing to provide verbal and written consent
h. Current Medicare card holder

5.2 Exclusion Criteria

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

a. History of pro coagulative state/condition (e.g. previous deep vein thrombosis
b. Current hypertension (e.g., systolic >139 OR diastolic >89 mmHg)
c. Currently on any anti-coagulant or platelet inhibitor medication. Use of NSAIDs and aspirin will be documented however not exclusionary.

d. Hemophilia or any current or history of bleeding disorder or tendency

e. Presence or report of current blood borne disease/infection (e.g. hepatitis, HIV, leukemia, lymphoma)

f. Difficult vascular access (i.e., vein must be readily palpable and cannulatable – no less than ~2.55 mm diameter to maintain ≤45% C/V ratio) as indicated by standard 52 of the INS guidelines[27]

g. Allergy or sensitivity to chlorhexidine gluconate, isopropyl alcohol, latex, or skin adhesives

h. BMI <18.5 kg/m^2 or ≥35 kg/m^2

i. Positive results for the urine drug screen at screening or check-in (including opiates, methadone, cocaine, amphetamines)

j. History or presence of alcoholism (self-reported) or drug abuse within the past 2 years

k. A current or previous medical, physical, mental/cognitive disorders or anatomical conditions that, in the opinion of the investigator, would place the patient at risk, would make them unable to perform study procedures or has the potential to confound interpretation of the study results. (e.g., musculo-skeletal injury, chronic back pain)

l. Employed by Becton Dickinson, Teleflex Medical, Smiths Medical or B Braun (conflict of interest)

5.3 Lifestyle Considerations

5.3.1 Lifestyle restrictions

During the participant's commitment in the study the following lifestyle restrictions will apply:

1) They will not be able to attend work on the days of your participation (Days 1-4 and Visits 2-5 inclusive), although limited typing, making phone calls may be possible, pending approval of the study team.
2) They will not be able to participate in any sport;
3) They will not be able to shower away from CTU (sponge bath acceptable-avoiding areas of insertion/securement dressings) while catheters are in place
4) They will not be able to go for a swim; and
5) They will not be able to undertake any physically vigorous activity.

This is so that the catheters do not dislodge from the participant's arm and so that we can minimize the chance of the participant bruising and/or getting an infection.

5.3.2 Dietary restrictions

The following items will not be consumed for the duration of the study as they impact on the participant's blood clotting capability:

1) beetroot[34];
2) energy drinks high in taurine content (e.g., Monster, Red Bull, Mother)[35]; and
3) alcohol[36,37].

5.3.3 Medication restrictions

Some medications may be prohibited (e.g., ibuprofen, high-dose aspirin), while other medications are fine (e.g., magnesium): the participant will need to complete a medical history questionnaire where they indicate any medications, including over-the-counter medications, that they are currently taking to ascertain participant eligibility in the event medications may impact study results; note, if participant meets inclusion criteria and no exclusion criteria the use of current medications would not be stopped. Should a participant need to take any medications during their time participating in the study, they will be asked to please contact a member of the study team. The participant should not take any illegal drugs during involvement in the study. Similar to the dietary restrictions, these medication restrictions apply as they impact on the participant's blood clotting capability. Recreational drugs (i.e., alcohol) will also be prohibited during the period of catheterization.

5.3.4 Blood donation restrictions

The participant will not be able to donate blood during involvement in the current study. As we are already taking some of the participant's blood for the current study, the participant may feel fatigued, short-of-breath and dizzy due to losing too much blood over a short period of time if they were to also donate blood.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who do not meet the inclusion criteria, or who meet the exclusion criteria. All data collected for screen failures will not be reported in the final clinical trial report.

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

6 STUDY INTERVENTIONS

6.1 Study Device

The BD Nexiva closed IV catheter systems are intended to be inserted into a patient's vascular system for short term use to sample blood, monitor blood pressure, or administer fluids. These devices may be used for any patient population with consideration given to adequacy of vascular anatomy, procedure being performed, fluids being infused, and duration of therapy.

BD Nexiva closed IV catheter systems are over-the-needle, intravascular (IV) catheters. These devices have a radiopaque BD Vialon catheter, needle, needle shield, septum, stabilization platform, integrated extension tubing, clamp, Luer adapter, and vent plug. The needle and catheter are protected by a needle cover

The closed system is designed to keep blood contained within the device throughout the insertion process. The septum is designed to wipe visible blood from the needle surface as the needle is withdrawn from the catheter, further reducing the risk of blood exposure. The needle tip is passively protected when the needle is removed, reducing the risk of accidental needlestick injury.

These devices have BD Instaflash^{TM} Needle Technology, allowing for immediate visualization of blood along the catheter.

Continuous blood return is seen in the extension tubing. The vent plug prevents blood leakage from the extension tubing during insertion. Both the stabilization platform and Luer connector are color coded to

indicate catheter gauge size (24 GA (0.7 mm) = Yellow, 22 GA (0.9 mm) = Blue, 20 GA (1.1 mm) = Pink, 18 GA (1.3 mm) = Green).

See the IFU included in the Appendix (16.1) for full details on the device.

6.2 Control Device/Standard of Care

Not applicable; this is a single-arm study.

6.3 Ancillary Devices/Products

The details of the ancillary devices/products that are critical to the use of the study device and/or execution of the protocol (e.g., device/procedure components that are used with the study device) are provided in Table 2 below.

Table 1. Ancillary products

Description	Manufacturer
3M™ Tegaderm™ IV Securement Dressing, Nexiva or equivalent	3M
BD MaxZero™ Needleless Connector	BD
BD Vacutainer® Luer-Lok™ Access Device	BD
BD Vacutainer® EDTA, 2 mL	BD
BD Vacutainer® Citrate, 2.7 mL	BD
BD Vacutainer® EDTA, 6 mL	BD
BD PosiFlush™ SP Pre-filled Saline Syringe, 10 mL	BD
BD Vacutainer® UltraTouch™ push button blood collection set (21G) w/ holder	BD
Pressure Transducer, Model TNF-R	Argon Medical

Table 2. Ancillary devices-Data Acquisition

Description	Manufacturer
SG-Link Data Logger	Lord Corporation
WSDA Base station	Lord Corporation

Pressure Transducer DTX Interface Cable, Flying Leads	Merit Medical
Custom Graphical User Interface (GUI)	BD
Laptop Computer • 7th Generation Intel® Core™ i7-7820HQ (Quad Core, 2.90Gz, 8MB cache • Intel® Tri-Band Wireless-AC 18265 WiGig + Wi-Fi + BT4.2 Wireless Driver • 512GB Solid State Drive M.2 PCIe) • 32GB (2x16GB) DDR4 Memory	Dell

The data acquisition system will be utilized to collect in-line fluid pressure measurements during catheter flush procedures. The data logger is used to acquire raw pressure data from the transducer and wirelessly transmit the data to the base station. The transducer is powered by the data logger via interface cable connection between the two components. Calibration of data logger will occur prior to use in the study to generate a calibration curve to translate bit values measured by the transducer directly to pressure data. The transceiver base station attaches to the computer via USB and provides the communication link between the data loggers and LabVIEW GUI software application. The LABVIEW based GUI application is loaded on the laptop computer and will be utilized to present the user with functions that allow initialization of data acquisition, real-time visualization of pressure data, and downloading data stored on internal memory.

6.4 Device Labeling

All products (Table 1) utilized in the protocol are commercially available in Australia. These products will be supplied as labeled by the manufacturer.

6.5 Treatment Allocation and Measures to Minimize Bias

The allocation of participants to a particular intervention (e.g., 20G or 22G) and randomization processes are described in the following sub-sections.

6.5.1 Randomization

Participants will be randomized using R statistical software*[1] (R 3.6.2 or higher). The generation of the randomization list will be conducted by a staff member not involved in data acquisition or analysis. Each randomization number will have a corresponding code (e.g., LA_20G_1.75 – indicating a Nexiva 20G 1.75

*[1] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2016. URL https://www.R-project.org/.)

will be first inserted into the left arm). The participant will then have the other length PIVC of the same gauge inserted into the contralateral arm.

Intervention kits will be created for each participant using large ziplock bags with all necessary (plus extra) consumables inside. Each kit will be separated via separate ziplock bags into consumables required for the right arm and left arm. Once the kits have been created, the appropriate randomization number will be recorded on the outside of each. Subsequently, the corresponding code will be placed in an envelope and sealed with the randomization number written on the outside of the envelope. These envelopes will be produced in duplicate with the second envelope sealed in a locked cabinet in the CTU for the circumstance where unblinding is required. Thereafter, the randomization list excluding the corresponding code will be given to the postdoctoral research fellow for storage until a randomization number is requested for the study.

