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Cover page for Study Protocol

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IN.PACT BTK Study

Randomized Study of IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter vs. Optimal Percutaneous Transluminal Angioplasty for the treatment of chronic total occlusions in the infrapopliteal arteries

Clinical Investigational Plan (CIP)

CIP IDENTIFIER: APV-IN.PACT BTK OUS

VERSION 7.0

11/JUN/2020

Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	*Randomized Study of IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter vs. Optimal Percutaneous Transluminal Angioplasty (PTA) for the treatment of chronic total occlusions (CTO) in the infrapopliteal arteries* *IN.PACT BTK*
Clinical Investigation Plan Identifier	*APV-IN.PACT BTK OUS*
EUDAMED generated unique identifier	*provided under separate cover (once available)*
Study Product Name	*Investigational Device: IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter (hereinafter referred as "IN.PACT 014")*
Sponsor/Local Sponsor	*Sponsor* *Medtronic Aortic and Peripheral Vascular* *3576 Unocal Place* *Santa Rosa, CA 85403* *United States* *Local Sponsor* *Medtronic Bakken Research Center B.V.* *Endepolsdomein 5* *6229 GW Maastricht* *The Netherlands*
Document Version	*7.0*
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Lead Principal Investigator(s)	*Prof. Francesco Liistro* *Prof. Antonio Micari* *Italy*
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1. Version History

See Appendices 18.3 Version History

2. Investigator Statement

Study product Name	*IN.PACT 014*
Sponsor	*Medtronic Aortic and Peripheral Vascular* *3576 Unocal Place* *Santa Rosa, CA 85403* *United States* *Local Sponsor* *Medtronic Bakken Research Center B.V.* *Endepolsdomein 5* *6229 GW Maastricht* *The Netherlands*
Clinical Investigation Plan Identifier	*APV-IN.PACT BTK OUS*
Version Number/Date	*7.0, 11/JUN/2020*

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with all applicable regulatory guidelines, under which the study is being conducted, e.g., United Stated Food and Drug Administration regulations and the latest version of ISO 14155. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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3. Glossary

Term	*Definition*
ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
ASA	Aspirin
AT	As Treated
BMS	Bare Metal Stent
BTK	Below-The-Knee
CA	Competent Authority
CBC	Complete Blood Count
CD	Clinically Driven
CEC	Clinical Events Committee
CLI	Critical Limb Ischemia
CRF	Case Report Form
DAPT	Dual Anti-Platelet Therapy
DCB	Drug Coated Balloon
DEB	Drug Eluting Balloon
DES	Drug Eluting Stent
DS	Diameter Stenosis
DMC	Data Monitoring Committee
DUS	Duplex Ultrasound
EC	Ethics Committee
eCRF	Electronic Case Report Form

Term	*Definition*
EDC	Electronic Data Capture
EQ-5D	EuroQol Five Dimension Scale
FU	Follow Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IFU	Instruction For Use
ISO	International Organization for Standardization
ITT	Intention-to-Treat
LLL	Late Lumen Loss
MAE	Major Adverse Events
MD-TLR	Mechanically-Driven Target Lesion Revascularization
NHLBI	National Heart, Lung, and Blood Institute
NOAC	Novel Oral Anticoagulants
P3	3rd Segment of the Popliteal Artery
PAD	Peripheral Artery Disease
PI	Principal Investigator
PTA	Percutaneous Transluminal Angioplasty
PTX	Paclitaxel
QVA	Quantitative Vascular Angiography
RBP	Rated Burst Pressure
RCC	Rutherford Clinical Category
RCT	Randomized Controlled Trial
RVD	Reference Vessel Diameter

Term	*Definition*
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFA	Superficial Femoral Artery
SoC	Standard of Care
TL	Target Lesion
TLR	Target Lesion Revascularization
TV	Target Vessel
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect
WIfI	Wound, Ischemia and foot Infection

4. Synopsis

Title	Randomized Study of IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter vs. Optimal Percutaneous Transluminal Angioplasty for the treatment of chronic total occlusions in the infrapopliteal arteries [IN.PACT BTK]
Clinical Study Type	First In Human, Interventional, Pre-market
Product Name	Investigational Device: IN.PACT 014 Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter (hereinafter referred as "IN.PACT 014")
Sponsor	Funding Source: Medtronic Aortic and Peripheral Vascular 3576 Unocal Place Santa Rosa, CA 85403 United States
Local Sponsor	Medtronic Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands
External Organizations	**Independent Angiographic Core Laboratory** Beth Israel Deaconess Medical Center, Inc., 375 Longwood Ave., MA 02215 Boston, USA **Independent Duplex Ultrasound (DUS) Core Laboratory** Vascore Ultrasound Core Laboratory, Bowdoin Square 10th Floor Boston, MA 02114, USA **Clinical Event Committee (CEC)** Syntactx Europe BVBA, independent CRO, Tolstraat 26, 9550 Herzele, Belgium **Data Monitoring Committee (DMC)** Syntactx Europe BVBA, independent CRO, Tolstraat 26, 9550 Herzele, Belgium

	Imaging Contract Research Organization (CRO) Medidata Solutions, Inc., a Delaware corporation, 350 Hudson Street, 9th Floor, New York, New York 10014, USA **Interactive Web Response System (web-based randomization system)** Bracket, 303 Second Street, Suite 700, 7th Floor, South Tower, San Francisco, California 94107, USA
Indication under investigation	Treatment of chronic total occlusions (CTO) in the infrapopliteal arteries.
Investigation Purpose	To assess the safety and efficacy of the paclitaxel drug-eluting balloon IN.PACT 014 versus conventional, optimal percutaneous transluminal angioplasty (PTA) for the treatment of patients with chronic total occlusions in the infrapopliteal arteries. This information can be used for regulatory purposes.
Product Status	IN.PACT Paclitaxel-Eluting Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter (IN.PACT 014) is the investigational combination product used in the study.
Primary Objective(s)	To assess the efficacy of the IN.PACT 014 by comparing the Late Lumen Loss (LLL) 9 months after the index procedure of the investigational product vs optimal (conventional) PTA

Secondary Objective(s)	• Composite Safety Endpoint: A composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically-driven TLR within 9 months post-index procedure.
	• Major Adverse Event (MAE) rate, defined as a composite of all-cause mortality, target limb major amputation and clinically-driven TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Functional flow assessment at 3, 6, 9, 12, 24 and 36 months, defined as absence of target lesion occlusion (no flow) assessed by duplex ultrasound.
	• Death of any cause and cardiovascular related deaths through 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Rate of major target limb amputation through 30 days, 3, 6, 9 ,12, 24, 36,48 and 60 months.
	• Rate of CD-TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Rate of Mechanically Driven TLR through 37 days.
	• Rate of TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Rate of CD-TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Rate of TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Status of wound healing (completely healed - improvement – unchanged – worsened) at 30 days, 3, 6, 9, 12, 24 and 36months.
	• Rate of thrombosis at the target lesion through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months.
	• Device success (for investigational device only)
	  ○ Device success is defined as successful drug delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP).
	• Clinical success
	  ○ Clinical success is defined as residual stenosis of ≤ 30% without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.

Study Design	This is a prospective, multi-center, randomized (1:1) study to evaluate the efficacy and safety of the IN.PACT 014 in the treatment of CTOs in the infrapopliteal arteries. All subjects will be followed with baseline, procedure, discharge, and follow-up evaluations at 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months post procedure.
Randomization	1:1 randomization of IN.PACT 014 and optimal PTA

Sample Size	At a minimum 50 patients are planned for enrollment.
Inclusion/Exclusion Criteria	**Inclusion Criteria** 1. Age ≥18 years. 2. Subject has been informed of the nature of the study, agrees to participate and has signed an Ethics Committee (EC) approved consent form. 3. Female subjects of childbearing potential have a negative pregnancy test ≤7 days before the procedure and are willing to use a reliable method of birth control for the duration of study participation. Female subjects will be exempted from this requirement in case they are sterile, infertile, or have been post-menopausal for at least 12 months (no menses). 4. Subject has documented chronic Critical Limb Ischemia (CLI) in the target limb prior to the study procedure with Rutherford Clinical Category 4 or 5. 5. Subjects with documented infection grade 0-2 and ischemia grade 2-3 according to the WIfI classification. 6. Life expectancy >1 year in the Investigator's opinion. 7. Reference Vessel Diameter (RVD) 2 - 4 mm, and confirmed by DUS assessment. 8. Total occlusions (100% stenosis) with total lesion length ≥40mm (by visual estimate). 9. The lesion must be located in the infrapopliteal arteries and above the ankle joint. Lesions may not extend above the tibioperoneal trunk (P3 segment of the popliteal artery) or below the ankle joint (arteries of the foot), nor can the treatment (investigational device or standard PTA, including pre-dilatation) extend beyond these indicated regions for more than 1 cm.

Note:

- A target lesion can extend into the P3 segment in case it involves a straight lesion extending from the target vessel.
- Non-significant stenosis below the ankle joint can be allowed in case this is not part of the target lesion and does not require treatment

10. Multiple lesions can be treated if they are located in separate vessels but all lesions must meet the protocol specified criteria.
11. Presence of documented run-off to the foot (clearly visible dorsalis pedis, pedal arch or plantar arteries by angiography). Target vessel should give direct or indirect run-off to the foot.
12. Inflow free from flow-limiting lesion confirmed by angiography. Patients with flow-limiting inflow lesions (≥ 50% stenosis) can be included if lesion(s) have been treated successfully before enrollment, with a maximum residual stenosis of ≤30% per visual assessment. If an inflow lesion must be treated within or above the P3 segment of the popliteal artery, there must be a minimum of 3 cm healthy tissue between this (treated) lesion and the infrapopliteal target lesion.
13. Successful pre-dilatation of the (entire) target lesion. Success being documented by angiographic visual estimate of ≤30% Residual diameter stenosis of the target lesion and by functional assessment of the distal flow by intra-operative Doppler: recording of biphasic or triphasic wave signal with rapid take-off distal to the target lesion.

Exclusion Criteria

1. Subject unwilling or unlikely to comply to the appropriate follow-up times for the duration of the study.

   Note: the investigator should discuss the follow-up requirements extensively during the Informed consent process to ensure that the subject is fully aware about the expectations and is willing to comply with the follow-up schedule.
2. Planned index limb amputation above the metatarsal level, or any other planned major surgery within 30 days pre or post-procedure. A planned amputation including and below the metatarsal level (1 or multiple rays) is accepted.
3. Lesion and / or occlusions located or extending in the popliteal artery or below the ankle joint space.

	Note: • A target lesion can extend into the P3 segment in case it involves a straight lesion extending from the target vessel. • Non-significant stenosis below the ankle joint can be allowed in case this is not part of the target lesion and does not require treatment. 4. Significant (≥50% DS) inflow lesion or occlusion in the ipsilateral Iliac, SFA and popliteal arteries left untreated. 5. Failure to obtain a ≤30% residual stenosis in pre-existing, hemodynamically significant (≥50% DS) inflow lesions in the ipsilateral iliac, SFA and popliteal artery. Inflow lesions should be treated per standard of care. 6. Prior stent(s) or bypass surgery within the target vessel(s) (including stents placed within target vessels during the index procedure prior to randomization). 7. Previous DCB procedure in the target vessel within 6 months prior to index procedure. 8. Aneurysm in the target vessel. 9. Angiographic evidence of thrombus within target limb. 10. Pre-dilation resulted in a major (≥ Grade D) flow-limiting dissection (observed on 2 orthogonal views) or residual stenosis >30%. 11. Use of alternative therapy, e.g. atherectomy, cutting balloon, laser, radiation therapy, stents as part of target vessel treatment. Note: Use of stents is only allowed for bailout stenting. 12. Recent MI or stroke <30 days prior to the index procedure. 13. Heart failure with Ejection Fraction <30%. 14. Known or suspected active infection at the time of the index procedure (abnormal white blood cell count, fever, sepsis or positive blood culture), excluding an infection of a lower extremity wound on the target limb (only WIfI infection grade 0-2 allowed). 15. Subjects with infection grade 3 and ischemia grade 0 and 1 according to WIfI classification. 16. Subjects with neurotrophic ulcers, heel pressure ulcers or calcaneal ulcers with a risk for major amputation. 17. Subjects with documented active osteomyelitis, excluding the phalanges, that is beyond cortical involvement of the bone per clinical judgement.

	18. Impaired renal function (GFR <20 mL/min) or patients on dialysis. 19. Subject with vasculitis, systemic Lupus Erythematosus or polymyalgia rheumatica on active treatment. 20. Patient receiving systemic corticosteroid therapy (expected dosage exceeding 5 mg of prednisolone or equivalent, per day, during the initial 9 months after procedure). 21. This criteria has been removed. 22. Known allergies or sensitivities to heparin, aspirin (ASA), other anticoagulant/anti-platelet therapies which could not be substituted, and/or paclitaxel or an allergy to contrast media that cannot be adequately pre-treated prior to the index procedure. 23. The patient is currently enrolled in another investigational device or drug trial that is interfering with the endpoints of this study. 24. Female subjects who are breast-feeding at the time of enrollment.
Study Procedures and Assessments	Describe procedure schedule by visit **Screening visit:** • Screening Inclusion/Exclusion and consent • Physical Exam • Pregnancy test when applicable • Medical history and demographics • Baseline Medications • Rutherford Classification • WIfI assessment • EuroQol-5D questionnaire (EQ-5D) **Procedure visit:** • Angiographic inclusion/exclusion • DUS study specific procedure for RVD sizing • Successful pre-dilatation of the target lesions • Intra-operative Doppler examination • Randomization and enrollment • Medications • Adverse Events Assessment **Discharge visit:**

	• Physical Exam • DUS if available • Medications • WIfI assessment • Wound assessment and wound care* • EuroQol-5D questionnaire (EQ-5D) • Adverse Events Assessment **30 days and 3, 6 months visits:** • Physical Exam • DUS study specific procedure • Rutherford Classification • Medications • WIfI assessment • Wound assessment and wound care* • EuroQol-5D questionnaire (EQ-5D) • Adverse Events Assessment **9 months visit:** • Physical Exam • DUS study specific procedure • Angiographic study specific procedure • Rutherford classification • Medications • WIfI assessment • Wound assessment and wound care* • EuroQol-5D questionnaire (EQ-5D) • Adverse Events Assessment **12, 24 and 36 months visits:** • Physical Exam • DUS study specific procedure • Rutherford Classification • Medications • WIfI assessment • Wound assessment and wound care* • EuroQol-5D questionnaire (EQ-5D) • Adverse Events Assessment **48 and 60 months phone calls:** • Adverse Events Assessment **Unscheduled Visits:** • Physical Exam • DUS study specific procedure • Angiography (if available) • Rutherford Classification • Medications

	• WIfI assessment • Wound assessment and wound care* • EuroQol-5D questionnaire (EQ-5D) • Adverse Events Assessment **Upon Early Termination Phone Calls:** • (Vital) Health Status
Safety Assessments	Clinical Event Committee and Independent Data Monitoring Committee will supervise study conduct, subject safety and adjudicate clinical events related to both Primary and Secondary Endpoints.
Statistics	The primary analysis for the study objectives will be Intention-to-Treat (ITT) analysis. The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of treatment received. Late Lumen loss in each arm and the difference between the two arms (with 95% 2-sided confidence intervals) will be presented at 9 months. Frequency and percentage will be calculated for endpoints that are categorical. Summary statistics (mean, standard deviation, median, min, max) will be presented for endpoints that are continuous.

* Wound assessment and wound care is only applicable for subjects that present with (ischemic) wounds on the target limb at baseline or for subjects who develop new (ischemic) wounds on the target limb during the conduct of the study. In case of planned amputations (that meet the inclusion criteria for this study) the amputation wound(s) will be monitored throughout the study.

5. Introduction

5.1. Background

Peripheral arterial disease (PAD) is a commonly occurring medical condition that involves atherosclerosis in vessels located outside the heart and brain. PAD affects an estimated 27 million adults in Europe and North America.[1] Patients suffering from PAD generally experience a significant reduction in health-related quality of life (QOL). In some cases, PAD can cause patients to suffer from debilitating symptoms including loss of limbs. Based on objective testing conducted across a variety of epidemiologic studies, the prevalence of PAD is estimated to be between 3% and 10%. In patients greater than 70 years of age, the estimated prevalence is much higher, at 15% to 20%.[2] Despite the potentially devastating consequences of PAD, it is estimated that nearly 75% of patients suffering from PAD fail to undergo treatment for the condition.[3] With respect to prognosis, one-fourth to one-third of all patients with PAD will experience disease progression, with one to five percent eventually needing amputation.[4-6]

Patients with PAD tend to experience an increase in morbidity and a reduction in health status measures of health-related QOL. Potential consequences of lower extremity arterial disease include reduced mobility, limb pain, gangrene, and amputation, as well as increased mortality, amongst others.[2,7,8] Critical limb ischemia (CLI) refers to severe persistent rest pain requiring treatment with analgesics, ulceration or gangrene on the distal extremity.[9] CLI is so severe that patients suffering from it experience physical function, pain, and general health perception that are similar to or worse than patients with congestive heart failure or recent myocardial infarction. Patients with PAD generally have a number of comorbidities including cardiovascular disease (CVD), which may explain the increased risk of mortality from myocardial infarction (MI) and stroke.[7,10,11] Mortality rates at five years range from 30% to 44% in patients with PAD.[12,13]

PAD located below-the-knee is more likely to be diffuse and progressive than above-the-knee PAD, which is often characterized by multilevel disease and heavily calcified lesions.[9,14] Patients often present with symptoms of CLI as opposed to claudication. Comorbidities such as diabetes and renal failure occur rather frequently alongside PAD.[9] The instruments used to treat PAD differ based on whether the location is above- or below-the-knee. Arteries below-the-knee are narrower than those above-the-knee. As such, below-the-knee arteries are appropriately managed with instruments of smaller sizes than the instruments used to treat above-the-knee diseases.

Below-the-knee arteries are often treated with devices originally intended for use in coronary artery disease, such as 0.014" guidewires and PTA balloons less than 4 mm in diameter.[9]

Open surgical interventions and endovascular techniques are available as treatment modalities for patients with PAD. Bypass surgery has been shown to be effective in treating PAD. However, it is associated with a number of serious risks including wound complications, death, myocardial infarction (MI), infection, and leg edema.[15,16] Endovascular treatments for PAD include percutaneous angioplasty and stenting. These endovascular modalities are associated with decreased morbidity and faster recovery times than surgical bypass. The downside to endovascular treatment is decreased longevity, as shown by the high rates of restenosis following PTA and stent implantation.[17] If stenting in the infra-popliteal arteries proves to be unsuccessful, patients may be limited in terms of their ability to undergo surgical interventions moving forward. In light of these concerns, recommendations for below-the-knee stenting have been limited to stent placement following sub-optimal angioplasty results or severe dissection. [18,19]

Outcomes of percutaneous angioplasty interventions and/or stenting for below-the-knee PAD are available throughout the literature. A meta-analysis of 30 studies conducted between 1990 and 2006 of infra-popliteal PTA for chronic CLI reported a pooled estimate of 89% technical success with one-year results of 58% primary patency, 86% limb salvage, and 87% patient survival.[20] Schmidt et al. reported on 77 infra-popliteal arteries treated with angioplasty. Their results showed a 68.8% angiographic restenosis rate at 3 months and 50% reintervention rate.[21] A randomized controlled trial (RCT) comparing stenting and PTA of the infra-popliteal arteries showed no advantage of stenting over PTA. The 1-year patency rate was 56% in patients that were stented vs. 66% in patients treated with PTA.[18] A meta-analysis of bail-out stenting, including studies with bare-metal stents and drug-eluting stents, reported a pooled 1-year patency rate of 78.9%. The stent coated with sirolimus demonstrated the greatest benefit over bare-metal stents (93.1% vs. 73%). These findings suggest that use of stents that elute anti-proliferative agents may result in further benefit in terms of restenosis rates as compared to uncoated PTA and bare metal stents.[22]

The local application of anti-proliferative drugs such as sirolimus and Zotarolimus via stent delivery system has been successful for prevention of restenosis in coronary arteries. Clinical studies have proven these agents successful in their attempts to inhibit or reduce restenosis.[23-34] Preliminary study results were favorable towards increased use of drug-eluting stents (DES) in the superficial femoral and proximal popliteal arteries. Unfortunately, these promising early results have not been sustained over time.[35,36] Several nonrandomized studies suggested promising results with use of DES in management of patients with below-the-knee PAD.[37-41] RCTs have demonstrated the superiority of DES over bare metal stents (BMS) for below-the-knee disease. The YUKON-BTK study randomized 161 patients to DES or BMS. Results showed higher rates of event-free survival and freedom from target lesion revascularization at the 3-year follow-up in the DES group than the BMS group.[42] The DESTINY trial randomized 140 patients with CLI to Everolimus-eluting stents or BMS. Results from the DESTINY trial demonstrated significantly higher primary patency and freedom from target lesion revascularization at 12 months in the DES group.[43] The ACHILLES study randomized patients with CLI to sirolimus-eluting stents (n=99) or PTA (n=101). The 1-year results showed significantly less restenosis for the DES group (22.4%) than the PTA group (41.9%; p=0.019).44 Despite the generally favorable results, there are outstanding concerns regarding use of below-the-knee stents. These concerns are centered around the potential for stent fractures, in-stent thrombosis, and reduction of future surgical options.

Moreover, studies assessing the efficacy of DES in infrapopliteal lesions, included mostly short lesions: a metanalysis of DES for revascularization of infrapopliteal arteries showed that the median lesion length was only 26.8 mm which could be perceived as not representative for patients encountered in daily practice, which often present with very diffuse disease (> 10cm).[45]

Paclitaxel-Coated Angioplasty Balloons

Paclitaxel is an antineoplastic drug that has demonstrated sustained inhibition of smooth muscle cell proliferation in several pre-clinical studies.[46-49] Publications assessing effectiveness of local administration of paclitaxel on restenosis via drug-coated balloons in the femoropopliteal artery have shown promising results, as seen by reduced neointimal proliferation in the peripheral arteries.[50-56] Recent publications have discussed outcomes regarding use of paclitaxel-coated balloons in patients with below-the-knee disease.

The first assessment of paclitaxel-coated balloons in the infra-popliteal arteries was published by Schmidt et al. in 2011.[57] A total of 109 long-segment infra-popliteal lesions in 104 patients were treated for CLI (82.6%) or severe claudication (17.4%) with the IN.PACT Amphirion Paclitaxel-coated balloon.

The vast majority of patients (77.1%) in the study suffered from occlusion of all three infra-popliteal arteries. A single infra-popliteal artery was treated in 104 of the 109 patients in the study. The mean lesion length for treated arteries was 176±88 mm. Clinical improvement, defined as reduction in ulcer size or depth of at least 50% or increase of at least one Rutherford-Becker clinical classification, was achieved in 75.8% of the treated limbs amongst the 94 patients available at 3-month follow-up. Angiographic evaluation was done at 3 months in 84 of the treated arteries. Amongst this group, 72.6% of arteries remained free of significant restenosis. Most of the 27.4% lesions with restenosis of more than 50% experienced restenosis as opposed to occlusion. Most of these arteries demonstrated restenosis that was focal in nature (<20% of length of initial treated lesion). At one year, 86 patients with 91 lesions were available for follow-up evaluation. Clinical improvement was achieved in 91.2% of limbs from this group. Target lesion revascularization occurred in 17.3% of lesions. There were no bypass surgeries performed during the follow-up period. The rate of limb salvage was 95.6% in patients with CLI patients. The vast majority of patients with CLI (74.2%) experienced complete wound healing. These early studies using paclitaxel-coated balloons to manage complex below-the-knee lesions have shown paclitaxel-coated balloons to be superior to uncoated balloons with regard to restenosis rates.

The DEBATE-BTK study was a randomized trial designed to evaluate the use of drug-coated balloons for below-the-knee angioplasty in diabetic patients with CLI.[58] A total of 132 patients with 158 infra-popliteal lesions were enrolled. Sixty-five patients with 80 lesions in 71 limbs were randomized to angioplasty with a drug-eluting balloon (IN.PACT Amphirion), while 67 patients with 78 lesions in 72 limbs were randomized to angioplasty with an uncoated balloon (Amphirion Deep). Patients presenting with occlusions at baseline (CTO) was similar in both groups (77.5% in the drug-eluting balloon group vs 82.1% in the PTA group). Binary restenosis, defined as reduction in luminal diameter greater than 50%, at 12 months was significantly lower at 12 months in lesions treated with the drug-eluting balloon (DEB, 27%) than in lesions treated with an uncoated balloon (74%; p<0.001). Patients treated with DEB experienced occlusion of fewer target vessels and occlusion of shorter target vessels than those treated with uncoated balloons (17.6% vs. 55.4%; p<0.001). The freedom from TLR was significantly higher in the DEB group (85% vs. 63%; p=0.02). The DEB group also experienced a significantly lower major adverse event rate than the uncoated balloon group (31% vs. 51%; p=0.02). Complete ulcer healing was also higher at 12 months for the DEB group than the PTA group (86% vs. 67%; p=0.01). Longer-term results showed similar benefits of DEB over PTA extended out to at least 24 months.[59]

The first multi-center, prospective, single-blinded RCT (randomized-controlled trial), IN.PACT DEEP, comparing DEB (IN.PACT Amphirion) to uncoated PTA consisted of a 2:1 randomization to either DEB (n=239) or PTA (n=119).[59] The baseline patient characteristics were similar between groups. The only significant difference was a greater number of previous target limb revascularizations in the DEB arm than the PTA arm (32.2% vs. 21.8%). In both groups, a minority of patients presented at baseline with CTO-lesions (38.6% in the DEB group vs 45.9% in the PTA group. Lesion and procedural characteristics which differed between the groups included longer lesions in the PTA group, more pre-dilation in the DEB group (90.5% vs. 36.0%), more procedural complications in the DEB group (9.7% vs. 3.4%), and more post-procedural dissections in the PTA group (12.3% vs. 19.2%). At baseline, wounds were significantly deeper in the PTA group than the DEB group. The primary efficacy endpoints were 12-month clinically-driven TLR as well as late lumen loss for the 167-patient subset with angiographic data at 12 months. Differences between the DEB and PTA groups were not significant with respect to either endpoint. The clinically-driven TLR rate was 9.2% for the DEB group and 13.1% for the PTA group (p=0.29). Late lumen loss was 0.61±0.78 for the DEB group and 0.62±0.78 for the PTA group (p=0.95).

The composite safety endpoint of all-cause death, major amputation, and clinically-driven TLR at 6 months was also similar between arms, occurring at a rate of 17.7% in the DEB group and 15.8% in the PTA group.

While the difference was not statistically significant, there was a higher rate of major amputations in the DEB group (8.8% vs. 3.6%; p=0.08). It is difficult to determine why the results obtained by the PTA arm were much better than one may have estimated using historical data. The binary restenosis rate (35%) and major amputation rate (3.6%) observed in the PTA arm were both much lower than expected based on the literature involving PTA in management of patients with CLI.[20,21,44] To obtain a more thorough understanding of the risks and benefits associated with use of DEB in the management of patients with CIL, additional studies using a more controlled standardization of amputation definitions and wound management protocols are needed.

It would also be necessary to obtain core laboratory adjudication as well as clinical event committee and data safety and monitoring board oversight.[60-62]

The BIOLUX P-II trial investigated the efficacy and safety of the Passeo-18 LUX Paclitaxel coated balloon. In this prospective, multicentre randomized first-in-man study, 72 subjects were randomized 1:1 to either a Passeo-18 Drug Eluting Balloon (DEB) (n = 36) or a non-coated Passeo-18 PTA (n = 36). In order to be included, the lesions had to be occluded or show high-grade stenosis (≥ 70% diameter reduction). The primary safety endpoint (a composite of all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularization at 30 days) was 0% in the DEB group versus 8.3% in the PTA group (p = 0.239). The primary performance endpoint (patency loss at 6 months) was 17.1% in the DEB group versus 26.1% in the PTA group (p = 0.298), and major amputations of the target extremity occurred in 3.3% versus 5.6% of the patients at 12 months, respectively.[63]

More recently, the results of a retrospective analysis of the Lutonix Paclitaxel coated balloon were published.[64] Fifty-five patients with symptomatic PAD and Rutherford stage > 3 were treated with the Lutonix DCB in the BTK vessels and followed to assess safety and efficacy. 72.2% of patients were treated for CTO disease (total occlusion at baseline). Taking into consideration the inherent limitations of a retrospective analysis and a small sample size, the results were favourable for DCB treatment in the BTK vessels: TLR occurred in 21.8% of patients, two below-the-ankle amputations were performed and no patients died. Freedom from death or major amputation was 96.5% and wound healing was 89.1%. This let the authors conclude that the Lutonix DCB showed safety and efficacy in BTK interventions in CLI patients.

5.2. Purpose

To assess the safety and efficacy of the paclitaxel drug-coated balloon IN.PACT 014 versus conventional percutaneous transluminal angioplasty (PTA) for the treatment of patients with chronic total occlusions in the infrapopliteal arteries. This information can be used for regulatory purposes.

6. Objectives and Endpoints

6.1. Objectives

6.1.1. Primary Objective(s)

To assess the efficacy of the IN.PACT 014 by comparing the Late Lumen Loss (LLL) of the investigational product vs optimal (conventional) PTA.

6.1.2. Secondary Objective(s)

To assess the safety of the IN.PACT 014 by comparing pre-specified safety parameters of the investigational product vs optimal (conventional) PTA. Other pre-specified parameters assessing efficacy and safety and clinical utility measures will be evaluated and rates will be compared for the IN.PACT 014 vs optimal PTA.