6.5.2 Blinding/Masking

Due to the concealment of intervention allocation, most staff members, other than the inserter and study manager (research assistant), will be blinded to which gauge and length catheter the participant is receiving. To avoid bias sonographic data measurements (e.g., vessel diameter, C/V ratio, blood flow velocity) will be acquired on a separate day at the end of each working week. The acquisition of the sonographic measurements will be conducted by the sonographer). All concealed data will be transferred into an excel spreadsheet that will be subsequently grouped into 2 groups in a separate excel spreadsheet by a staff member not involved in data analysis and is unblinded. This will allow the researchers to analyze the data without having access to information about the allocation

6.5.2.1 Procedures for Unblinding

In the unlikely scenario of a SAE, the study manager or post-doctoral research fellow will open the duplicate envelope located in the locked cabinet of the CTU that has the randomization number written on the outside and contains the corresponding code within. The information will be provided to any personnel that require the information (e.g., the study Medical Doctor) as deemed necessary by the Principal Investigator.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Venipuncture-blood collection

Blood obtained via venipuncture at screening will be collected into vacutainer tubes (2mL (waste tube), 2mL BD Vacutainer® EDTA, 1.8mg/ml–1; 6 x 2.7mL BD Vacutainer® Citrate, 109 mol/m3; Becton Dickinson, USA; total volume: 20.2 mL) for assessment of inclusion and exclusion criteria (e.g., platelet aggregation, coagulation). During the study, blood will be collected from a prominent antecubital vein of the participant's non-dominant arm using a 21G needle and collection set; Becton Dickinson, USA), and a Luer-Lok™ access device and vacutainer tubes (2mL (waste tube), 2mL BD Vacutainer® EDTA, 1.8mg/ml–1; 6mL BD Vacutainer® EDTA, 1.8mg/ml–1; Becton Dickinson, USA; Total Volume: 10mL). As per Infusion Therapy Standards of Practice guidelines[27], the application of a tourniquet will be applied prior to venipuncture but will be limited to less than 1 minute. Once the needle has been inserted and blood has begun to flow into the waste vacutainer tube, the tourniquet will be loosened to minimize the incidence of haemolysis.

7.2 PIVC- Insertion

Sonographic assessment and surface description of underlying anatomical features will be completed for lower arm cephalic veins on both arms to guide catheter insertion.

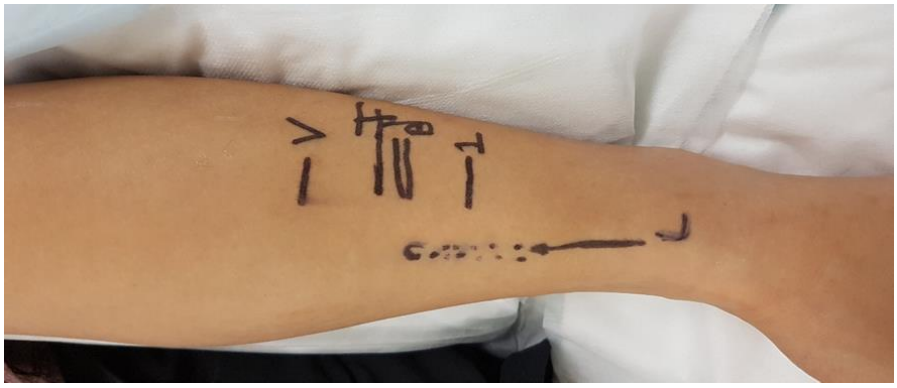


Figure 1. Vessel surface description based on ultrasound imaging. V, valve; T, termination; B, bifurcation; 1, insertion; dotted-line, vein path; arrow, direction of insertion.

Next, a PIVC will be inserted according to the Instructions For Use into the lower cephalic vein of one arm in accordance with a previously established standard operating procedure (see Appendix 16.2) of the participant by a trained phlebotomist or nurse using commercially approved devices with sonographic guidance. After successful cannulation a BD MaxZero™ needleless connector will be attached to the extension and flushed with 3-5 mL saline (0.9%, BD PosiFlush™; 306575; Becton Dickinson, USA), and site stabilized using a Tegaderm IV™ securement dressing[27].

7.3 PIVC-blood collection and pressure monitoring

A Luer-Lok™ access device, connected to the needless connector, and vacutainer tubes (2mL (waste tube), 2mL BD Vacutainer® EDTA, 1.8mg/ml–1, REF 367841; 6mL BD Vacutainer® EDTA, 1.8mg/ml–1, REF 367873; Becton Dickinson, USA; total volume: 10mL) will be utilized to collect blood and ascertain blood quality (haemolysis; see Appendix 16.3 for methodology). Prior to blood collection a pressure transducer (DTXPlus TNF-R, Cat. no. 682021; Argon Medical, USA) and flush syringe will then be connected to the needless connector and zeroed against venous blood pressure. The catheter will be flushed while collecting pressure data in real-time with a custom-designed LabVIEW© routine. Thereafter, the extension set will be clamped and pressure transducer/flushing syringe disconnected from needleless connector.

7.4 Image acquisition of indwelling catheter and cephalic vein

The insertion loci will be assessed prior to, and immediately after, insertion of the PIVC using clinically approved ultrasound with a wide-band, high frequency linear array probe from which all B-Mode, color-flow (CF), and pulse wave doppler (PWD) images will be acquired. At each visit prior to flushing and blood collection the following images will be recorded: a) three cross-sectional, B-mode images with the indwelling PIVC in view; b) three cross-sectional, B-mode images proximal to the PIVC tip; c) three longitudinal, B-mode images encompassing close to the insertion point of the PIVC to beyond the PIVC tip; and d) a 15 s longitudinal, PWD-CF duplex cine loop with the sample volume set ~1cm proximal to the PIVC tip. The sampling frequency for all images will be chosen high enough to avoid frequency aliasing. Coded harmonic imaging will be utilized for all images to improve visual clarity via enhancement of near-field resolution.

7.4.1 Blood flow velocity

A 15 s longitudinal, PWD-CF duplex scan positioned 1 cm past the tip of the PIVC will be utilized for the measurement of blood flow velocity. The PWD sample volume will be positioned at the center of the vein with the axial dimension set to between the upper and lower boundaries of the vessel diameter during data acquisition. Due to variations in echogenicity between participants, the gain will not be kept constant for PWD and CF image acquisitions. The velocity spectrum boundary will be traced and the velocities in the area underneath utilized for subsequent calculations (i.e. maximum and mean velocity of 5 seconds of data).

7.4.2 Angle of insertion, catheter length in vessel

Calculation of the angle of insertion, and catheter length in vessel will be achieved via assessment of the three longitudinal, B-mode scans to be taken where the probe is positioned in-line with the superior surface of the PIVC tip. These measurements (superior and inferior angles) will be taken with the internal calculations of the clinically approved ultrasound. The data will be reported as the average of the values taken from the three images.

7.4.3 Vessel diameter, C/V ratio

Calculation of the vessel diameter, and C/V ratio will be achieved via assessment of the three cross-sectional, B-mode scans to be taken with the indwelling tip PIVC in view. The vessel diameter and catheter diameter will be calculated from the horizontal axis using the internal calculations of the clinically approved ultrasound. The data will be reported as the average of the values taken from the three images.

7.4.4 Valve, side branch location

Identification of a valve/s and/or a side branch vessel will be achieved via assessment of the longitudinal, B-mode scans with the indwelling PIVC in view. The number of valves and side branches that are within 1 cm proximal to the PIVC tip will be recorded and reported. Valves and side branches great than 1 cm from the PIVC tip have not been shown to influence blood flow around the catheter and will not be recorded.

7.4.5 Visualization and quantification of intraluminal/intravascular thrombus formation

Visualization and quantification of thrombi will be assessed using three longitudinal, B-mode scans taken where the probe was positioned in-line with the superior surface of the PIVC tip. Intraluminal and/or intravascular thrombus will be recorded as a 'positive' event if the brightness intensity and position of an echogenic mass is maintained throughout three individual scans. The length of the thrombus will subsequently be measured in millimeters. If the thrombus is greater than 5 cm (i.e., 50 mm) in length, the participant will be sent to the medical doctor for assessment of appropriate treatment and the participant's involvement will be terminated (see section 2.3.1). The three-image confirmation approach will be incorporated into the analysis in order to eliminate the potential for false-positives. This is done because wall shadowing, harmonic distortion and operator movement can all contribute to variations (e.g., brightness) in the appearance of the image [38].

7.5 Blood analyses

A lipid panel, liver function test, blood glucose test, and complete blood count, including white blood cell differentials, will be acquired from blood samples anticoagulated with EDTA during screening for assessment of inclusion and exclusion criteria. An automated biochemistry analyzer (AU480, Beckman Coulter, USA) will be employed for the lipid panel, liver function test, and blood glucose test. An automated haematology analyzer (Beckman Coulter DxH 500™; Beckman Coulter, USA) will be used for the complete

blood count. The devices will be operated and maintained in accordance with the manufacturer's standard operating procedure. Blood clotting function and platelet aggregation will be assessed from blood samples anticoagulated with Citrate during screening for assessment of inclusion and exclusion criteria. The activated partial thromboplastin time (aPTT), prothrombin time (PT) will be quantified from the average of duplicate measurements, using an automated haemostasis analyser (Diagnostica Stago, STA-R Evolution; Diagnostica Stago, France). The ADP-induced, and Collagen-induced platelet aggregation will be assessed from the average of duplicate measurements, using an impedance aggregometer (Chrono-Log Corporation, USA). The measurements will be performed in accordance with the manufacturer's standard operating procedures.

If blood test results are not normal, a member of the study team will inform the participant. If the Principal Investigator (PI) believes the results may place the participant at increased risk during the study, the participant will not be able to continue in the study. A member of the study team will provide the participant with the relevant test results, if the participant would like to discuss them with his/her healthcare practitioner.

7.6 PIVC-Failure

The definition of PIVC failure in the current study will be defined as: 1) an inability to flush or collect blood through the PIVC or 2) removal of the PIVC based on medical doctor's assessment of an AE. A device rescue decision tree will be utilized to identify if the PIVC has failed.

7.7 PIVC Removal

Upon completion of the protocol or if the PIVC fails, the device and attached dressing will be removed and disposed of according to the Instructions For Use in biohazard bins and incinerated as per Griffith University waste management protocol. Initially, the dressing will be detached from the participant's skin from distal to proximal direction. Once the dressing has been detached the PIVC, needless connector and dressing will be removed (proximal to distal) together from the participant's arm and later assessed for extravenous thrombus (see section 7.8). Upon removal, a cotton ball will be immediately placed over the insertion site to stem bleeding. Once bleeding has stopped, the arm and insertion site will be wiped clean with a ethanol wipe, a fresh cotton ball placed over the insertion site and taped down with 3M Transpore™ tape.

7.8 Extravenous Thrombus Assessment (Post-Removal)

To assess extravenous thrombus in the removed PIVC and needless connector, a camera will be utilized to take digital photographs of the hub of the PIVC (internal surface), the PIVC (external surface), needless connector (internal surface) and material ejected from the catheter tip. For each site (e.g., the hub of the PIVC), the presence or absence of an extravenous thrombus will be recorded.

7.9 Video/Audio or Photography

To assist the sponsor BD in best capturing and evaluating all the study results, a technician may photograph or video procedures conducted throughout the study. The technician will concentrate only on the procedure, but it is possible that the participant's face may be filmed. Participants are given the right to refuse consent for video/photography, per the informed consent document, and may participate in the study if consent for video/photography is refused.

The recording belongs to BD and will be handled with the same confidentiality as all other information obtained from the participant during this research study. Recorded material will be labeled only with the ID

number that was assigned during the study. The participant's identity will not be revealed by any use of the video recording/photography.

7.10 Safety Assessments

7.10.1 Insertion Site Assessment

Participants will be provided instructions to take care of the catheters while they are away from Clinical Trials Unit (see Appendix 16.4). These include, but are not limited to, instructions on how to take care of the device while at home and instructions on how to look out for health-related complications. Additionally, the document provides instructions on what to do and who to contact if the participant does experience any health-related complications while at home with the indwelling PIVCs. Additionally, a nurse will complete visual inspection of the insertion sites including assessment of redness, swelling or any signs of infection or other complications prior to each blood draw. This assessment will be done according to the Infusion Therapy Standards of Practice guidelines[27] using the Visual Infusion Phlebitis Scale. Where the site assessment indicates a score of ≥ 4 (Table 4), the participant will be referred to the study medical doctor for medical decision. If an adverse event is suspected by the nurse, the patient will be referred to an on-site clinician for assessment and/or clinical decision.

Table 3. Visual infusion phlebitis scale

Score	Observation
0	PIVC insertion site appears healthy
1	One of the following is evident: Slight pain near PIVC insertion site OR slight redness near PIVC insertion site
2	Two of the following are evident: • Pain at PIVC insertion site • Erythema • Swelling
3	All of the following signs are evident: • Pain along path of catheter • Induration (hardening of the tissue) at PIVC site
4	All of the following signs are evident and extensive: • Pain along path of catheter • Erythema (redness) • Induration (hardening) at PIVC site • Palpable venous cord
5	All of the following signs are evident and extensive: • Pain along path of catheter • Erythema (redness) • Induration (hardening) at PIVC site • Palpable venous cord • Pyrexia (fever)
Adapted from 'A battle in vein infusion: phlebitis' [39]	

7.10.2 Securement Dressing Assessment

A nurse will complete visual inspection of the securement dressing, including the entire infusion system, prior to each blood draw. This assessment will be done according to the Infusion Therapy Standards of Practice guidelines[27] and the securement dressing changed if the dressing integrity becomes damp, loosened, visibly soiled, or if moisture or blood are present under the dressing. If the dressing integrity is compromised, a photo will be taken for observational records and as it is not considered an endpoint of the current study, the data will not be assessed.

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, any indwelling catheters will be safely removed and disposed of in accordance with the Instructions For Use as per standard protocol without any data collected. Additionally, the sites of insertion will be assessed for signs of infection and extravasation. The participant will be followed-up within 96 hours for participant safety and to ensure no adverse events have occurred following removal of indwelling catheters.
- 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.2 Lost to Follow-Up

A participant will be considered lost to follow-up and summarily withdrawn if he or she fails to return for consecutive study visits post PIVC insertion (Visits 2 through 5).

The following actions must be taken if a participant fails to return for/complete a required study visit:

- The site must attempt to contact the participant and attempt to schedule catheter removal and follow-up as designated by Visits 5 and 6 procedures.
- These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Participants lost to follow-up after Visit 1 but successfully contacted prior to PIVC placement may be allowed to continue with Visits 2 through 6 at PI discretion.

8.3 Patient replacement

Any participants lost to the current study (withdrawn or lost to follow-up) will be replaced through normal screening processes and allocated to the incomplete experimental group to ensure at least 20 participant completers for each catheter gauge. Replacement participants will be started in the same order as drop-out/withdrawal; drop-outs will not be considered eligible for readmission due to potential effects of prior catheter placement on subsequent study outcomes.

9 ADVERSE EVENTS AND DEVICE DEFICIENCIES

9.1 Definitions of Events

9.1.1 Adverse Events (AEs)

An AE 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 study device [ISO14155:2011(E)].

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. Exacerbation of an existing condition should be reported as an AE if the event meets the protocol definition of an AE.

9.1.2 Serious Adverse Events (SAEs)

A serious adverse event is defined by ISO 14155 and/or 21 CFR 803.3 as an adverse event that:

a. led to death;
b. led to serious deterioration in health that resulted in life-threatening illness or injury, resulted in permanent impairment;
c. required inpatient hospitalization/prolonged hospitalization, or resulted in medical/surgical intervention to prevent life-threatening illness/injury or permanent impairment; or
d. led to fetal distress, fetal death, or a congenital abnormality or birth defect.

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, or operation or any malfunction of the investigational device (study device) and includes any event that is a result of a user error.

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 all applicable regulatory authorities as per the respective regulatory authority guidelines.

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 device used.

- Procedure: A procedure includes any study-related activity performed.

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

Relatedness	Description
Not Related	Event is independent of study intervention and/or evidence exists that the event is related to another etiology. There must be an alternative etiology documented by the clinician.
Unlikely Related	Event in which the temporal relationship to study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time of the study device use) and in which underlying disease provides plausible explanations (e.g., the participant's clinical condition other concomitant treatments).
Likely Related	Event in which there is evidence to suggest a causal relationship and the influence of other factors is less likely. The event occurs within a reasonable time after use of the study device and is less likely to be attributed to concurrent disease.
Related	Event in which there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. The event occurs in a plausible time relationship to use of the study device and cannot be explained by concurrent disease.

9.4 Reporting of Events

In this study, AE collection will be limited to those occurring in the arm in which the study device is inserted, as well as any other undesirable clinical event judged to be related or possibly related to the study device, or

a study procedure regardless of anatomical region an event that, in the opinion of the investigator warrants reporting.

The Investigator must report any AEs which are serious, unanticipated/unexpected and probably or possibly related to the study product or procedures to the reviewing HREC in accordance with the relevant HREC reporting requirements.

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

For all adverse events collected, all sections of the appropriate Case Report Form (CRF) must be completed.

All SAEs, SADEs, and/or UADEs/USADEs must be reported to the Sponsor within one (1) working day 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.

The Sponsor will provide results of any evaluation of an unanticipated/unexpected adverse product effect to appropriate Regulatory/Health Authorities and to all Investigators within the respective reporting timelines, after the Sponsor is notified of the event. The PI will assume responsibility for submitting reports of evaluation results to their relevant HREC. The PI must notify the Sponsor in writing the report has been submitted to HREC 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 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.