6.2. Endpoints

6.2.1. Primary Endpoint

The primary efficacy endpoint will be Late Lumen Loss (LLL) at 9 months post procedure for the IN.PACT 014 Investigational device vs optimal PTA. LLL will be assessed by means of Quantitative Vascular Angiography (QVA) by an independent angiographic core lab at 9 months post procedure or at the time of TLR (prior to any intervention on the target lesion).

Restenosis of the target lesion remains an important problem in the treatment of occlusive lesions in below the knee arteries. Neointimal proliferation is a major culprit leading to a decrease in the arterial luminal diameter and eventually (re)stenosis. As it is expected that paclitaxel will reduce this neointimal proliferation, LLL has been selected as primary endpoint.

6.2.2. Secondary Endpoint(s)

- Composite Safety Endpoint: A composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically-driven TLR within 9 months post-index procedure.
- Major Adverse Event (MAE) rate, defined as a composite of all-cause mortality, target limb major amputation and clinically-driven TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Functional flow assessment at 3, 6, 9, 12, 24 and 36 months, defined as absence of target lesion occlusion (no flow) assessed by duplex ultrasound.
- Death of any cause and cardiovascular related deaths through 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Rate of major target limb amputation through 1, 3, 6, 9 ,12, 24, 36, 48 and 60 months.
- Rate of CD-TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Rate of Mechanically Driven TLR through 37 days.
- Rate of TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Rate of CD-TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Rate of TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Status of wound healing (completely healed - improvement – unchanged – worsened) at 30 days, 3, 6, 9, 12, 24 and 36 months.
- Rate of thrombosis at the target lesion(s) through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months.
- Device success (for investigational device only)

  Device success is defined as successful drug delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP).

- Clinical success

  Clinical success is defined as residual stenosis of ≤ 30% without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.

7. Study Design

This is a prospective, multi-center, randomized (1:1) study to evaluate the efficacy and safety of the IN.PACT 014 in the treatment of CTOs in the infrapopliteal arteries. Enrollment per site should be limited around 30% of the total enrollment.

The study will enroll at a minimum 50 subjects that will be randomized to the investigational product (IN.PACT 014) or a standard PTA balloon. Randomization will happen after screening of the subject, to assess the subject meets all the inclusion criteria and does not meet any of the exclusion criteria specified in this protocol; this includes meeting the criteria for successful pre-dilatation of the target lesion(s). Patient randomization will be determined centrally by means of a web-based system.

In addition to the randomization outlined above, the following measures have been taken to avoid bias:

- A multi-center design is used to help ensure a representative sample of the physicians performing the procedure and to provide a reasonable enrollment period.
- Enrollment per site should be limited around 30% of the total sample-size.
- Clinical endpoints are reviewed and assessed by an independent Clinical Event Committee.
- Endpoints that are based on imaging will be reviewed and assessed by independent core labs.
- Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results are covered by the Inclusion and Exclusion criteria.
- Preferably, one interventional operator per site will be identified to perform all procedures to minimize intra-operator induced bias.
- A blinding plan will be implemented according to 'Randomization and Blinding Plan'.

7.1. Duration

The estimated duration of the study is approximately 84 months from the time of first subject enrollment to the last study protocol-required follow-up contact. Each subject will be followed for 60 months.

7.2. Rationale

The treatment of patients presenting with CLI by using standard PTA (without drug coating: Plain Old Balloon Angioplasty or POBA) is associated with a significant rate of restenosis (loss of patency).[21] Neointimal proliferation is expected to play an important role in the development of restenosis. The comparison of Late Lumen Loss (LLL) after treatment with the IN.PACT 014 (coated with Paclitaxel) versus PTA (POBA) is intended to provide more information on the inhibitory effects of paclitaxel delivered onto the vessel wall towards neointimal proliferation in subjects with below-the-knee arterial occlusive disease. For the design of this first-in-human study, randomization against POBA was selected, with the intention to show the effect of the addition of Paclitaxel. This will enable for the analysis to compare to a control group that was subjected to the same PTA during the index procedure. The endpoint of LLL at 9 months post index procedure was selected, as the available evidence (there is only limited evidence obtained from controlled randomized controlled trials) have shown a trend for reduction of CD-TLR at 12 month follow up in favor of the DCB (which was not statistically significant).[62] This trend in favor of DCB are suggestive to appear as of 6 months of follow up (careful interpretation of the Kaplan-Meier curve, Medtronic Data on File), and for this reason this study is intended to show any difference in the selected primary endpoint (LLL) at 9 month follow up. For the study population, patients with CTO were selected. These CTOs are typically difficult to treat, and because of complete stenosis (occlusion) at baseline, maintaining a sufficient luminal diameter is considered essential. For this reason, while assessing LLL as primary endpoint, subjects with CTO at baseline are at increased risk for "lumen loss", and a potential benefit of the investigational device compared to PTA can be considered clinically significant in this subject population. This potential increased benefit of PTX coated balloons over PTA in CTO-lesions has previously been suggested by Liistro during an oral presentation[65] when comparing the rates of patients presenting with CTO-lesions at baseline in the DEBATE-BTK trial and in the IN.PACT DEEP trial: in the DEBATE-BTK trial this rate was approximately 80% in both groups, while only approximately 40% in both groups in the IN.PACT DEEP trial, and might have played a role in the outcomes of both trials.

8. Product Description

8.1. General

The IN.PACT 014 is a medical device that contains an ancillary medicinal substance. The product consists of an over-the-wire (OTW) balloon catheter with a drug-coated balloon at the distal tip. The product is indicated for percutaneous transluminal angioplasty in patients with obstructive disease of peripheral arteries. The IN.PACT 014, including its components, is considered an investigational product.

The medicinal substance component, referred to as the Freepac™ drug coating, consists of the medicinal substance paclitaxel and the excipient urea provides a nominal drug dose density of 3.5µg/mm^2. The device component physically dilates the vessel lumen by Percutaneous Transluminal Angioplasty (PTA) (primary mode of action), and the medicinal substance provides a pharmacological agent targeted towards reducing the injury response that leads to restenosis (secondary mode of action).

Balloon coating

The balloons are coated with the FreePac™ drug formulation which consists of a solvent mixture that is 9 parts tetrahydrofuran (THF) to 1 part water by volume, while the solute is 50 mg/mL of paclitaxel (drug) and 7 mg/mL urea (excipient) by weight. The FreePac™ coating is applied at a nominal drug dose density of 3.5 µg per mm^2 to the balloon surface area. The drug coating consists of a single layer applied along the entire working length of the balloon. Paclitaxel was approved for use for the treatment of stenotic or obstructive vascular lesions in the lower extremities in various CE Marked commercial products such as disease of the peripheral arteries: IN.PACT Admiral (Medtronic), Lutonix ® 014 (Bard), Ranger SL (Boston Scientific), and the Passeo-18 Lux (Biotronik).

The IN.PACT 014 balloon components are made of polyamide (nylon [PA 12]). This material is utilized in the commercially available IN.PACT™ Admiral balloons. The IN.PACT 014 drug-coated balloon (DCB) design shown in Figure 1 is identical to all the other IN.PACT DCB family designs in formulation and target dose per surface area applied. Utilization of the existing FreePac™ coating and similar balloon material used on IN.PACT Admiral will allow this product to leverage the large pool of existing clinical data, which shows strong safety and efficacy in drug eluting balloons.

Catheter design

IN.PACT 014 is a dual lumen product (co-axial), available in two usable catheter lengths, 100 cm and 150 cm, in a range of balloon sizes from 2.0 to 4.0 mm in cylindrical balloon diameter and 40 to 120 mm in length. The guidewire lumen (central lumen) will permit the use of guidewires to facilitate advancement of the IN.PACT 014 catheter to and through the stenosis to be dilated. The catheter will be compatible with 0.014" diameter guidewires. In order to correctly position the balloon of either product under fluoroscopy, two Platinum-Iridium radio-opaque markers are swaged on the guidewire shaft under the balloon itself to define the dilatation area.

Figure 1: Engineering diagram of the IN.PACT 014 Balloon Catheter

The IN.PACT 014 delivery catheter has an OTW construction consisting of a proximal luer, a coaxial dual lumen shaft, and a distal balloon. The tri-layer inner tubing with black colorant (guidewire tube) serves as guidewire lumen and is compatible with guidewires of 0.014" as maximum diameter. The annular space surrounding the guidewire tube and the outer polyamide tubing (shaft tube) is the balloon inflation/deflation lumen. The shaft tube is compatible with 4 Fr (1.33mm) introducer sheaths. Distally, the balloon is welded to the distal shaft portion and to the distal guidewire tube. The balloon design is a standard cylindrical balloon. Two radiopaque platinum-iridium markers, applied to the inner tubing by a swaging process, provide visual reference points to facilitate positioning of the balloon across the target lesion. Proximally, the shaft and guidewire tube are bonded by an ultraviolet (UV) adhesive process to the polycarbonate luer. The luer, compatible with monomeric syringes in conformity with ISO 594, EN1707, has a straight channel connected to the guidewire lumen to load the guidewire (guidewire port). The lateral luer channel is the balloon inflation port, which is used to inflate and deflate the balloon with a mixture of contrast medium and saline solution.

The catheter construction and balloon are designed so that a specific balloon diameter can be reached, depending on the balloon size and defined pressure.

There are two key differences in the design of the IN.PACT 014 catheter when compared to the CE-marked IN.PACT Admiral. First, the IN.PACT 014 utilizes a co-axial shaft design, whereas the IN.PACT Admiral utilizes a bi-lumen design. Second, the guidewire compatibility for the IN.PACT 014 is 0.014" whereas the Admiral is 0.035".

IN.PACT 014 is built on the platform of the CE marked Amphirion Plus catheter. Compared to the Amphirion Plus platform, the IN.PACT 014 will have:

- The same balloon raw material (Polyamide 12) but medical grade.
- No hydrophilic coating.
- Fully automated coating process with FreePac paclitaxel solution.

Figure 2: Example 2.0x40 mm IN.PACT 014 coated in open configuration

Sizing Matrix

The IN.PACT 014 available matrix for this study is shown in Table 1. The entire IN.PACT 014 investigational product matrix utilizes a 3-fold balloon wrap configuration.

The nominal pressure for all sizes is 8 atm. while the rated burst pressure (RBP) is 14 atm. for all sizes.

Table 1: Balloon Diameters and Lengths

Diameter (mm)	Balloon Length (mm)					Fold Design
	40	60	80	100	120	
2.0	✓	✓	✓	✓	✓	3 folds 
2.5	✓	✓	✓	✓	✓	
3.0	✓	✓	✓	✓	✓	
3.5	✓	✓	✓	✓	✓	
4.0	✓	✓	✓	✓	✓	

Table 2: Model Numbers Mix of IN.PACT 014

Reference Number	Balloon Diameter (mm)	Balloon Length (mm)	Shaft Length (cm)
BTK02004015P	2.0	40	150
BTK02006015P	2.0	60	150
BTK02008015P	2.0	80	150
BTK02010015P	2.0	100	150
BTK02012015P	2.0	120	150
BTK02504015P	2.5	40	150
BTK02506015P	2.5	60	150
BTK02508015P	2.5	80	150
BTK02510015P	2.5	100	150
BTK02512015P	2.5	120	150
BTK03004015P	3.0	40	150
BTK03006015P	3.0	60	150
BTK03008015P	3.0	80	150
BTK03010015P	3.0	100	150
BTK03012015P	3.0	120	150
BTK03504015P	3.5	40	150
BTK03506015P	3.5	60	150
BTK03508015P	3.5	80	150
BTK03510015P	3.5	100	150
BTK03512015P	3.5	120	150
BTK04004015P	4.0	40	150

BTK04006015P	4.0	60	150
BTK04008015P	4.0	80	150
BTK04010015P	4.0	100	150
BTK04012015P	4.0	120	150

Biocompatibility testing has categorized the IN.PACT 014 Paclitaxel-eluting PTA catheter as an externally communicating device with limited (< 24 hours) exposure to circulating blood.

Overall, no signs of delayed or systemic toxicity could be detected in the preclinical investigations or biocompatibility testing performed.

8.2. Manufacturer

The IN.PACT 014 drug-coated, peripheral balloon catheter is manufactured by Medtronic, Inc. Minneapolis, USA.

8.3. Packaging

As the IN.PACT 014 is non-CE marked in the regions involved in this study, this will be clearly indicated on the label by the following statement: "Exclusively for clinical investigations". See Appendix A Device labeling for the specific device label.

Inner packaging

A protective stylette is inserted into the distal tip. The device is then loaded into a hoop, which locks onto the device luer and has a clip to hold the compliance chart. The hoop is inserted into a pouch and sealed. A label is placed on the pouch indicating the product name, size/diameter and lot number. The label also contains a serial number that can be used for tracking purpose.

Outer packaging

An identical product label from the pouch is placed on the shelf carton. The sealed pouch (containing the finished product and compliance chart) are inserted into the carton with both product labels facing the same direction. An instruction for use (IFU) booklet is inserted into the carton and closed. Stickers are placed on either end of the sample carton to maintain integrity of each unit. The IFU will be provided in English (unless otherwise required by local laws).

Sterilization

IN.PACT 014 product is sterilized by an Ethylene Oxide (EtO) sterilization cycle at Medistri SA, located in Switzerland. The sterilization cycle and provider are identical to the commercially available IN.PACT Family of products.

8.4. Intended Population

The intended population to be treated with the IN.PACT 014 device will be adult patients suffering from advanced peripheral arterial disease (PAD) located in the infrapopliteal arteries.

8.5. Equipment

Any test equipment critical to be used for assessing endpoints (e.g., Duplex Ultrasound, Angiography) will be maintained/calibrated according to the site's standard protocol. Maintenance and calibration reports will be monitored periodically.

8.6. Product Training Requirements

The implanting Investigator will be evaluated to ensure that he/she is qualified by training, education, and experience to perform DCB procedures in the infrapopliteal arteries.

The implanting Investigator(s) will be trained on the Instructions for Use. Performed training will be documented prior to start of study activities. Medtronic and/or its designees are responsible for the training of appropriate clinical site Personnel. The overview of training requirements for clinical site Personnel is documented in the study training plan and based on a risk assessment.

8.7. Product Receipt and Tracking

All sites will be trained to proper product tracking processes to meet Medtronic policies and regulatory standards for Product Accountability, including the return of open or unopened products (for defect, damage, malfunction, expired inventory).

Once the site has been activated, investigational products will be ordered and shipped to the site. Investigational products will be tracked during the clinical study by assigning unique identifiers to each product. The investigator or designee is responsible for maintenance of a Product Accountability Log in the investigator site file. On this log, the receipt, use, return, and disposal of the investigational devices/products shall be documented.