9.4.1 Pregnancies

Investigators must instruct participants to inform them immediately if they become pregnant during the trial.

In case of a pregnancy during the participation in the trial, the participant will be immediately considered for premature discontinuation.

The pregnancy will be registered on the CRF protocol deviation form. In addition, the Pregnancy Form (which is independent of the CRF) will be completed with all the available information within the same time frame and following the same routing as for a SAE, described previously.

All pregnancies discovered by the Investigator after the termination of the trial but which were initiated during the participation in the trial will be reported to BD as occurring during the trial.

9.5 Adverse Event (AE) Management

Collection of adverse events will begin after the participant has signed the Consent Form through the end of the participants participation in the study.

The participant will be questioned in an open-ended manner regarding any new or worsening undesirable signs or symptoms they may have experienced since starting the study. Signs and symptoms must be

comprehensively documented on the appropriate source documentation. All related signs and symptoms should be grouped under one diagnosis if possible.

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

Any worsening or undesirable signs or symptoms of the PIVC insertion sites that results in the withdrawal of the participants from the study or, in the opinion of the Investigator or designate, warrants medical attention or medication will be considered AEs that will be subjected to the same criteria as all other AEs. Overall medical coverage for study participants will be provided by Griffith University affiliated general practitioners (GP), e.g. GPs at Griffith University Health Clinic and emergency physicians at the Gold Coast University Hospital.

If an AE or SAE occurs around the PIVC insertion site, it may be needed to take photographs of the site only. Only the Principal Investigator, Sub-investigator, study staff and Sponsor will have access to the de-identified photographs for review and assessment.

9.5.1 Follow-up of Adverse Events (AE)

Adverse events that are ongoing at the time of the participant's scheduled completion visit will be followed until resolution of the event means of the investigational site contacting the participant via telephone or by any other means considered appropriate. The Investigator will communicate with the sponsor Medical Monitor (via telephone and/or email) as to the need for further follow-up. In the case of discrepancies, the Investigator's judgement will prevail. All communications with the participant and medical monitor will be documented appropriately.

The clinical course of any serious adverse 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 as it relates to the study product and/or study procedures.

9.5.2 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, Information for Use (IFU) or Investigator's Brochure.

All adverse events, regardless of the Investigator's opinion of expectedness or relationship to the study product, must be reported to the Sponsor and Safety vendor, in case sponsor should consider outsourcing any safety management or reporting tasks, within 24 hours. The Investigator or designee must report the event by telephone or email to the Study Monitor. In addition, the Investigator must notify the local Field Assurance team within 24 hours of the receipt of the information about any device-related (unlikely related, likely related, related) AEs and SAEs by sending the completed AE/SAE form to the following email address: complaints.australia@bd.com

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

David Maggs, MD
VP, Medical Affairs, BDTI, Medical Affairs
Office: +1- 919-597-6255
Mobile: +1-858-344-1339
e-mail: David.Maggs@bd.com

9.6 Device Deficiencies

The Investigator will record a device deficiency if a device used in the study procedure failed to meet its performance specifications 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 mechanical failures, malfunctions, missing components, and defects of the study devices must be promptly reported to the Sponsor within 24 hours; **notification by email** (complaints.australia@bd.com) with copy to Sponsor Study Monitor and Sponsor local representative. Information required: Product Code; Batch/Lot; Date of event; Did the event occur before, during or after use; Description of the event; Did an adverse event occur. In all events, the device(s) in question should be returned to the Sponsor as instructed by the Sponsor monitor or sponsor appointed local representative, for analysis. If it is not possible to return the device(s), the reason it could not be returned as well as its final disposition should be documented.

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. 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 responsible HREC of such device deficiencies in accordance with the HREC reporting requirements.

10 STATISTICAL METHODS

10.1 Overview of Study Design

This is a single-centre, open-label, multi-visit, self-controlled study design, in ~40 healthy participants, randomized by cannula gauge of peripheral intravenous catheter (PIVC) device into the lower arm cephalic vein of both arms.

More details about the statistical methods used for primary, secondary and exploratory objectives will be provided in a separate Statistical Analysis Plan (SAP). This SAP will include mock tables and figures whenever possible.

10.2 Sample Size Considerations

There is limited published data investigating the impact of PIVC catheter length on indwell time; a single article was found in the literature comparing catheter survival between a BD PIVC catheter (20 gauge; 4.78 cm/1.88 inch length) and midline catheter (POWERWAND™, 19.5 gauge; 6 cm/2.3 inch length)[9]. The indwell time results for this research were utilized to calculate a sample size estimate. As this an exploratory study no statistical justification for sample size is required; however, an estimate was compiled to provide an initial assessment of potential sample requirements. Based on the available dataset, a sample size of ~20 participants per PIVC gauge would be required given median failure times of catheter lengths at 1 and 3 days (Figure 2)

Logrank Tests

Numeric Results for the Logrank Test in Terms of Sample Size

Alternative Hypothesis: Two-Sided

Power	N1	N2	N	Haz Ratio (HR)	Ctrl Med Surv Time (M1)	Trt Med Surv Time (M2)	Acc-rual Pat'n	Acc-rual Time/ Total Time	Ctrl Loss	Trt Loss	Ctrl to Trt	Trt to Ctrl	Alpha	Beta
0.8054	19	20	39	0.3333	1.00	3.00	Equal	0 / 3	0.0000	0.0000	0.0000	0.0000	0.0500	0.1946

Figure 2. Details of estimation of sample size calculation.

10.3 Analysis Population

The following populations are defined as:

Population	Description
Enrolled	All participants who sign the ICF
Evaluable	All participants who complete the study until either the catheter fails or the protocol is completed (i.e., 72 hours)

10.4 General Considerations

Participants who have withdrawn consent for continuation of the study (i.e., dropouts or non-compliant) will be included in the analysis by modern imputation methods for missing data. In the unforeseen circumstance of a protocol violation (e.g., 20G PIVC instead of 22G PIVC; blood was collected into 6mL vacutainer before 2mL for a specific participant), the data will be analyzed 'as treated' – that is, data will be analyzed as the participant's actual received intervention. However, in the unforeseen circumstance of a protocol violation whereby a participant receives the wrong intervention (e.g., two different gauge catheters; two 20G catheters of the same length), they will be treated as per protocol and thus their data will be excluded from the study.

10.5 Primary Endpoint(s)

Comparisons across and between device configurations (i.e., length/gauge) will be made using logrank tests for indwell time. The primary endpoint will be evaluated using statistical modeling software (Prism, Release 8.3; GraphPad Software Inc., USA) or R (R 3.6.2 or higher).

10.6 Secondary Endpoint(s)

Linear mixed-effects models will be used to evaluate the following endpoints over time and determine the effect on PIVC indwell time for a given configuration (i.e., length/gauge):

1) cfHb concentration;
2) blood draw fill time;
3) blood flow velocities above or below the catheter
4) vessel dimensions; and
5) intravenous thrombus size.

Underlying normality assumptions will be verified and if not fulfilled non-parametric tests will be used. Multivariate analysis (to be defined in the SAP) will be employed to assess the effect of baseline characteristics on catheter indwell time and thus identify their power as predictive biomarkers using the following the independent variables including, but not limited to:

1) angle of insertion;
2) vessel dimension;
3) presence of side branches and/or intravenous valves;
4) age;
5) sex;
6) height;
7) weight;
8) BMI;
9) medical history questionnaire responses; and
10) exploratory endpoints.

A multiple-logistic regression analysis will be employed to assess the effect of baseline characteristics on catheter failure over a period of 72 hours and thus identify their power as predictive biomarkers using the independent variables including, but not limited to:

1) angle of insertion;
2) vessel dimension;
3) presence of side branches and/or intravenous valves;
4) age;
5) sex;
6) height;
7) weight;
8) BMI;
9) medical history questionnaire responses; and
10) exploratory endpoints.

A chi squared analysis will be employed to assess the proportion of individuals in each group (i.e., PIVC length and gauge) that have presence of the following at failure/end-of-protocol:

1) vein collapse;
2) intravenous thrombus; and

3) extravenous thrombus.

All data will be evaluated using statistical modeling software (Prism, Release 8.3; GraphPad Software Inc., USA) or R (R 3.6.2 or higher). P-values ≤0.05 will be considered statistically significant.

10.7 Tertiary/Exploratory Endpoint(s)

Exploratory endpoints collected at baseline will be included in the multiple-regression analysis described in section 10.6

10.8 Other Analyses

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

10.9 Interim Analysis

A formal interim analysis is not planned; however, after 5 participants have completed their follow-up visit (V6), in-situ catheter positions will be compared to the expected position based on the catheter lengths as described in Section 4.1.

11 DATA COLLECTION AND RECORD MAINTENANCE

11.1 Data Management

All participant data relating to the study will be recorded on paper or electronic CRFs.

The PI or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

All entries to paper CRFs will be made clearly in black or dark blue ink. Corrections will be made using the principles of Good Documentation Practice.

A Data Management Plan (DMP) will be developed that outlines the procedures used for data review, database cleaning and issuing/resolving data queries. Procedures for validations and data storage will also be contained within the DMP.

The PI must maintain accurate documentation (source data) that supports the information entered in the CRF.

The PI must permit study-related monitoring, audits, HREC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the PI upon request. The PI agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to correct deficiencies in the study documentation and CRFs/worksheets.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Participant ID will be used to track participant information throughout the study. Participant personal information will be de-identified.

The transmission of paper CRFs to the sponsor (i.e., Becton Dickinson) will be conducted via scans of the CRFs once per week.

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 study file of each enrolled participant. Where there is no prior written or electronic record of data, such as for subjective data (e.g., pain scales, questionnaires), these data may be recorded directly on the CRF(s) and the CRF is then considered to be the source. Typical source documents can include the laboratory report, clinician notes, patient record, recorded data from automated instruments or other documentation prepared and maintained by the investigator/staff which contains a record of all observations and other data pertinent to the investigation on a study participant. Electronic data sources included in the database will comprise:

- A PDF that provides raw cfHb absorbance at three wavelengths obtained from Thermo Scientific MultiSkan GO and SkanIT software
- A scanned document that provides the calculated haemolysis value and whether it is above 200 mg/dL, obtained from Beckman Coulter AU480
- A scanned document that provides the blood glucose, lipid and liver function test results and whether they are above healthy limits, obtained from Beckman Coulter AU480
- A scanned document that provides the FBC values and reference ranges obtained from Beckman Coulter DxH500
- A digital photograph (JPEG/TIFF) that provides evidence of an extravenous thrombus (or not)
- A digital photograph (JPEG/TIFF) that provides visual assessment of haemolysis
- A digital photograph (JPEG/TIFF) that provides visual assessment of drug test result (dipstick)
- DICOM/JPEG images and cine loops (video capture) that allow for the measurement of blood flow velocity, C/V ratio, and other sonographic raw data (e.g., angle of insertion, presence of side branches and/or intravenous valves)
- A CSV file and MATLAB file that provides raw pressure reading data and the analysis and interpretation of the pressure trace

The PI 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 the Sponsor 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.

All source documents will be held within the Clinical Trial Unit, Griffith University, which has strict access provisions/processes. Additionally, electronic data sources listed in section 11.2 will be printed and included in the medical study file; however, the DICOM images and cine loops will not be kept in the medical study file. Subsequently, there will be an electronic file for each participant which will contain all electronic data sources (Figure 3).

Electronic source documents and data will be securely stored on the Griffith University Research Space and will be accessible by only the investigational staff, Griffith University Research support staff, and the Sponsor monitor. Additionally, electronic source documents will be backed up onto an external hard drive at the end of each day which will be password protected and held securely within the Clinical Trial Unit, Griffith University, which has strict access provisions/processes.

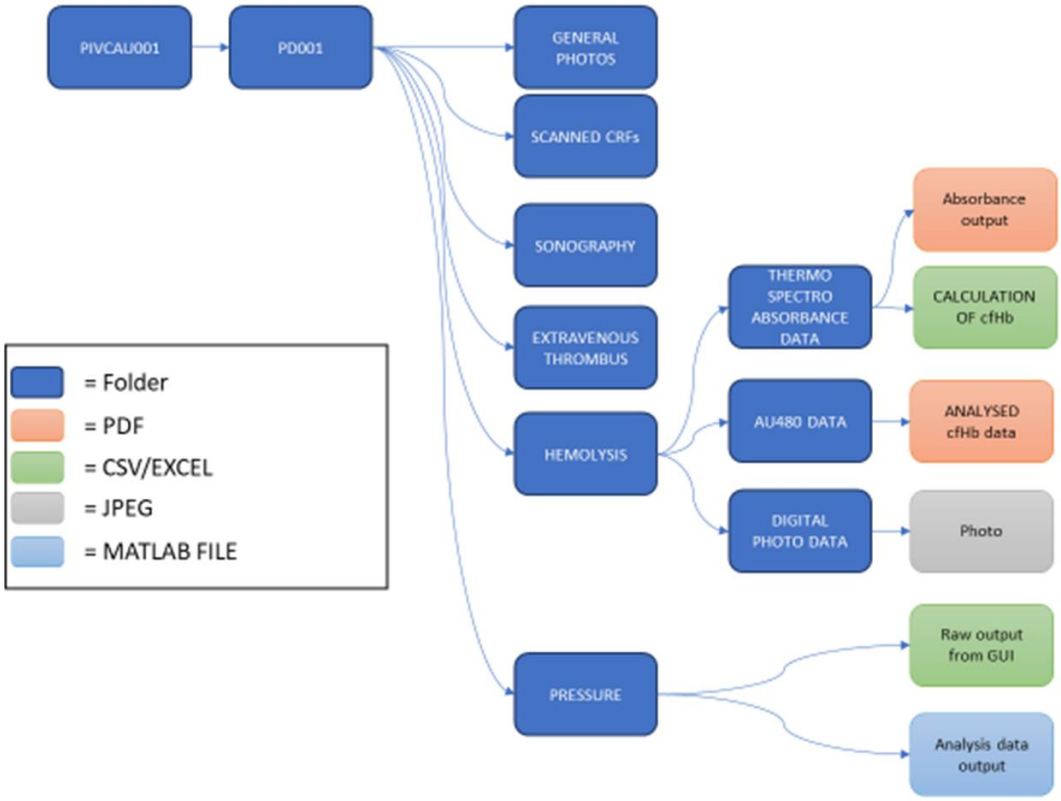


Figure 3: Electronic data sources

11.3 Record Retention

Records and documents, including PICF, pertaining to the conduct of this study must be retained by the PI for 15 years after the study completion in line with local regulations or unless institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

Investigational study product will be released only for use by PI/Investigational site who has obtained written HREC approval (as required) to conduct this study, who has completed all required study documentation, and who has been qualified by the Sponsor. The PI must maintain control over all study product, and ensure the study device 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 (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 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.

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 PI, Sub-Investigator(s) and study 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 HREC 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 HREC, 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 visit 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 HREC acceptance of the study.

At the completion of the study, the Sponsor Monitor will conduct a final close-out visit. The purpose of this visit may include but is not limited to collecting all outstanding study data documents, confirming that the Investigator files are accurate and complete, reviewing the record retention requirements with the PI, 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 PI and his team will make themselves available during the visit. The PI 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/eCRFs. The participant's anonymity must be ensured, and data checked during the audit must remain confidential.

As soon as the PI is aware of an upcoming inspection/audit by the Health Authorities, he/she will promptly inform the Sponsor. As agreed with the PI, 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 HREC 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 HREC requirement.

It is the PI responsibility to ensure that there are no deviations from the Protocol. Except in an emergency, a protocol deviation requires Sponsor approval.

Any and 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.

13 ADMINISTRATIVE REQUIREMENTS

13.1 Investigator and Site Selection

The PI 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 PI, Sub-Investigator(s) and Study Coordinator(s) will be maintained in the Sponsor's files as documentation of qualification by training and experience.

The PI 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. Federal or local databases will be searched to ensure that the Investigator(s) and/or the site are not prohibited from engaging in sponsored clinical research.

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

In addition to each Investigator and appropriate site personnel being trained on this protocol and study procedures during the Site Initiation Visit, product training will be provided by the Sponsor or designee and is required for each Investigator. Additional study staff (e.g., Sub-Investigator(s)) will also require device training provided from the Sponsor or proctoring by the PI. All training will be documented and filed at the investigational site and with the Sponsor.

Additional training requirements for support staff include the following:

- Advanced Vascular Ultrasound course provided by the Australian Institute of Ultrasound for principal investigator, and research assistant
- Beckman Coulter Access 2 and AU480 equipment advanced training provided by Beckman Coulter for post-doctoral research fellow, and research assistant
- Good documentation practice provided by Compliance Online for principal investigator, post-doctoral research fellow, and research assistant

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 CSA by PI/site (or designee)];
- [Signed Investigator Agreement Page by PI and Sub-Investigator(s)];
- [Signed Investigator Brochure Acknowledgement 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 HREC of both the protocol and ICF, and any other
- applicable protocol specific material]; and
- [HREC Membership List, Assurance of Compliance Form, or equivalent].

13.4 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 at the sponsor's discretion. The Investigational site will not publish any articles or make any presentations relating to the services or referring to any data or materials generated from the study, in whole or in part, without the prior written consent of BD, except for any disclosure that is necessary to comply will applicable law or regulation. 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 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.