The investigational products may only be used in the clinical study and must be used according to the clinical protocol and Instruction for Use. All unused product will be returned to Medtronic upon completion of study enrollment.

8.8. Product Storage

Investigational products must be stored in a secured area. The method of storage shall prevent the use of investigational devices/products for other applications than mentioned in this clinical investigation plan. In addition, all information for the use, storage, and handling of the investigational device/product as indicated in the Investigator's Brochure and Instructions for Use must be taken into account.

8.9. Product Return

All non-functioning investigational products will be returned to Medtronic for analysis. Relevant information should also be recorded on associated case report forms. Detailed instructions for the return of non-functioning devices will be provided in the investigational site file. At the end of the study enrollment period, all remaining investigational devices must be returned to Medtronic.

9. Selection of Subjects

9.1. Study Population

The study population will be comprised of patients with symptomatic Chronic Critical Limb Ischemia (CLI) who are candidates for percutaneous endovascular intervention and who meet the Inclusion/Exclusion criteria.

Subjects enrolled in this study will be comprised of adult male and female subjects derived from:

- Individuals referred to a non-invasive vascular laboratory for assessment of the peripheral arterial disease.
- Angiography suites
- Clinical practice: subjects presenting to the investigator's practice with chronic symptoms in the lower extremity(s), peripheral arterial disease are potential study candidates.

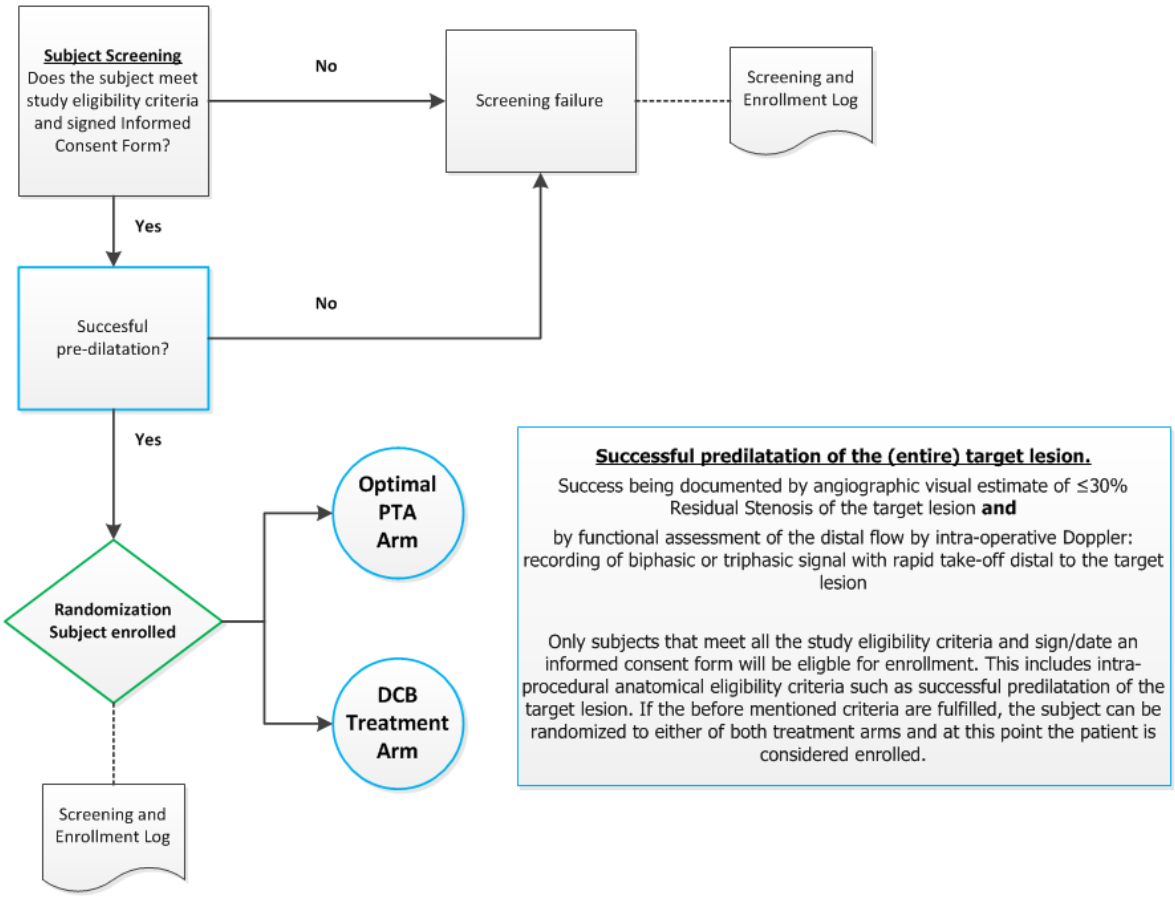
The study will enroll at a minimum 50 subjects at approximately ten (10) European sites.

9.2. Subject Enrollment

Only subjects that meet all the study eligibility criteria and sign and date an Informed consent form will be eligible for enrollment. This includes intra-procedural anatomical eligibility criteria such as successful pre-dilatation of the target lesion(s). If the aforementioned criteria are fulfilled, the subject can be randomized to one of the treatment arms and at this point the patient is considered enrolled. The point of enrollment is only considered after successful pre-dilatation because until then only standard of care procedures are followed. Enrolled subjects will be documented on the Screening and Enrollment log. Subjects who are enrolled, but in whom the device does not cross the (target) lesion will be followed through the 1 month follow-up only.

Subjects who do not qualify for enrollment will be documented as ineligible on the Screening and Enrollment log.

Figure 3: Subject Enrollment Flow



9.3. Inclusion Criteria

1. Age ≥ 18 years.
2. Subject has been informed of the nature of the study, agrees to participate and has signed an EC approved consent form.
3. Female subjects of childbearing potential have a negative pregnancy test ≤7 days before the procedure and are willing to use a reliable method of birth control for the duration of study participation; Subjects will be exempted from this requirement in case they are sterile, infertile, or have been post-menopausal for at least 12 months (no menses).
4. Subject has documented chronic Critical Limb Ischemia (CLI) in the target limb prior to the study procedure with Rutherford Clinical Category 4 or 5 .
5. Subjects with documented infection grade 0-2 and ischemia grade 2-3 according to the WIfI classification.
6. Life expectancy >1 year in the Investigator's opinion.
7. Reference Vessel Diameter (RVD) 2 - 4 mm, confirmed by DUS assessment.
8. Total occlusions (100% stenosis) with total lesion length ≥40mm (by visual estimate).
9. The lesion must be located in the infrapopliteal arteries and above the ankle joint. Lesions may not extend above the tibioperoneal trunk (P3 segment of the popliteal artery) or below the ankle joint (arteries of the foot), nor can the treatment (investigational device or standard PTA, including pre-dilatation) extend beyond these indicated regions for more than 1 cm.

   Note:
   - A target lesion can extend into the P3 segment in case it involves a straight lesion extending from the target vessel.
   - Non-significant stenosis below the ankle joint can be allowed in case this is not part of the target lesion and does not require treatment
10. Multiple lesions can be treated if they are located in separate vessels but all lesions must meet the protocol specified criteria.
11. Presence of documented run-off to the foot (clearly visible dorsalis pedis, pedal arch or plantar arteries by angiography). Target vessel should give direct or indirect run-off to the foot.
12. Inflow free from flow-limiting lesion confirmed by angiography. Patients with flow-limiting inflow lesions (≥50% stenosis) can be included if lesion(s) have been treated successfully before enrollment, with a maximum residual stenosis of ≤30% per visual assessment. If an inflow lesion must be treated within or above the P3 segment of the popliteal artery, there must be a minimum of 3 cm healthy tissue between this (treated) lesion and the infrapopliteal target lesion.
13. Successful pre-dilatation of the (entire) target lesion. Success being documented by angiographic visual estimate of ≤30% Residual Stenosis of the target lesion and by functional assessment of the distal flow by intra-operative Doppler: recording of biphasic or triphasic signal with rapid take-off distal to the target lesion.

9.4. Exclusion Criteria

1. Subject unwilling or unlikely to comply to the appropriate follow-up times for the duration of the study.

   Note: In case the subject lives far from the investigational site, the investigator should discuss the follow-up requirements extensively during the Informed consent process to ensure that the subject is fully aware about the expectations and is willing to comply with the follow-up schedule.

2. Planned index limb amputation above the metatarsal level, or any other planned major surgery within 30 days pre or post-procedure. A planned amputation including and below the metatarsal level (1 or multiple rays) is accepted.
3. Lesion and / or occlusions located or extending in the popliteal artery or below the ankle joint space.

   Note:

   - A target lesion can extend into the P3 segment in case it involves a straight lesion extending from the target vessel
   - Non-significant stenosis below the ankle joint can be allowed in case this is not part of the target lesion and does not require treatment.

4. Significant (≥50% DS) inflow lesion or occlusion in the ipsilateral Iliac, SFA and popliteal arteries left untreated.
5. Failure to obtain a ≤30% residual stenosis in pre-existing, hemodynamically significant (≥50% DS) inflow lesions in the ipsilateral iliac, SFA and popliteal artery. Inflow lesions should be treated as per standard of care.
6. Prior stent(s) or bypass surgery within the target vessel(s) (including stents placed within target vessels during the index procedure prior to randomization.
7. Previous DCB procedure in the target vessel within 6 months prior to index procedure.
8. Aneurysm in the target vessel.
9. Angiographic evidence of thrombus within target limb.
10. Pre-dilation resulted in a major (≥ Grade D) flow-limiting dissection (observed on 2 orthogonal views) or residual stenosis > 30%.
11. Use of alternative therapy, e.g. atherectomy, cutting balloon, laser, radiation therapy, stents as part of target vessel treatment. Note: Use of stents is only allowed for bailout stenting.
12. Recent MI or stroke < 30 days prior to the index procedure.
13. Heart failure with Ejection Fraction < 30%.
14. Known or suspected active infection at the time of the index procedure (abnormal white blood cell count, fever, sepsis or positive blood culture), excluding an infection of a lower extremity wound on the target limb (only WIfI infection grade 0-2 allowed).
15. Subjects with infection grade 3 and ischemia grade 0 and 1 according to WIfI classification.
16. Subjects with neurotrophic ulcers, heel pressure ulcers or calcaneal ulcers with a risk for major amputation.
17. Subjects with documented active osteomyelitis, excluding the phalanges, that is beyond cortical involvement of the bone per clinical judgement.
18. Impaired renal function (GFR < 20 mL/min) or patients on dialysis.

19. Subject with vasculitis, systemic Lupus Erythematosus or Polymyalgia Rheumatica on active treatment.
20. Patient receiving systemic corticosteroid therapy (expected dosage exceeding 5mg of prednisolone or equivalent, per day during the initial 9 months after procedure).
21. This criteria has been removed.
22. Known allergies or sensitivities to heparin, aspirin (ASA), other anticoagulant/anti-platelet therapies which could not be substituted, and/or paclitaxel or an allergy to contrast media that cannot be adequately pre-treated prior to the index procedure.
23. The patient is currently enrolled in another investigational device or drug trial that is interfering with the endpoints of this study.
24. Female subjects who are breast-feeding at the time of enrollment.

10. Study Procedures

10.1. Schedule of Events

The schedule of study procedures and assessments can be seen in Table 3.

Table 3: Schedule of study procedures and assessments

	Screening	Procedure	Discharge	30 days (± 7 days)	3 months (±15 days)	6 months (±30 days)	9 months (±60 days)	12 months (±30 days)	24 months (±30 days)	36 months (±30 days)	48 months (±30 days)	60 months (±30 days)	Unscheduled	Upon Early Termination
	Visits										Phone Calls		Visit	Phone Calls
Inclusion/Exclusion and consent	X										X[6]			
Physical Exam	X		X	X	X	X	X	X	X	X			X	
Medical history and demographics	X													
DUS		X[3]	X[4]	X	X	X	X	X	X	X			X[5]	
ANGIOGRAPHY		X					X						X[5]	
Rutherford Classification	X			X	X	X	X	X	X	X			X	
Medications	X	X	X	X	X	X	X	X	X	X			X	
WIfI assessment	X		X	X	X	X	X	X	X	X			X	
Wound care / Assessment[1]	X[2]		X	X	X	X	X	X	X	X			X	
EQ-5D	X		X	X	X	X	X	X	X	X			X	
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Status														X[7]

1. For as long as applicable
2. Includes WIfI classification at baseline visit
3. Duplex Ultrasound for Reference Vessel Diameter measurements and Procedural Duplex Ultrasound Doppler Examination to determine successful pre-dilatation
4. DUS assessment if available, should be prior to discharge,.
5. In case an angiography / DUS of the study limb is done during an unscheduled visit it has to be provided to sponsor
6.
   - Ensure subject is reconsented prior to conducting any study specific assessments after 36 months.
   - In case the subject exited the study at 36 months post procedure or before, ensure that the subject is picked up again in the study through reconsenting, prior to conducting any study-specific assessments after 36 months, if allowed by local regulations.
7. Collection of information about (vital) health status for exited subjects, upon subject's consent until 60 months after index procedure

10.2. Subject Screening

Subject eligibility to the study will be determined by the investigator or by a trained and delegated member of the investigational site's research team according to the criteria listed in section 9 of this protocol. In case they fulfil the criteria, subjects will be informed about the IN.PACT BTK study and asked for their interest and willingness to participate via the Informed consent process. Failure to meet all inclusion and exclusion criteria results in a Screening Failure and such subjects must not be enrolled to the study. A screening and enrollment log is provided to the site and should be completed by the site's study staff to maintain a cumulative log of all screened and enrolled subjects.

Screening/Baseline Assessments:

After the subject voluntarily has signed and dated the Informed Consent Form, the subject will be considered a study candidate. If a subject does not sign the Informed Consent Form, then no further screening can occur.

Collection of screening and baseline information will take place only after the subject has given voluntary, documented Informed consent and will include the following:

- Screening Inclusion/Exclusion and consent
- Physical Exam
- Pregnancy test for applicable subjects
- Medical history and demographics
- Baseline Medications (see 10.3. Prior and Concomitant Medications)
- Rutherford Classification
- WIfI Classification
- Wound assessment
- EuroQol-5D questionnaire (EQ-5D)

Subjects who do not qualify for enrollment will be documented as ineligible on the Screening and Enrollment log.

10.3. Prior and Concomitant Medications

Prior and concomitant medication schedules below are recommended but investigator's discretion and institutional standard of care should be followed.

Medication use: the subject's anti-platelet and anti-coagulant medication use will be documented at baseline and follow-up visits (see also 10.8. Medication Compliance).