13.5 Study Registration

The study will be registered on clinicaltrials.gov

13.6 Termination of Study

The Sponsor reserves the right to suspend enrollment or terminate the study at any time for any reason. 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 HREC and/or non-compliance with this protocol or other clinical research requirements. Written notice will be submitted to the PI in advance of such termination.

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

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 HUMAN RESEARCH ETHICS COMMITTEE Approval

The initial PICF (Participant Information Consent Form), any subsequent revised written PICF, and any written information provided to the participant must receive the relevant Human Research Ethics Committee (HREC) approval before it can be used. The informed consent will adhere to the HREC requirements, applicable laws and regulations, and Sponsor requirements.

The PI or designee must submit the study protocol, Informed Consent Form (if applicable), and all other locally required documentation to an appropriate HREC and obtain study-specific written approval (favorable opinion) before 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 HREC must give written renewal of the original approval at least annually to continue the study. A copy of the written renewal must be provided to the Sponsor.

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

14.1.1 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. 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 and local privacy laws 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 in accordance with 21 CFR Parts 50 and 56 and ISO 14155:2011.

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

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 or documentation submitted to the Sponsor. Participants will only be identified by a unique participant identification (e.g., PD001). A master list that includes the participant identification, full name, address, telephone number and email address of all participants will be created and kept separate from study documents on the Griffith University Research Drive, of which only Griffith University staff team members will have access.

Any data collected meeting the definition of protected/confidential health information or personal identifying information will be collected and maintained using the designated authorisations and following all applicable privacy laws.

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.

14.2 Regulatory Status

The Sponsor has determined and documented this to be a non-significant risk device study based on congruency with 21 CFR 812.3. This determination is based on the following assessment of the investigational device:

- Is not intended as an implant;
- Is not purported or represented to be for a use in supporting or sustaining human life;
- Is not intended for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and,

- Does not present a potential for serious risk to the health, safety, or welfare of a participant.

Classification of NSR is documented in the Study Risk Assessment Form. The study device is registered with the Australian TGA: ARTG 243114.

This study is a feasibility study in healthy volunteers. The study is not a registration study to receive a regulatory approval.

14.3 Statement of Compliance

This clinical investigation will be conducted in compliance with all stipulations of this protocol, the conditions of the Human Research Ethics Committee approval(s), the NHMRC National Statement on ethical conduct on Human Research (2007); ISO 14155:2011; GCP and in accordance with the ethical principles of the Declaration of Helsinki; and all applicable federal, state and local laws and regulations.

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

15 REFERENCES

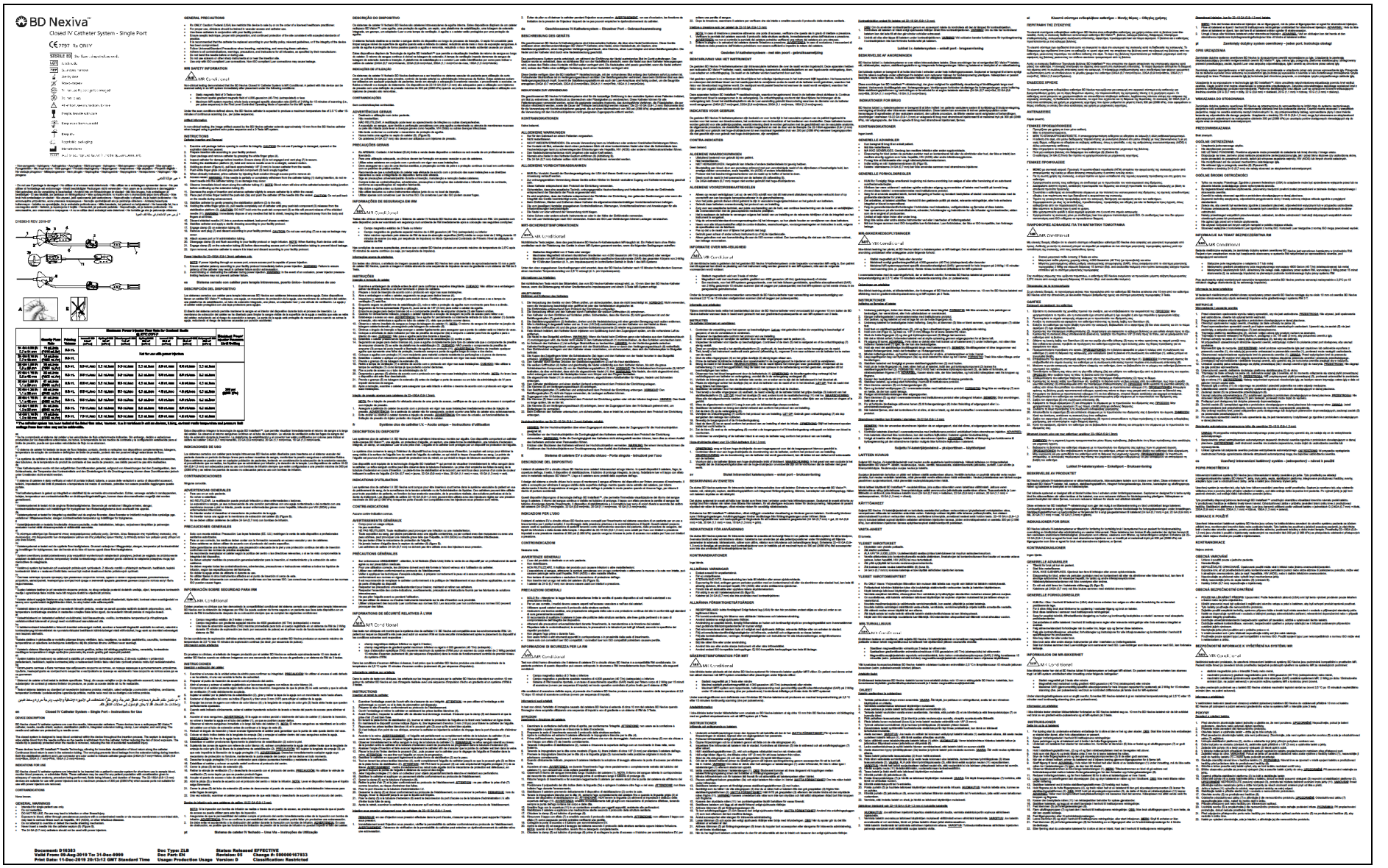
1. Zingg W, Pittet D. Peripheral venous catheters: an under-evaluated problem. *Int J Antimicrob Agents.* 2009;34 Suppl 4:S38-42.
2. Cheung E, Baerlocher MO, Asch M, Myers A. Venous access: a practical review for 2009. *Can Fam Physician.* 2009;55(5):494-496.
3. Keogh S, Flynn J, Marsh N, Higgins N, Davies K, Rickard CM. Nursing and midwifery practice for maintenance of vascular access device patency. A cross-sectional survey. *Int J Nurs Stud.* 2015;52(11):1678-1685.
4. Helm RE, Klausner JD, Klemperer JD, Flint LM, Huang E. Accepted but Unacceptable: Peripheral IV Catheter Failure. *J Infus Nurs.* 2019;42(3):151-164.
5. Bolton D. Improving peripheral cannulation practice at an NHS Trust. *Br J Nurs.* 2010;19(21):1346, 1348-1350.
6. Rickard CM, McCann D, Munnings J, McGrail MR. Routine resite of peripheral intravenous devices every 3 days did not reduce complications compared with clinically indicated resite: a randomised controlled trial. *BMC Med.* 2010;8:53.
7. Smith B. Peripheral intravenous catheter dwell times: a comparison of 3 securement methods for implementation of a 96-hour scheduled change protocol. *J Infus Nurs.* 2006;29(1):14-17.
8. Piper R, Carr PJ, Kelsey LJ, Bulmer AC, Keogh S, Doyle BJ. The mechanistic causes of peripheral intravenous catheter failure based on a parametric computational study. *Sci Rep.* 2018;8(1):3441.
9. Bahl A, Hang B, Brackney A, et al. Standard long IV catheters versus extended dwell catheters: A randomized comparison of ultrasound-guided catheter survival. *Am J Emerg Med.* 2019;37(4):715-721.
10. Fields JM, Dean AJ, Todman RW, et al. The effect of vessel depth, diameter, and location on ultrasound-guided peripheral intravenous catheter longevity. *Am J Emerg Med.* 2012;30(7):1134-1140.
11. Horowitz SH. Venipuncture-induced neuropathic pain: the clinical syndrome, with comparisons to experimental nerve injury models. *Pain.* 2001;94(3):225-229.
12. Mrazek C, Simundic AM, Wiedemann H, et al. The relationship between vacuum and hemolysis during catheter blood collection: a retrospective analysis of six large cohorts. *Clin Chem Lab Med.* 2017;55(8):1129-1134.
13. Sowemimo-Coker SO. Red blood cell hemolysis during processing. *Transfus Med Rev.* 2002;16(1):46-60.
14. Cadamuro J, von Meyer A, Wiedemann H, et al. Hemolysis rates in blood samples: differences between blood collected by clinicians and nurses and the effect of phlebotomy training. *Clin Chem Lab Med.* 2016;54(12):1987-1992.
15. Baskurt OK, Boynard M, Cokelet GC, et al. New guidelines for hemorheological laboratory techniques. *Clin Hemorheol Microcirc.* 2009;42(2):75-97.
16. Cengiz M, Ulker P, Meiselman HJ, Baskurt OK. Influence of tourniquet application on venous blood sampling for serum chemistry, hematological parameters, leukocyte activation and erythrocyte mechanical properties. *Clin Chem Lab Med.* 2009;47(6):769-776.
17. Wollowitz A, Bijur PE, Esses D, John Gallagher E. Use of butterfly needles to draw blood is independently associated with marked reduction in hemolysis compared to intravenous catheter. *Acad Emerg Med.* 2013;20(11):1151-1155.
18. Teilmann AC, Falkenberg MK, Hau J, Abelson KS. Comparison of silicone and polyurethane catheters for the catheterization of small vessels in mice. *Lab Anim (NY).* 2014;43(11):397-403.

19. Lippi G, Cervellin G, Mattiuzzi C. Critical review and meta-analysis of spurious hemolysis in blood samples collected from intravenous catheters. *Biochem Med (Zagreb).* 2013;23(2):193-200.
20. Raisky F, Gauthier C, Marchal A, Blum D. Haemolyzed samples: responsibility of short catheters. *Ann Biol Clin (Paris).* 1994;52(7-8):523-527.
21. Lippi G, Avanzini P, Cervellin G. Prevention of hemolysis in blood samples collected from intravenous catheters. *Clin Biochem.* 2013;46(7-8):561-564.
22. Heyer NJ, Derzon JH, Winges L, et al. Effectiveness of practices to reduce blood sample hemolysis in EDs: a laboratory medicine best practices systematic review and meta-analysis. *Clin Biochem.* 2012;45(13-14):1012-1032.
23. McNamee AP, Horobin JT, Tansley GD, Simmonds MJ. Oxidative Stress Increases Erythrocyte Sensitivity to Shear-Mediated Damage. *Artif Organs.* 2018;42(2):184-192.
24. Lippi G, Salvagno GL, Montagnana M, Brocco G, Guidi GC. Influence of hemolysis on routine clinical chemistry testing. *Clin Chem Lab Med.* 2006;44(3):311-316.
25. Lippi G, Bonelli P, Cervellin G. Prevalence and cost of hemolyzed samples in a large urban emergency department. *Int J Lab Hematol.* 2014;36(1):e24-26.
26. In: *WHO Guidelines on Drawing Blood: Best Practices in Phlebotomy.* Geneva2010.
27. Gorski LA. The 2016 Infusion Therapy Standards of Practice. *Home Healthc Now.* 2017;35(1):10-18.
28. Mulloy DF, Lee SM, Gregas M, Hoffman KE, Ashley SW. Effect of peripheral IV based blood collection on catheter dwell time, blood collection, and patient response. *Appl Nurs Res.* 2018;40:76-79.
29. Phelan MP, Reineks EZ, Berriochoa JP, et al. Impact of Use of Smaller Volume, Smaller Vacuum Blood Collection Tubes on Hemolysis in Emergency Department Blood Samples. *Am J Clin Pathol.* 2017;148(4):330-335.
30. Rickard CM, Marsh N, Webster J, et al. Dressings and securements for the prevention of peripheral intravenous catheter failure in adults (SAVE): a pragmatic, randomised controlled, superiority trial. *Lancet.* 2018;392(10145):419-430.
31. Dietrich H. One poke or two: can intravenous catheters provide an acceptable blood sample? A data set presentation, review of previous data sets, and discussion. *J Emerg Nurs.* 2014;40(6):575-578.
32. Bertolino G, Pitassi A, Tinelli C, et al. Intermittent flushing with heparin versus saline for maintenance of peripheral intravenous catheters in a medical department: a pragmatic cluster-randomized controlled study. *Worldviews Evid Based Nurs.* 2012;9(4):221-226.
33. Wallis MC, McGrail M, Webster J, et al. Risk factors for peripheral intravenous catheter failure: a multivariate analysis of data from a randomized controlled trial. *Infect Control Hosp Epidemiol.* 2014;35(1):63-68.
34. Velmurugan S, Kapil V, Ghosh SM, et al. Antiplatelet effects of dietary nitrate in healthy volunteers: involvement of cGMP and influence of sex. *Free Radic Biol Med.* 2013;65:1521-1532.
35. Santhakumar AB, Fozzard N, Perkins AV, Singh I. The Synergistic Effect of Taurine and Caffeine on Platelet Activity and Hemostatic Function. *Food and Public Health.* 2013;3(3):147-153.
36. Renaud SC, Ruf JC. Effects of alcohol on platelet functions. *Clin Chim Acta.* 1996;246(1-2):77-89.
37. Bulle S, Reddy VD, Padmavathi P, Maturu P, Puvvada PK, Nallanchakravarthula V. Association between alcohol-induced erythrocyte membrane alterations and hemolysis in chronic alcoholics. *J Clin Biochem Nutr.* 2017;60(1):63-69.
38. Knudson GJ, Wiedmeyer DA, Erickson SJ, et al. Color Doppler sonographic imaging in the assessment of upper-extremity deep venous thrombosis. *AJR Am J Roentgenol.* 1990;154(2):399-403.
39. Jackson A. Infection control--a battle in vein: infusion phlebitis. *Nurs Times.* 1998;94(4):68, 71.
40. Fairbanks VF, Ziesmer SC, O'Brien PC. Methods for measuring plasma haemoglobin in micromolar concentration compared. *Clin Chem.* 1992;38(1):132-140.

41. Henkelman S, Rakhorst G, Blanton J, van Oeveren W. Standardization of incubation conditions for hemolysis testing of biomaterials. *Materials Science and Engineering: C.* 2009;29(5):1650-1654.
42. Malinauskas RA. Plasma haemoglobin measurement techniques for the in vitro evaluation of blood damage caused by medical devices. *Artif Organs.* 1997;21(12):1255-1267.
43. Horobin JT, Sabapathy S, Simmonds MJ. Repetitive Supra-Physiological Shear Stress Impairs Red Blood Cell Deformability and Induces Hemolysis. *Artif Organs.* 2017;41(11):1017-1025.
44. Horobin JT, Simmonds MJ, Nandakumar D, et al. Speed Modulation of the HeartWare HVAD to Assess In Vitro Hemocompatibility of Pulsatile and Continuous Flow Regimes in a Rotary Blood Pump. *Artif Organs.* 2018;42(9):879-890.
45. Pauls JP, Nandakumar D, Horobin J, et al. The Effect of Compliant Inflow Cannulae on the Hemocompatibility of Rotary Blood Pump Circuits in an In Vitro Model. *Artif Organs.* 2017;41(10):E118-E128.
46. Harboe M. A method for determination of haemoglobin in plasma by near-ultraviolet spectrophotometry. *Scand J Clin Lab Invest.* 1959;11:66-70.
47. Leon L, et al. Clinical Significance of Superfical Vein Thrombosis. *Eur J Vasc Endovasc Surg.* 2005;29:10-17.

16 LIST OF APPENDICES

16.1 IFU



16.2 PIVC cannulation protocol

1. Assess the venous anatomy. In particular note and identify the location of nerves, arteries and muscle.

2. Asses the target vein for bifurcation, insertion point and valves.

3. Mark the target vessel with key pen dots. Using a sterile pen

1. Site of insertion “Mark 1”
2. Location of the valves “Mark V”
3. Location of catheter tip termination “Mark T”

When a sterile pen is not used place the marking parallel to the identified structures. When the skin antisepsis is applied the marking will be removed.

4. The clinician is to wash their hands prior to opening procedural equipment. No gloves are required at this stage.

5. Open the sterile Mutligate basic dressing pack layout this as your sterile field. Do not touch anything on the field without sterile gloves. This is your sterile working field. Place the following sterile items on the dressing field.

1. The desired PIVC
2. Foliodrape protect
3. The 15cm micro bore extension set
4. BD IV starter pack
5. Pro Pax Gauze swabs
6. A BD 1ml luer-lock syringe

120cm pull-up sterile non latex probe covers

6. Empty one sachet of sterilisation fluid and wipe area of insertion – allow to dry.

7. Open and put on gloves without touching portions of gloves that will make contact with the sterile field.

8. Place the sterile field under the patients' arm. Ensure the arm/ hand does not come in contact with the sterile working field.