Prior to the index procedure: Administer dual antiplatelet therapy (aspirin and clopidogrel, ticlopidine or equivalent) before the procedure. *Any loading dose can be given as per institutional standard of care; patients already receiving oral anticoagulants (warfarin or Novel Oral Anticoagulants (NOAC) should receive concomitant to their anticoagulant 1 or both antiplatelet drugs, per investigator's discretion evaluating the risk of bleeding and thrombotic events.*
During the index procedure: Use of systemic heparinization as per institutional standard of care.
Following the index procedure: Subjects should be prescribed daily acetyl-salicylic acid (ASA) and daily clopidogrel (ticlopidine, or equivalent if required) for at least 4 weeks following the procedure. For the purpose of the study recommended duration of DAPT within this study is 3 months. Prolonged antiplatelet therapy can be given at the discretion of the physician and should be considered after placement of stents. Patients already receiving oral anticoagulants (warfarin or Novel Oral Anticoagulants (NOAC) should receive concomitant to their anticoagulant 1 or both antiplatelet drugs, per investigator's discretion evaluating the risk of bleeding and thrombotic events.

10.4. Subject Consent

10.4.1. Consent Materials

Medtronic, the Competent Authorities (CA), and Ethics Committees (where applicable) shall approve all Informed consent documents prior to implementation in the study. Medtronic, Ethics Committees, and CAs, where applicable must pre-approve all language changes to the Informed consent throughout the course of the study prior to implementation; this includes initial submission, annual reviews (if applicable) and protocol amendment reviews. The original approved Informed consent must be retained at the investigational site.

Any revisions required by the Ethics Committee must be forwarded to Medtronic for review and approval before the revised consent form is returned to the Ethics Committee for final review and full approval.

Medtronic will provide any important new information that impacts the health, safety or welfare of study subjects, for inclusion in Informed consent updates as it becomes available. Sites should follow any Medtronic, CA or Ethics Committee requirements for disseminating new information and re-consenting subjects during the course of the study.

The Informed consent form will be provided separate from this CIP.

10.4.2. Informed Consent Process

The investigator (or authorized designee) must administer the approved Informed consent to each prospective study patient without coercion or undue improper influence on, or inducement of, the patient to participate. During the consent discussion the investigator (or authorized designee) must fully inform the patient of all pertinent aspects of the study, using native non-technical language that is understandable to the patient. The patient must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled, and also informed that withdrawal from the study will not jeopardize their future medical care. The patient must also be informed that by participating in the study, they are not waiving their legal rights. The patient must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the patient. All items discussed in the Informed consent must be explained.

Informed consent will be obtained in writing from the patient. The date of consent and process by which the consent was obtained (including documentation of special circumstances, if applicable; see Section 10.2) will be documented in the patient's medical record prior to any study-specific procedures. The Informed consent shall be documented before any procedure specific to the clinical investigation is applied to the subject except when special circumstances apply. Informed consent must be obtained in accordance with the national and local laws, regulations and guidelines of each site. The institutional standard procedure consent form does not replace the study Informed consent.

The patient's signature and date of consent serve to document that they understand the written and verbal information that the investigator (or designee) provides, and their agreement to participate and collect their medical data. The investigator (or designee) who conducted the Informed consent process must provide their handwritten signature and date the consent was completed on the Informed consent form. The original signed Informed consent will be retained in the patient's study records. A copy of the signed Informed consent will be provided to the patient.

10.4.3. Special Circumstances for Informed Consent Process and Signature

If a patient cannot read or write, an impartial witness must be present during the entire Informed consent discussion. The written Informed consent (and any other information) shall be read aloud and explained to the patient and witness. The witness signs and personally dates the Informed consent attesting that the information was accurately explained and that consent was freely given. The patient will sign and date if possible.

Given the investigational status of the IN.PACT 014, emergency cases are not allowed under this protocol.

In case national or local legislation contains requirements on the Informed consent process that are in addition to or different from the requirements outlined in this CIP, then the national or local requirements should be complied to.

10.4.4. Subject Accountability for Follow-up Extension

Subjects in follow-up and willing to extend their follow-up from 36 to 60 months are to be re-consented.

Where locally allowed, study extension until 60 months can occur for subjects who exited the study at the 36-month follow-up visit or before, as soon as the required competent authorities and ethics commitees approve the required study documents.

Subjects who already exited the study, are picked up again in the study through re-consenting prior to conducting any study-specific assessments. Exited subjects who refuse to participate in the extension beyond 36 months remain listed as exited.

Subjects who are not willing to participate in the follow-up extension, may still give their consent for the collection of information around health (vital) status. Please refer to the inform consent form for detailed information.

10.5. Randomization and Treatment Assignment

Randomization will be 1:1 and be stratified by study site. Due to the nature of the procedure, it is not possible to blind the patient, implanting investigator or study site staff.

Randomization will be performed after confirmation the subject meets all inclusion/exclusion criteria, including successful pre-dilatation of the target lesion(s). Randomization will be processed centrally by means of a web-based system that will provide the randomization treatment arm (investigational device (IN.PACT 014) or optimal PTA).

Once subjects are assigned a study group (DCB or PTA) they are considered randomized. A deviation is required if a subject does not receive the study device per their randomized assignment.

10.6. Index Procedure

The following section describes the required assessments and activities during the index procedure. There should be preferably one operator per site.

10.6.1. Vascular Access

Vascular access should be obtained as per site standard of care (depending on lesion location, patient factors or any other factors that would impact the choice of vascular access).

10.6.2. Angiography

Angiography must be conducted according to the Angiographic Corelab Protocol. The Angiographic Corelab Protocol will be available outside of this CIP.

A radiopaque ruler will be placed on the subject prior to the start of the procedure and will be used to define anatomical measurement references and assess the lesion length. Detailed instructions for the placement of the ruler are specified in the Angiographic corelab protocol. As a next step, a compatible sheath should be inserted and anticoagulation should be administered as per the Investigators discretion to obtain or maintain appropriate clotting time (see 10.3. Prior and Concomitant Medications). In order to identify the anatomical characteristics of the vasculature and to visualize and define the lesion(s), a selective angiography of the index limb will be performed that must include: ipsilateral femoral, popliteal and tibioperoneal vessels (up and including the pedal level).

10.6.3. Treatment of Non-Target Lesions

Significant (≥ 50% DS or occlusions) inflow lesions in the ipsilateral iliac, SFA and popliteal arteries, must be treated prior to enrollment of the subject, no other non-target lesions (including out-flow lesions) in the index limb may be treated during the index procedure. Any contralateral disease (that requires treatment) should be 30 days after the index procedure.

The inflow lesions should be treated per institutions standard of care, and based on the relevant evidence with regards to the efficacy of these treatments. If an inflow lesion must be treated within or above the P3 segment of the popliteal artery, there must be a minimum of 3 cm healthy tissue between this (treated) lesion and the infrapopliteal target lesion.If significant inflow lesions are present, successful treatment must be performed prior to the treatment of any target lesion(s). Successful treatment of inflow lesion(s) will be defined as: obtaining a residual diameter stenosis of ≤30%.

BTK vessels that have non-CTO lesions are considered as Non-Target Vessels / Lesions. These lesions should be treated first per standard of care.

10.6.4. Target Vessel / Lesion pre-dilatation

1. Identify the target vessel(s) / lesion(s)
2. Perform digital substraction angiographic (DSA) images of the target lesion(s) that demonstrate the occlusion (in a view that minimizes the degree of vessel overlap)
3. Perform Duplex Ultrasound according to corelab guidelines for Reference Vessel Diameter measurements

Perform pre-dilatation of the target lesion with a non-drug coated standard semi compliant balloon (no other devices, such as cutting/scoring balloons are allowed). In case there are multiple target lesions, the Investigator will select the first target lesion upon his discretion and proceed with pre-dilatation of this lesion.

For the pre-dilatation, a non-drug coated standard semi compliant balloon must be selected with:

- A diameter that will provide at least 1:1 ratio with the Reference Vessel Diameter (RVD)
- A length that covers the entire length of the lesion

  Note that more than one pre-dilatation balloon may be used, and that this balloon may be inflated more than once.

- Inflate the balloon for at least 3 minutes
- Any CE-marked PTA balloon can be used

4. Record an image of the target lesion post pre-dilatation. Ensure to perform an angiography distal to the target lesion (including run-off and visualize the entire vessel distally through the pedal arch). Assess the subject for any angiographic complications post pre-dilatation and confirm the angiographic inclusion and exclusion criteria. An intra-procedure Doppler examination distal of the target lesion must also be performed.

Successful pre-dilatation of the target lesion is defined as:

- Residual stenosis of ≤ 30% after pre-dilatation (per visual estimate) AND
- Intra-procedure Doppler examination records a biphasic (with rapid take-off) or triphasic wave signal.
- No major (≥ Grade D) flow-limiting dissection (observed on 2 orthogonal views).

Enrollment: If the above criteria have been met, the subject can be randomized and will be considered enrolled (at the time the patient has been randomized).

In case the subject does not meet the criteria above, the subject cannot be randomized and should be considered and documented as a screening failure, treated by standard of care.

Subjects with multivessel disease are allowed and multiple target lesions can be treated during the index procedure. In case of subjects with multiple target lesions, the randomization is at "subject" level. All lesions that meet the specifications detailed in the inclusion and exclusion criteria (lesion anatomical characteristics) including the pre-dilatation criteria will be considered as target lesions.

All target lesions must be treated with the assigned (randomized) treatment. Following the treatment of first target lesion per the randomization arm, the subsequent lesion(s) must receive the same treatment as the first treated target lesion.

10.6.5. Treatment of Target Vessels/Lesions

All vessels that have a CTO lesion and are intended for treatment at the time of the index procedure, meeting all inclusion criteria and none of the exclusion criteria will be considered the target vessels.

The lesion(s) intended for treatment at the time of the index procedure that meet the inclusion criteria and none of the exclusion criteria will be considered the target lesion(s).

Multiple lesions in one vessel should always be treated as one lesion, no gaps should be left untreated. In case the lesion has following characteristics: a CTO section and a section of stenosis that requires treatment, the entire lesion (occluded and stenosed section) must be treated as one lesion.

In case the patient is randomized to the PTA arm, no further treatment of the target lesion(s) should be performed (a ≤30 % residual diameter stenosis has been obtained in the absence of flow limiting dissections).

In case the patient is randomized to the IN.PACT 014 arm, an appropriate balloon must be selected. The diameter of the IN.PACT 014 balloon will be selected based on the reference vessel diameter (approximating 1:1 ratio).

The length of the IN.PACT 014 balloon should be sized to ensure the balloon extends beyond the proximal and distal edges of the target lesion by 1 cm. In case the target lesion requires treatment with multiple IN.PACT 014 balloons, the Investigator must ensure an overlap of 1 cm to maintain continuous coverage of the target lesion. The IN.PACT 014 balloon catheters will be delivered and deployed per the Instructions for Use (IFU).

IN.PACT BTK Inflation Time: Maintaining balloon inflation for 3 minutes is strongly recommended.

After the treatment of the target lesion(s) is considered complete by the Investigator, an angiographic image should be captured that visualizes the entire target lesion(s) treatment area. A final image should now be recorded that documents the target lesion treatment area(s) and includes run-off of all vessels distal to the treatment area including the dorsalis pedis, pedal arch or plantar arteries.

In case multiple paclitaxel coated balloons are used (inflow treatment and index procedure), consider the total paclitaxel dosage from all devices. Medtronic has not evaluated systemic safety of implanting multiple IN.PACT DCBs with a total drug dosage exceeding 34,854 µg paclitaxel.

To minimize risk of embolic events due to drug coating, when treating long lesions, maximize single balloon length.

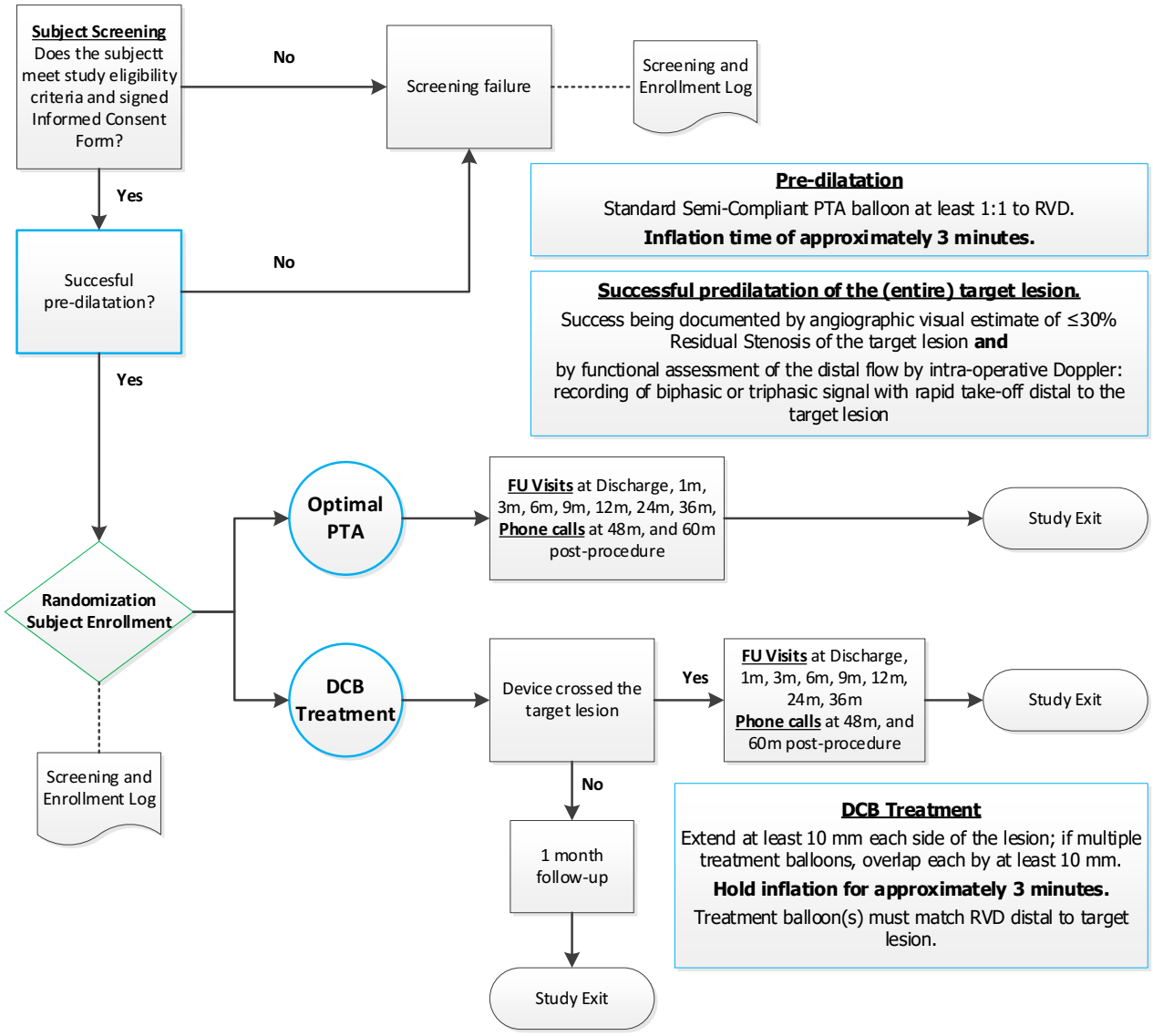
10.6.6. Adjunctive Therapies

Adjunctive therapies should be avoided if possible. In case of suboptimal procedure result (>50 % residual stenosis, perforation, occlusive complication (recoil) or flow limiting dissection) prolonged balloon inflation should be attempted. If prolonged balloon inflation does not provide the expected result, bail-out stenting is allowed. All other adjunctive therapies (including but not limited to: laser, atherectomy, cryoplasty, cutting/scoring balloons or brachytherapy) are not allowed.