An additional sterile field found in the additional insertion pack can be placed under the back of the hand.

9. Attach tourniquet making the assistant aware to tighten it when needed.

10. Place sterile fenestrated drape around the site of insertion- fold to reduce fenestration (adhesive is very sticky)

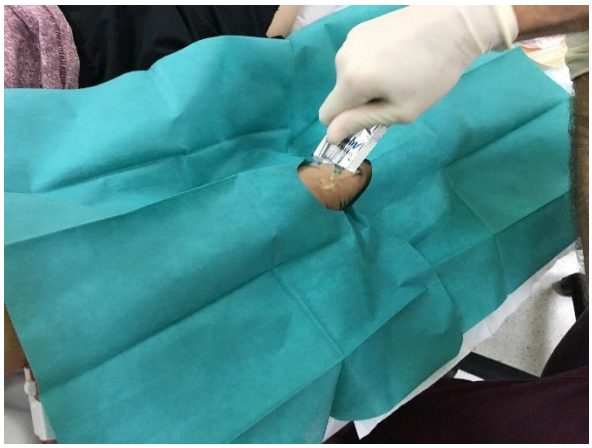
Clean area again (circular movement) and allow to dry.

11. Apply the swab-stick using liberal movements. If some solution remains in the packaging the assistant can pour this over the site of insertion.

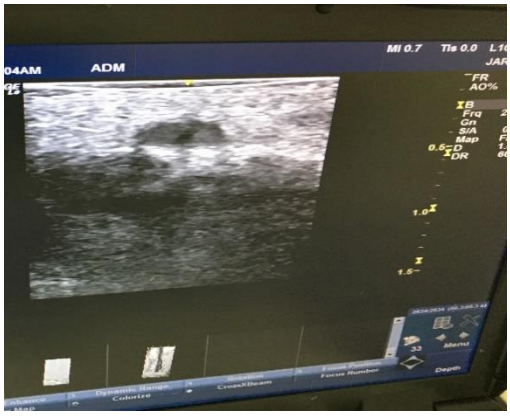
12. Gently squeeze inner cardboard sterile ultrasound cover. Apply gel into the ultrasound probe cover.

13. Ask the assistant to drop carefully the paediatric probe into the sterile probe cover. Tighten membrane to ultrasound transducer surface and apply the blue elastic bands.

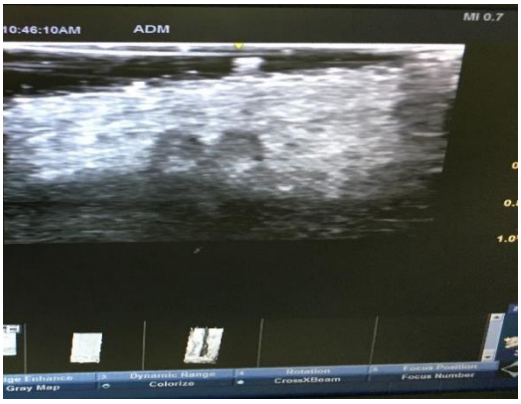
14. Apply a small amount of ultrasound gel on the area for insertion. Apply tourniquet if necessary (<0.2cm).



15. Ensure the vein is centre of the screen. Using the yellow guide on the screen and the centre mark on the probe line up the PIVC to pierce the skin. You can orientate your probe from Transverse to longitudinal.

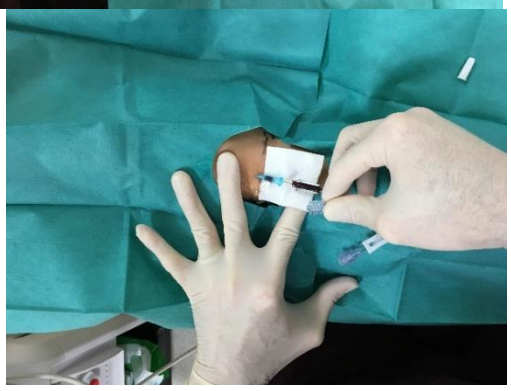


16. Insert the PIVC through the skin ensuring you are looking at the USG image. A white echogenic dot signifies the needle tip. Be careful to consider shadowing and therefore orientate the probe from Transverse to longitudinal. Advance the probe mms forward and then the PIVC mm (prevents damage)



17. Once you are satisfied that the PIVC is well in the vein or in as far as it can go advance the catheter off the needle stylet.

18. Withdraw the needle from the catheter another 1cm. Then distally occlude the target vein, then; proximally occlude the cannulated vein the intension to stop any blood spillage. Remove the needle and insert in the sharps bin.



16.3 Quantification of cell-free haemoglobin

In accordance with previous research that has indicated the advantages and precision of the Harboe method for detection of cfHb [40-42], the study will measure cfHb via a direct spectrophotometric technique in conjunction with the Harboe assay which we have previously employed [43-45] and is an approved ISO test method for haemolysis (ISO 10993-4:2017). The measurement of cfHB will be performed within 12 hours of sample collection. To quantify cfHb via the Harboe assay, whole blood collected and anticoagulated with Ethylenediaminetetraacetic acid (EDTA), will be centrifuged at 1200 x g for 10 min. The top half of the supernatant will be added to 0.01% Na_2CO_3 (1:6) and the absorbance of each sample will be measured at 380, 415 and 450 nm using a spectrophotometer (MultiSkan GO, Thermo Fisher Scientific; MA, USA). The cfHb will subsequently be calculated from these absorbances using the Harboe method [46] (Eq. 1).

Equation 1.

$$cfHb\ \left(\frac{mg}{dL}\right) = \left(\frac{167.2Abs_{415} - 83.6Abs_{450}\ - 83.6Abs_{380}}{10}\right) \times \frac{1}{dilution\ in\ Na_2CO_3}$$

Additionally, an automated biochemistry analyzer (AU480, Beckman Coulter, USA) will be employed for a clinical measurement of haemolysis; however, the accuracy of the device is not sensitive to measurements below 50 mg/dL. Lastly, visual assessment of haemolysis will be checked, and photographs taken of each sample.

16.4 Participant Instructions

Griffith UNIVERSITY
Queensland, Australia

School of Medical Sciences
Gold Coast campus
Griffith University,
Queensland 4222
Australia
griffith.edu.au

Participant lifestyle changes

Whilst you have the catheters in your arm, you there will be some lifestyle changes that you will need to make to avoid potential health complications. Below is a list of the changes that you will need to make.

Lifestyle restrictions

- Do not participate in any sport
- Do not go for a swim
- Do not undertake any physically vigorous activity
- Do not donate blood
- Do not shower at home (showering at clinical trials unit is ok, with a dressing cover)
- Do not participate in any other research trials

Dietary restrictions

- Try to avoid beetroot consumption
- Try to avoid consuming energy drinks high in taurine content (e.g., Monster, Red Bull, Mother)
- Do not consume alcohol

Consumption of these items may impact on the results of this trial

Medication restrictions

- Try to avoid consumption of ibuprofen, aspirin unless instructed by a medical practitioner
- Do not consume, inhale or inject, any illicit drugs

Participant instructions for use

Below is a set of guidelines, to help you take care of the catheters in your arm whilst away from the Clinical Trial Unit.

- ALWAYS keep the catheters and dressings covered with the daytime cover that has been provided
- DO NOT USE or ACESS the devices under ANY circumstances

Participant safety instructions

There is a very small risk that you will develop a health complication related to the catheter while at home. Below is a list of health-related complications that you should look out for. If you observe any of these complications, or have any other concerns, contact the clinical contact person listed on the following page.

- Pain along path (beyond the insertion site) of the catheter
- Redness (more than a 50 cent coin in size)
- Bruising (beyond the border of the dressing)
- Itchiness at the site
- Bleeding into the dressing or from the catheter
- Pus at the insertion site

The research team will provide you with some example pictures, so that you are better informed.

GU Ethics Ref: 2020/262

Griffith UNIVERSITY
Queensland, Australia

School of Medical Sciences
Gold Coast campus
Griffith University,
Queensland 4222
Australia
griffith.edu.au

CALL 000 IMMEDIATELY IF YOU HAVE ANY OF THE FOLLOWING SYMPTOMS, THEN NOTIFY PRINCIPAL INVESTIGATOR

- Excessive bleeding (i.e., that won't stop) from the site or catheter
- Pain along path of the catheter AND redness at area of catheter AND hardening of skin tissue at site of catheter insertion AND unanticipated sweating

Declaration by Participant

I have read the instructions, or someone has read it to me in a language that I understand.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

Clinical contact person

Name	Andrew Bulmer
Position	Principal Investigator
Telephone	0459 466 375
Email	a.bulmer@griffith.edu.au

GU Ethics Ref: 2020/262