Final angiographic images will be collected once treatment of the target lesion(s) is complete. This will include capturing images that demonstrate the residual stenosis post-treatment of the target lesion treatment area(s) and run-off of all vessels distal to the target lesion treatment area(s) including the dorsalis pedis, pedal arch or plantar arteries.

Note: The end of the procedure is defined as the time after a complete final angiogram has been performed and the last guidewire and catheter have been removed. In case the subject needs to return to the procedure room and a guiding catheter is reinserted for dilatation, this is considered a reintervention. Removal of the sheath(s) may be done at the Investigators discretion.

Figure 4: Randomization and Treatment Assignment flow



10.7. Follow-Up Requirements

10.7.1. Discharge Follow-Up Requirements

All subjects are required to have a discharge assessment.

Please refer to Table 3 (schedule of events) for the mandatory assessments during this follow up.

10.7.2. Follow-up Visit Requirements

Following hospital discharge, all subjects are required to have follow-up visits at predetermined time points during the study, as specified in table 3. If necessary, the follow-up assessments can take place outside of the investigational site, as long as the study protocol requirements and local regulations are met.

10.7.3. Follow-up phone calls

Subjects that consented for the study extension will be contacted by telephone at 48-months, and 60-months post-procedure. At this time, an evaluation for AEs per protocol requirements will be completed and documented as specified in table 3.

10.7.4. Unscheduled visits

A subject who returns to the investigational site between protocol-required visits with an ischemic event of the target limb, is considered to have an unscheduled visit. The requirements for unscheduled visits must be followed as specified in table 3 and the data will be collected in the eCRF.

10.7.5. Follow up Duplex Ultrasound Examination

The DUS should be performed by an experienced DUS-operator that has been trained on the study protocol and should follow the DUS corelab protocol (refer to DUS corelab manual of operation). Since the DUS examination is operator dependent, all efforts should be made to have 1 dedicated operator performing all study required DUS examinations.

10.7.6. Follow up Angiography

At 9 months follow up, there will be a required angiographic follow up. These angiographic images will be reviewed by the angiographic corelab to assess the study's primary efficacy endpoint of Late Lumen Loss (LLL). It is therefore required that this angiography will be performed per the standards provided by the angiographic corelab protocol (refer to angiographic corelab manual of operation).

These images must be captured and labelled as such prior to any intervention on the target lesion (if applicable). If, per the Investigators discretion, any treatment deemed necessary on the target lesion during this 9 month follow up angiography, this should be documented at the applicable location in the eCRF. Specific attention should be given to document such intervention as being incidental (eg revascularization done because of incidental finding during follow up angiography) or if this (re-) intervention was done for clinical symptoms (CD-TLR).

10.7.7. Wound Care Follow-up Assessments

Required wound care and assessment follow up is provided in Table 3 (Section 10.1. Schedule of Events). This pertains to the follow up assessments for which the information on wounds needs to be provided to the sponsor in the eCRF. In addition to the before mentioned assessments, the following wound care will be mandatory as a minimum requirement:

* A minimal of 3 assessments between the study procedure and the 1 month visit inclusive (including visit windows), is required.

These wound care follow up assessments should take place at a dedicated wound-care clinic (or foot clinic) by a wound care specialist who will also be part of the study team.

Wound assessment and wound care is only applicable for subjects that present with (ischemic) wounds on the target limb at baseline or for subjects who develop new (ischemic) wounds on the target limb during the conduct of the study. In case of planned amputations (that meet the inclusion criteria for this study) the amputation wound(s) will be assessed throughout the study.

During the protocol required follow up visits, data will be collected on:

Wound status by visual estimation

- Worsened
- Unchanged
- Improved
- Completely healed
- Amputation
- Skin graft

Identification of new wounds (if applicable)

If any wound is assessed for planned amputation (below the metatarsal level), the amputation should only be performed once the necrotic tissue is clearly and completely demarked from the healthy tissue.

It is recommended that assessment for major amputation is done in agreement with the interventionalist and wound care specialist.

10.8. Medication Compliance

Medication usage for antiplatelet and anticoagulant therapy will be assessed at appropriate time points in accordance with Table 3. The medication compliance will be documented in the Electronic Data Capture (EDC).

10.9. Assessment of Efficacy

The primary efficacy endpoint is evaluation of the Late Lumen Loss (LLL) assessed by QVA and determined by independent angiographic core lab.

10.10. Assessment of Safety

There are multiple secondary endpoints that will assess safety of the IN.PACT 014 device. One of the secondary endpoint will provide significant information to assess the safety of the IN.PACT 014 device and is described in section 6.2.2. as composite safety endpoint: A composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically-driven TLR within 9 months post-index procedure.

10.11. Recording Data

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the principal investigator or co-investigator, and filed in the subject's medical file.

Only authorized persons can complete eCRFs. The investigator (physicians only) shall sign eCRFs as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes, or corrections in eCRFs. If a person is only authorized to complete eCRFs or to make changes to an already signed eCRF, the investigator shall re-sign this eCRF.

Any source documentation as well as any imaging (e.g., procedure reports, imaging material, lab reports, death certificates, autopsy reports) that is sent to the sponsor should have all subject identifiers removed and replaced with the subject's study ID.

Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

The source documents must be made available for monitoring or auditing by the sponsor's representative or representatives of the competent authorities and other applicable regulatory agencies.

An electronic PDF version or paper copy of the eCRFs as well as access to the EDC system will be provided to the investigation site prior to subject enrollment.

10.11.1. Investigator records

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, if applicable, any amendments
- Investigator's Brochure and 1 copy of the Instructions for Use
- Medtronic and EC approved Informed Consent Form and, if applicable, any amendments
- Competent Authority approval or notification
- Fully signed Clinical Trial Agreement and confidentiality agreement (if not included in the Clinical Trial Agreement)

- Financial disclosures; If the financial interests change during the course of the study or within 1 year, the study is completed the investigator is obliged to inform the sponsor of such financial change
- Insurance certificates
- Completed Delegated Task List and Curriculum Vitae of all investigational site personnel
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log and/or subject identification log
- Signed, dated, and fully executed Informed consent
- The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.
- Fully executed eCRFs and corrections (in the EDC)
- Reports of Adverse Events and Device Deficiencies
- Device accountability records
- EC correspondence

10.11.2. Investigator reporting responsibilities

Investigator reporting responsibilities

Report	Submitted to	Description
Adverse Events	Sponsor, EC, and local Competent Authority, where applicable	Refer to section 12.2 for reporting requirements.
Progress Report	Sponsor and EC	Provide if required by local law or EC. (ISO 14155).
Withdrawal of EC approval	Sponsor	Investigator will inform Medtronic in case EC approval is withdrawn.
Final Report	EC	A copy of the Final Clinical Study Report will be provided to the EC.
Deviations from Investigational Plan		
Planned deviation	Sponsor, EC, Competent Authority, if applicable	Prior approval from Medtronic must always be obtained from Medtronic. If the deviation affects scientific soundness of the clinical study or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from the EC and Competent Authority.
Other Deviations	Sponsor, EC, Competent Authority, if applicable	Deviations that are beyond the control of the investigator (such as subject who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the clinical study or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the investigational site or Medtronic staff.

10.11.3. Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential correspondence related to the clinical study
- Signed Investigator Agreement
- Signed and dated current curriculum vitae for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event and device deficiency information
- Device complaint documentation
- All data forms, prepared and signed by the Investigators, and received source documentation and core lab reports
- CIP, investigator brochure and subsequent amendments
- Site monitoring reports
- Financial disclosure information
- Trial training records for site participants and internal trial staff members
- Contact lists of all participating investigators/investigative sites, Ethics Committee information, trial monitors and Sponsor staff members; Sponsor will maintain these lists and provide updates to the necessary parties.
- Sample of device labeling
- Insurance certificates
- Ethics Committee approval documentation and voting list
- Competent Authority notification and approval documentation
- Statistical analyses
- Clinical investigation report

10.11.4. Sponsor reporting responsibilities

Table 4: Sponsor records and reporting responsibilities

Sponsor Reports for Europe		
Report	**Submit To**	**Description/Constraints**
Unanticipated Serious Adverse Device Effects (USADE)	Ethics Committee, Investigators, Competent Authorities	Medtronic will notify investigators and Ethics Committee in all geographies as soon as possible. For reporting to Competent Authorities, all USADEs are classified as SADEs and should follow the applicable reporting requirements. (ISO 14155) and Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 3.A.1). Reporting timeframe as per local competent authority. (ISO 14155)

Sponsor Reports for Europe		
Report	**Submit To**	**Description/Constraints**
Serious Adverse Event (SAE) Serious Adverse Device Effects (SADE) Device Deficiency that might have led to an SAE Serious Health Threat	Ethics Committee, Competent Authorities	Submit to Ethics Committee and Competent Authority in compliance with local legislation.
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Competent Authorities	Provide prompt notification of termination or suspension and reason(s). (ISO 14155)
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, Competent Authorities	All applicable investigators will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of Competent Authority approval	Investigators, Ethics Committee, and Competent Authorities	Investigators and Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee, Competent Authority (if required)	This will be submitted to the Ethics Committee and/or Competent Authority as required per local regulations. .
Final Report	Investigators, Ethics Committee, and Competent Authority (if required)	The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). Where required by national regulations, the sponsor and coordinating investigator shall be asked to provide their signatures, indicating their agreement with the content of the clinical investigation report. (ISO 14155)
Deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific deviations will be submitted to investigators on a regular basis. (ISO 14155)

Sponsor Reports for Europe		
Report	**Submit To**	**Description/Constraints**
Significant new information	Ethics Committee and Competent Authority	Ensure that the Ethics Committees and Competent Authorities are informed of significant new information about the clinical investigation (ISO 14155)

10.12. Deviation Handling

A deviation is any event in which the study is not conducted according to the CIP and/or agreement. Deviations may include, but are not limited to the following:

- Failure to obtain Ethics Committee approval before the start of enrolling subjects in the study
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Unauthorized use of investigational device
- Adverse events or device deficiencies not reported in the required timeframe by country regulation
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of subjects during lapse of Ethics Committee approval
- Enrollment limits exceeded
- Non-compliance to obtain subject's Informed consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow subjects per scheduled follow-ups
- Failure to follow-up with findings on monitoring reports
- EC approval expiration
- EC suspension of the center

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study), such as those included in, but not limited to, the list above. Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrollment or ultimately terminate the investigator's participation in the clinical study.

The investigator is not allowed to deviate from the CIP, except when necessary to protect the life or physical well-being of a subject in an emergency situation. Deviations must be reported to Medtronic on the Deviation eCRF.

If a center is terminated or suspended, no additional enrollments will be allowed at the center. Unused investigational product allocated to the center will be returned to Medtronic.

Medtronic will provide site-specific reports to the investigators on a periodic basis (minimally yearly) summarizing information on deviations that occurred at the investigational site.

The investigator shall adhere to EC requirements and procedures for reporting study deviations.

10.13. Subject Exit, Withdrawal or Discontinuation

Subjects are urged to remain in the study as long as possible but may withdraw from the clinical study at any time and for any reason. If a subject decides to withdraw from the clinical study and agrees to provide the reason for withdrawal, the investigator will document the reason and indicate any relationship of the withdrawal to the study or products being investigated in the subject's hospital record in the subject's file.

If discontinuation is because of safety or lack of efficacy, the subject shall be asked to be followed as per their institution's standard of care outside the clinical study. In addition, subject withdrawal and reason for withdrawal will be documented on the Study Exit eCRF. If the subject is unable to be followed, the investigator is to notify the sponsor in a timely manner.

Information about subject's (vital) health status will be collected until 60 months after index procedure, upon subject's consent, for subjects who will terminate the study earlier.

10.13.1. Missed follow-up

A missed follow-up visit should be documented by the investigator and reported in the eCRF including the reason. If the date the subject is last known to be alive is obtained, this should be recorded on the Follow-up visit eCRF and the method of obtaining this date should be documented in the medical record.

10.13.2. Upon Early Termination Phone Calls

Information about subject's (vital) health status will be collected until 60 months after index procedure, upon subject's consent, for subjects who will terminate the study earlier.

10.13.3. Study Completed

At the completion of the 60-month follow-up period, the 60-month follow-up phone call and study exit should be combined, and both the 60-month follow-up phone call CRF and Study Exit CRF need to be completed.

Images and data obtained from subjects, during enrollment, may be used for scientific purposes also after the subjects exit the clinical investigation.

Where locally allowed, subjects who exited the study at the 36-month follow-up visit or before and who are willing to extend their follow-up period to 60 months, will be picked up in the study, through re-consenting.

After exiting, subjects will be followed-up by their physicians, per standard of care.

10.13.4. Lost-to-follow-up

A subject may be considered lost to follow-up once the investigator and/or research staff has made at a minimum three documented unsuccessful attempts to contact the subject.

Subjects unable to complete the study follow-up period should agree with their general practitioner upon a plan for future health care follow-up, as reflected in the Informed consent form.

10.13.5. Medical care after study exit

After study exit the subjects will be followed as per routine standard of care by the investigational site or a treating physician.

Relevant medical records may be made available by the investigational sites for the treating physician per local laws and regulations if needed for further subject treatment. As per local law and regulation the trial investigator may be contacted by the treating physician in case of questions related to the study device and treatment.

11. Risks and Benefits

11.1. Potential Risks

The risk analysis process for the IN.PACT 014 DCB is being performed in accordance with ISO 14971, and will ensure that the level of risk is acceptable prior to starting the study.

11.1.1. Risks associated with the use of the study product

A peripheral balloon dilatation procedure may be associated with the following potential complications (but may not be limited to):

- Abrupt vessel closure/thrombosis (acute total occlusion/reocclusion that may require surgical intervention)
- Access site pain, hematoma, hemorrhage, and/or local infection (bleeding may require transfusions)
- Allergic reaction to contrast medium, antiplatelet therapy, or catheter system components
- Aneurysm, pseudoaneurysm, or arteriovenous (AV) fistula
- Arrhythmias
- Balloon rupture
- Death
- Detachment of a component of the balloon and/or catheter system
- Dissection, perforation, or rupture of the artery
- Drug reactions
- Failure of the balloon to perform as intended (inflation/deflation/retrieval)
- Failure to deliver the balloon as intended (may release drug into unintended arterial segment)
- Hypotension/hypertension
- Ischemia/infarction of tissue/organ (severe ischemic events in treated limb may require amputation)
- Local or distal thromboembolic episodes
- Pain and tenderness at puncture sites
- Pyrogenic reaction
- Renal insufficiency or failure
- Restenosis of the dilated artery
- Sepsis/infection
- Short-term hemodynamic deterioration
- Systemic embolization
- Vessel spasms or recoil/prolonged arterial spasms

Potential adverse events not captured above, that may be unique to the paclitaxel drug coating include, but are not limited to:

- Allergic/immunologic reaction
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/arthralgia
- Myelosuppression
- Peripheral neuropathy

There is one updated potential risk of long-term increased mortality associated with drug coated (paclitaxel coated) balloons. Drug coated balloons used to treat peripheral artery disease have been shown in an FDA analysis[69] to have an increased relative risk of mortality compared to uncoated devices. These devices used in the legs are the same or similar to those used in PAD BTK. However, the association of paclitaxel coated device use in PAD BTK with increased mortality risk is unclear. The risk of long-term increased mortality is being evaluated by the FDA.

Any device that requires mechanical deployment and retraction (such as the IN.PACT 014 product as well as the used standard PTA balloon) have an inherent risk of mechanical failure. This might result in a potential surgical intervention to remove the device.

The fluoroscopy time of the index procedure is expected to be similar to that of procedures performed in a non-clinical study setting and will not pose an additional risk to the subject or the study personnel.

11.1.2. Risks related to the study procedures

The required follow up (as per the schedule of events, Section 10.1.) might be perceived as an inconvenience for the subject, as it might involve more frequent follow up visits compared to standard of care. The sponsor does not anticipate any additional risks related to the required follow up visits, other than the required visit at 9 months. This visit includes an angiographic assessment of the target lesion. Any angiography has inherent risks, such as (but not limited to):

- Abrupt vessel closure/thrombosis (acute total occlusion/reocclusion that may require surgical intervention)
- Access site pain, hematoma, hemorrhage, and/or local infection (bleeding may require transfusions)
- Allergic reaction to contrast medium
- Aneurysm, pseudoaneurysm, or arteriovenous (AV) fistula
- Arrhythmias
- Death
- Dissection, perforation, or rupture of the artery
- Hypotension/hypertension
- Ischemia/infarction of tissue/organ (severe ischemic events in treated limb may require amputation)
- Local or distal thromboembolic episodes
- Pain and tenderness at puncture sites
- Pyrogenic reaction
- Renal insufficiency or failure
- Restenosis of the dilated artery
- Sepsis/infection
- Short-term hemodynamic deterioration
- Systemic embolization
- Vessel spasms or recoil/prolonged arterial spasms

The fluoroscopy time of this angiographic follow up assessment is expected to be very limited and expected to be no longer than any routine diagnostic angiography. The sponsor considers that this assessment does not pose additional risks to the subject or laboratory personnel.

11.2. Potential Benefits

Subjects who undergo Percutaneous Transluminal Angioplasty (PTA) of the infrapopliteal arteries may benefit by the use of the paclitaxel coated IN.PACT 014 because paclitaxel is known to reduce restenosis after PTA.

Subjects may benefit from this study because the use of IN.PACT 014 may eliminate, decrease and/or delay the chance of restenosis and re-occlusion in the treated arteries with expected subsequent clinical benefit in terms of symptoms relief. However, there are no guaranteed benefits from participation in the study.

In addition, the information obtained during this study may be used scientifically. It can help physicians better understand the prevention of restenosis and re-occlusion in the infrapopliteal lesions related to the use of IN.PACT 014. Information collected in this study can support the improvement of the Medtronic DCBs and the development of new devices.

11.3. Risk-Benefit Rationale

Based on our current knowledge, participation into the IN.PACT BTK Clinical Study does not impose significant additional risks to the subject comparing to existing treatment option (ie. PTA, stenting). There is a high probability that subjects benefit when using a DCB as studies have shown clinical and angiographic superiority when compared to standard PTA in related treatment areas.

It is anticipated that the potential benefits of the study outweigh the potential risks; therefore the investigation is considered justified. It is possible in any clinical trial that unanticipated effects can happen which are not yet known at this time.

The study design will minimize the risk through observance of strict center and investigator selection criteria, careful subject selection and management, and rigorous adherence to a standardized schedule of evaluations. Risks may be further limited by providing medications (such as aspirin and/or clopidogrel) and continuing to monitor subjects following the index procedure. The investigator in addition performs continuous monitoring, assessment and documentation of any risks.

The design for the IN.PACT 014 balloon catheter underwent hazard analysis by industry standard methods including analysis of contributing factors, human factors/usability, failure modes, effects, and criticality analysis. The results of the assessment concluded that all potentially critical failure modes have been appropriately mitigated to an acceptable level based on the products intended use and the product is therefore suitable for clinical evaluation.

Standard risks associated with the medical device used in this study and an analysis of Adverse Device Effects listed in the investigator's brochure.

12. Adverse Event Assessments

12.1. Definitions/Classifications

For the purpose of this clinical investigation Medtronic will define and classify the following events per the latest version of ISO14155. In case country specific definitions and safety reporting regulations are stricter than mandated per the latest version of ISO14155, reporting will be done in compliance with the country specific safety regulations.

All adverse events identified from the point of enrollment until patient's exit from the study will be reported to the sponsor and documented on the Adverse Event eCRF and in the subject's medical records.

All assessments prior to subject enrollment are considered standard of care.

Medical occurrences that are inherent to a surgical procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include, but are not limited to, those listed in Table 5. These medical occurrences should not be to be reported as adverse events during this study.

Table 5: Expected and not to be reported adverse events related to a surgical procedure

Event Description	Timeframe (hours) from the procedure
Anesthesia related nausea / vomiting (with or without treatment)	24
Low-grade fever (<100°F or 37.8°C)	48
Pain at access site (with or without standard treatment and patient not returning to clinic to have additional treatment)	72
Mild to moderate bruising / ecchymosis at access site(s)	168
Sleep problems (insomnia) (with or without treatment)	72
Back pain related to laying on table (with or without treatment)	72
Bleeding at access site (not requiring treatment)	24

12.1.1. Definitions / Classifications

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE):

Adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
NOTE 3: this includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE):

Adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, , including chronic disease ,or
   3) in-patient or prolonged hospitalization, or
   4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Unanticipated Serious Adverse Device Effect (USADE):

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Serious Health Threat:

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Device deficiency:

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

NOTE 1: Device deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

12.1.2. Recording and reporting of Adverse Events

Adverse Event (AE) information will be collected throughout the study and reported to Medtronic on the Adverse Event eCRF. All Adverse Events (except unavoidable events listed in table 5), regardless of relatedness or outcome, must be reported. The investigator is responsible for reporting all AEs to Medtronic and for their follow-up. Collection of AEs and AEs-related information will include the date of the adverse event, treatment, resolution, assessment of seriousness and the relationship to the device and comparator, to Paclitaxel and to the related procedure.

For Adverse Events that require immediate reporting (see table 4), initial reporting may be done by phone, e-mail (contact details will be provided in the investigational site file), or on the eCRF with as much information as is available. In case the investigator requires information from the Sponsor in an emergency situation, the contact details for emergency situations are given in the investigational site file.

12.1.3. Recording and reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies should be reported on a Device Deficiency Form in the eCRF. In case the eCRF is not available the Device Deficiency form needs to be completed manually and must be sent to Medtronic. Contact details are given in the investigational site file. The investigator is responsible for reporting all Device Deficiencies to Medtronic.

Device deficiencies that did not lead to an Adverse Event but could have led to an SAE

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

require immediate reporting. Initial reporting may be done by eCRF, phone or e-mail, with as much information as available.

12.1.4. Adverse Event and Device Deficiency review process

All Adverse Events and Device Deficiencies will be reviewed by Medtronic Study Management and/ or designee. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements. The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global and country specific regulatory requirements.

In case the Adverse Event/Device Deficiency is related to a Medtronic market released device used during the study, Medtronic Study Management and/ or designee will immediately report this device related Adverse Event/Device Deficiency to the Product Experience Management (PXM) group. The PXM group will ensure prompt review, and appropriate reporting.

12.2. Reporting of Adverse Events

Table 6: Adverse Event Reporting Requirements from Investigator to Medtronic

Serious Adverse Device Effects (SADE)	Immediately (but no later than 3 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event.
Serious Adverse Events (SAE)	
Adverse Device Effects (ADE)	
Device Deficiency (with SAE potential)	
All other AEs	Submit in a timely manner after the investigator first learns of the event.
All other Device Deficiencies	Submit in a timely manner after the investigator first learns of the deficiency.

In addition, Investigators are obligated to report AEs to their EC in accordance with the requirements and local regulations.

For subjects who consented to extend their participation in the trial to 60 months, all adverse events and device deficiencies that retrospectively occurred are to be reported.

12.3. Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with the outcome of death) as soon as possible after the investigator first learns of the death. In the case of death, there should be one AE with the outcome of death.

Local laws and procedures must be followed where applicable.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team.

If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When a death occurs at a remote study site, it is the investigative study site's responsibility to attempt the retrieval of information about the death.

13. Data Review Committees

13.1. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established. The DMC is composed of several members with pertinent expertise who are not directly involved in the conduct of the study.

The responsibility of the DMC is to evaluate safety data during the course of the study and to advise Medtronic about the continuing of the study, in order to ensure the well-being of the current participants and those yet to be enrolled as well as the continuing validity and scientific merit of the study. DMC composition, duties, procedures, deliberation rules are detailed and documented in the DMC Charter. For DMC meeting schedule and Data Review please refer to the DMC Charter.

Based on the safety data, the DMC may recommend that Medtronic modify or stop the study. DMC composition, duties, procedures, deliberation rules, are detailed and documented in the DMC Charter.

13.2. Clinical Event Committee

The Clinical Events Committee (CEC) is made up of clinicians (interventional and non-interventional) with pertinent expertise (i.e. vascular surgeon, interventional radiologist) who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC is charged with the development of specific criteria used for the categorization of adverse events and clinical endpoints in the study. Criteria will be established for selected complications and clinical events. At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify an event.

Database triggers, Medtronic Safety and the medical monitor from an independent external vendor will identify clinical events requiring adjudication (per the CEC Manual of Operations) and provide this information to the CEC. The CEC will meet regularly to review and adjudicate all events as specified in the CEC Manual of Operations and as requested by Medtronic, for which the required minimum data are available.

13.3. Core Laboratories

The Duplex Ultrasonography Core Laboratory (Duplex Core Lab) is responsible for developing DUS and RVD protocol requirements, reviewing and interpreting DUS and Doppler exams, and providing feedback on the quality of the DUS exams to participating sites. The Duplex Core Lab will review, analyze, and record data on the Duplex Core Lab Assessment eCRF. The Duplex Core Lab's interpretation of all DUS exams will be used for the data analyses.

The Angiography Core Laboratory is responsible for developing protocol requirements, reviewing and interpreting angiographies, and providing feedback on the quality of the imaging studies to participating sites. The Core Lab will review, analyze, and record data on the applicable Core Lab assessment eCRF. The Core Lab's interpretation of all images will be used for the data analyses.

14. Statistical Design and Methods

14.1. General Considerations

Medtronic employees or their designated representatives will perform all statistical analysis. An intention-to-treat (ITT) analysis will be performed and will serve as the primary analysis for all objectives in the study unless otherwise specified. The ITT analysis cohort will include all randomized subjects regardless of treatment received. Additionally, a separate Statistical Analysis Plan (SAP) will be developed to further describe statistical methods, pre-specified data handling rules, and pre-specified analyses that will be included in the final study report and primary publication(s). However, additional exploratory analyses of the data may be conducted as deemed appropriate. Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

14.2. Analysis Cohorts

Intention-to-treat (ITT): The ITT analysis cohort will include all randomized subjects in the groups to which they are randomized regardless of the treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified.

As Treated: The AT cohort includes randomized subjects but analyzes subjects using the treatment they actually received. The AT cohort excludes subjects that were randomized but never received a study device. Additionally, for example, if a subject were randomized to the DCB group, but received the PTA treatment the subject would be included in the PTA group for analysis purposes.

14.3. Sample Size Consideration

Limited studies in BTK reported LLL data. LLL results are displayed in the table below for four previous studies which reported LLL either at 6 or 12 months. Based on these previous studies, standard deviation of LLL at 9 months is estimated to be ~0.60 mm for DCB and PTA group. Randomization will be done in a 1:1 fashion. Assuming 15% attrition due to death and lost- to-follow up, and multiple lesions (~1.1 on average) per subject being allowed in the study, it is expected to have 21 subjects with 23 evaluable LLL measurements at 9 months for each arm. The precision, or margin of error, of the estimated LLL can be assessed by calculating the distance from the upper limit of the 95% confidence interval to the mean. With 23 lesions in each arm, the precision (half of the width of the confidence interval) is calculated to be 0.25 mm. The precision of the LLL difference between the two arms is calculated to be 0.35 mm.

Table 7: LLL results are displayed in the table below for four previous studies

Study Name	Endpoint Time	Drug Coated Balloon	Percutaneous Transluminal Angioplasty	Drug Eluting Stent
IDEAS[66]	6 months	1.15±0.3 mm	Not applicable	1.35±0.2 mm
DEBELLUM[67]	12 months	0.66±0.9 mm	1.69±0.5 mm	Not applicable
BIOLUX PII	6 months	0.56±0.65 mm	0.54±0.66 mm	Not applicable
IN.PACT DEEP	12 months	0.605±0.775 mm	0.616±0.781 mm	Not applicable

No formal hypothesis test is specified for this study. A sample of 50 subjects (25 in each group) will provide good precision to quantify the target parameter of LLL. Primary analysis will be performed when all subjects have completed 9-month visits. The study may be extended to a larger clinical study upon appropriate ethical and clinical justifications, to be included in the premarket clinical evaluation cohort in US . Statistical justifications including type I error control and power will be provided to retain a high level of scientific rigor. Additionally, an independent Data Monitoring Committee (DMC) will be appointed to closely monitor the study progress and make recommendations based on study outcomes.

14.4. Primary Objective

14.4.1. Objective

To assess the efficacy of the IN.PACT 014 by comparing the Late Lumen Loss (LLL) of the investigational product vs standard (conventional) PTA.

14.4.2. Endpoint

The primary efficacy endpoint will be Late Lumen Loss (LLL) at 9 months post procedure for the IN.PACT 014 Investigational device vs Standard PTA. LLL will be assessed by means of Quantitative Vascular Angiography (QVA) by an independent angiographic corelab at 9 months post procedure or at the time of TLR.

14.4.3. Analysis Method

Primary analysis will be performed by ITT principle, which constitutes all evaluable angiographic images at 9 months post procedure or at the time of revascularization, whichever comes first. The mean and standard deviation for LLL will be calculated for each randomized group. The difference between the two groups and the 95% confidence interval will be presented.

As treated analysis may be performed as sensitivity analysis if patient crossover occurs.

Interim analyses will be conducted and reviewed by an unblinded predesignated group when 15, 30, 45 and/or when all subjects enrolled are randomized and followed up for 9 months. After primary endpoint analysis, additional analysis may be performed upon discretion of the sponsor. A decision to stop, continue or extend the study can be made after each interim analysis has been reviewed.

As the study has no formal hypothesis testing at each of the interim analyses, no multiplicity adjustment is needed, and descriptive statistics will be reported.

14.5. Secondary Objectives

14.5.1. Composite Safety Endpoint

Endpoint

The composite safety endpoint will be a composite of freedom from device- and procedure-related mortality within 30 days, freedom from major target limb amputation and freedom from clinically-driven TLR within 9 months post-index procedure.

Analysis Method

The success rate of safety endpoint will be defined as the number of subjects without any device and procedure-related death within 30 days, major target limb amputation and CD-TLR within 9 months post-index procedure divided by number of evaluable subjects at 9 months.

Percentage and 95% confidence interval will be calculated for the safety endpoint success rate for each randomization arm respectively.

14.5.2. MAE Endpoint

Endpoint

Major Adverse Event (MAE) rate, defined as a composite of all-cause mortality, target limb major amputation and clinically-driven TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months .

Analysis Method

The MAE rate through 3 months will be calculated as the number of subjects who experience death, target limb major amputation or CD-TLR by 3 months post-index procedure divided by the number of evaluable subjects at 3 months. Percentage and 95% confidence interval will be calculated for the MAE rate through 3 months.

Similar analysis will be performed through 6, 9, 12, 24, 36, 48 and 60 months for each randomization arm respectively.

14.5.3. Functional flow assessment

Endpoint

Functional flow assessment at 3, 6, 9, 12, 24 and 36 months, defined as absence of target lesion occlusion (no flow) assessed by duplex ultrasound.

Analysis Method

Summary statistics (frequency percentage etc.) for occlusion rate among lesions with evaluable duplex ultrasound data at each visit will be provided for each arm.

14.5.4. Mortality Rate

Endpoint

Death of any cause through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Death rate through 3 months will be calculated as number of subjects die within 3 months post-index procedure divided by number of subjects known to be alive by 3 months plus number of subjects die within 3 months post-index procedure. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Death rate through 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

Endpoint

Cardiovascular related death through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Cardiovascular related death rate through 3 months will be calculated as number of subjects with cardiovascular related deaths within 3 months post-index procedure divided by number of subjects known to be alive by 3 months plus number of subjects die within 3 months post-index procedure. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Cardiovascular death rate through 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.5. Major Target Limb Amputation

Endpoint

Rate of major target limb amputation through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Major target limb amputation rate through 3 months will be calculated as number of subjects undergo major target limb amputation within 3 months post-index procedure divided by the number of evaluable subjects through 3 months. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Major target limb amputation rate through 30 days, 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.6. Clinical-Driven Target Lesion Revascularization (CD-TLR)

Endpoint

Rate of CD-TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months

Analysis Method

Rate of CD-TLR through 3 months will be calculated as number of subjects undergo CD-TLR within 3 months post-index procedure divided by the number of evaluable subjects at 3 months. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Rate of CD-TLR through 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.7. Mechanically-Driven Target Lesion Revascularization (MD-TLR)

Endpoint

Rate of MD-TLR through 37 days.

Analysis Method

Rate of MD-TLR through 37 days will be calculated as number of subjects undergo MD-TLR within 37 days post-index procedure divided by the number of evaluable subjects at 37 days. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

14.5.8. Target Lesion Revascularization (TLR)

Endpoint

Rate of TLR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of TLR at 3 months will be calculated as number of subjects undergo TLR within 3 months post-index procedure divided by number of subjects who either undergo TLR by 3 months or have been followed in the study for at least 3 months without TLR. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Rate of TLR through 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.9. Clinical-Driven Target Vessel Revascularization (CD-TVR)

Endpoint

Rate of CD-TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of CD-TVR through 3 months will be calculated as number of subjects undergo CD-TVR within 3 months post-index procedure divided by the number of evaluable subjects at 3 months. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Rate of CD-TLR through 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.10. Target Vessel Revascularization (TVR)

Endpoint

Rate of TVR through 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of TVR through 3 months will be calculated as number of subjects undergo TVR within 3 months post-index procedure divided by the number of evaluable subjects at 3 months. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Rate of TVR through 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.11. Status of Wound Healing

Endpoint

Status of wound healing at 30 days, 3, 6, 9, 12, 24 and 36 months.

Analysis Method

Wound status will be assessed by visual estimation from the wound care specialist. Wound status are classified as:

- Worsened
- Unchanged
- Improved
- Completely healed
- Amputation
- Skin graft

Percentage of wounds in each category will be presented for each treatment arm at 30 days, 3, 6, 9, 12, 24 and 36 months respectively. Number of new wounds will also be reported.

14.5.12. Thrombosis

Endpoint

Rate of thrombosis at the target lesion through 30 days, 3, 6, 9, 12, 24, 36, 48 and 60 months.

Analysis Method

Rate of thrombosis through 3 months will be calculated as number of subjects with thrombosis at the target lesion within 3 months post-index procedure divided by the number of evaluable subjects at 3 months. Percentage and 95% confidence interval will be presented for each randomization arm respectively.

Rate of thrombosis at the target lesion through 30 days, 6, 9, 12, 24, 36, 48 and 60 months will be calculated and presented similarly.

14.5.13. Device Success

Endpoint

Device success is defined as successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP).

Analysis Method

Device success rate will be calculated as the number of IN.PACT 014 Investigational devices with successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP), divided by the total number of IN.PACT 014 Investigational devices assessed in the study.

14.5.14. Clinical Success

Endpoint

Clinical success is defined as residual stenosis of ≤ 30% without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.

Analysis Method

Clinical success rate will be calculated as the number of index procedures with residual stenosis of ≤ 30% for all target lesions and without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge, divided by the number of total index procedures performed.

14.6. Missing Data

In general, all analyses will be performed using the ITT analysis set, which constitutes all available (or observed) cases. As treated analysis may be performed for some objectives if requested. Imputation of missing data will not be performed. For example, to determine the rate of freedom from MAEs, all subjects with MAEs reported or no MAEs observed during the defined time period will be counted in the analysis.

15. Ethics

15.1. Statement(s) of Compliance

The IN.PACT BTK Study is designed to reflect the good clinical practice (GCP) principles outlined in the latest version of ISO 14155. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted.

The study will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the Informed consent process, Ethics Committee approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.

In addition, the study will be conducted in compliance with 21 CFR Part 11 and 54, the latest version of ISO 14155, the Clinical Trial Agreement, and the procedures described within this CIP.

MDD 93/42/EEC and MEDDEV 2.7/3 rev 3 (May 2015), will be followed until date of application (DoA) of EU MDR 2017/745. After this time point, the study will be compliant to EU MDR 2017/745.

Competent Authority notification/approval to conduct the study is required in all participating geographies (where applicable). Investigational sites will be not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency has been obtained (as appropriate). The clinical investigation shall not begin until the required approval/favorable opinion from the Ethics Committee (EC) or notification/approval from a Competent Authority have been obtained.

Additionally, any requirements imposed by a local regulatory agency or Ethics Committee shall be followed, as appropriate.

Each site must provide Medtronic with a copy of the investigational site's Ethics Committee approval letter and the Ethics Committee-approved Informed Consent Form. Ethics Committee approval letters must contain the following elements:

- Study Title and the Medtronic Protocol Number;
- Medtronic's Protocol Version (revision letter and/or date of issue);
- A list of the documents reviewed at the meeting covered by the approval letter;
- If applicable, the required interval for the site's Continuing Review by the Ethics Committee; and
- Expiration date, if applicable and/or allowed by the site's system, of the current approval.

If applicable, approvals for the continuation of the study at each investigational site must be kept current in accordance with the Ethics Committee's review schedule. All site communications to and from the Ethics Committee must be forwarded to Medtronic as they are sent/received.

The Sponsor will be informed by the Ethics Committee and/or the investigator in case any action is taken by an Ethics Committee with respect to this investigation.

This study will be publicly registered on www.clinicaltrials.gov prior to first enrollment.

16. Study Administration

16.1. Investigator / Investigational site selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

An investigator may be included in the clinical study if compliant with the following requirements:

- Investigator is qualified, educated and has experience in the drug coated balloon treatment of the infrapopliteal arteries
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions.
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study. Each site should have a designated research coordinator assigned to the study.
- Investigator/site has access to an adequate number of eligible subjects.
- Investigator/site has the ability to comply with applicable Ethics Committee and regulatory requirements.
- Lack of potential conflict(s) of interest
- Anticipated study startup timeline, including contracting and Ethics Committee and regulatory submission and approval (if applicable) is acceptable.
- Anticipated competition for same subject population from competitive ongoing studies is at an acceptable rate.

A list of participating investigational sites and investigators will be available as a separate document.

Prior to study start, a recent signed and dated CV shall be collected from each principal investigator and key members of the investigation site team participating in this study, evidencing the required qualifications, including the year and where obtained, and shall include their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the site.

16.2. Clinical Trial Agreement

A clinical trial agreement shall be in place, signed by the participating investigational site and/or principal investigator of each investigational site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the clinical investigation plan and subsequent amendments, with a fully executed agreement.

16.3. Study Insurance /Subject Indemnification

Medtronic, Inc. (including all wholly owned subsidiaries) maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the Ethics Committee.

Medtronic will provide subject indemnification according to local laws where this trial will be conducted.

16.4. Subject Compensation

Subjects will not receive any compensation for their participation in this study (including follow up); however, Medtronic may, at its option, provide reimbursement for participants who will incur extraordinary travel costs related to their participation in the study, including airfare, mileage or hotel expenses, if locally allowed. Participating Institution will make such request(s) in writing to Medtronic (de-identified of participant information), detailing the unusual circumstances and the excessive costs that the participant will incur. Medtronic will evaluate requests on a case-by-case basis, and will notify the Participating Institution of its decision in writing.

16.5. Site Activation/Supply of Trial Materials

Investigational sites will receive a formal letter of site activation, upon receipt of or completion of the following:

- Curriculum vitae of the principal and sub-investigators and all key site staff
- A signed trial agreement
- Financial disclosure from the investigators
- Competent Authority approval (as applicable to the geography)
- A copy of the Ethics Committee approval letter, along with the voting roster
- The Ethics Committee approved patient information and Informed consent form
- Documented training of the investigative team
- Delegated Task List

Medtronic will control the supply of devices and study materials, and will only ship investigational devices once the above activation criteria are met, and the site receives a formal activation letter from Medtronic.

16.6. Monitoring

Monitoring and monitoring oversight will be provided by Medtronic (Maastricht, the Netherlands) and detailed in a Monitoring Plan separate from this CIP.

A site qualification visit may be conducted by Medtronic personnel (or designees) to review the clinical investigational plan and, regulatory and study requirements with the investigator and study personnel. A site initiation visit will be performed after it has been verified that the site is prepared for the study and that the site requirements for study participation are met.

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. Frequency and timing of monitoring visits shall be determined by the Sponsor for each site based on enrollment rate and volume, study compliance and findings from previous visits.

It will be verified whether signed and dated Informed consent forms have been obtained from each subject before any clinical study related procedures are undertaken. Medtronic or designee will conduct site monitoring visits to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

16.7. Data Management

Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection. The database is located on a secure server at a Medtronic facility located in the United States. All users will be trained on the use of the database prior to obtaining access. Once access is granted, users will have a unique User ID and will create their own password. Data stored electronically shall be maintained in compliance with 21CFR Part 11. The database for this study will be maintained according to corporate policy and record retention schedule.

Data Collection

It is the responsibility of the participating Investigator to ensure the quality of the data being collected. Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegated Tasks List. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study.

The investigator (or authorized sub-investigator) will electronically sign each eCRF.

The EDC system maintains an audit trail on entries, changes or corrections in eCRFs, once the eCRF is saved as complete. If changes are made to an already signed eCRF, the investigator shall re-sign this eCRF.

At the end of the study, the data will be frozen and will be stored for the period defined by the applicable laws.

Data Validation

The sponsor and/or assigned designee will be responsible for the processing and quality control of the data (data management) per the Data Management Plan, which describes the procedures for data review, database cleaning and issue/resolution of data queries. Data will be collected and stored in a validated, password protected database. Data analysis will be conducted utilizing validated software and analysis programs by qualified biostatisticians.

Study data collected will be monitored and verified against source documents in accordance with the latest version of ISO14155guidelines and international standards. Any data discrepancies will be addressed through queries posted within the EDC system.

Database storage

Image data (DUS, Angio) collected at office visits will be sent to Medtronic and uploaded to secure servers. Upon receipt, data will be maintained with databases and retrieved for analysis and reporting.

16.8. Direct Access to Source Data/Documents

The principal investigator(s), his/her delegate(s), and the study coordinator(s) shall be accessible to Medtronic personnel or designee(s) and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits. If direct access cannot be provided per local laws and regulations, certified copies need to be made available or monitor needs to obtain access by reviewing alongside with study staff. Additional details on source data verification requirements and rationale are provided in the IN.PACT BTK Monitoring plan.

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigational sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities, independent of the employees involved in the clinical study. Regulatory bodies may also perform inspections at participating investigational sites. Any Competent Authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC review, and regulatory inspections.

16.9. Confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (site number and subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

16.10. CIP Amendments

The investigator can propose any appropriate modification(s) of the clinical investigation plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the clinical investigation plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their EC. The investigator will only implement the amendment after approval or notification of the EC, Competent Authority and Sponsor. Administrative amendments to the clinical investigation plan will be submitted to the EC for notification. Furthermore investigators shall sign any approved amendment of the clinical investigation plan, if required per local regulation.

16.11. Record Retention

All study-related documents must be retained for a period of at least 2 years after market-release in his/her region and after study closure (or longer if required by local law). Medtronic will inform the investigator/site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. The Sponsor has to be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The sponsor will retain the study records for the life of Medtronic, according to Medtronic corporate policy and record retention schedule.

16.12. Publication and Use of Information

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigational sites:

Medtronic may use the study data for Competent Authority submission results, may publish the results in peer reviewed scientific journal(s) and present the data at major congresses. Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal with a maximum of 10 authors. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Medtronic owns the data of this clinical study, a single investigational site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Pooling data from several investigational sites for publication purposes, national projects and international projects all require prior approval from Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The clinical investigation will be registered in a publicly accessible database and the results will be made publicly available.

The study sponsor will collect data in such way that no subject can be identified. Participating subjects will not be identified by name in any published reports about the clinical study.

16.13. Suspension or Early Termination

Early study suspension or termination

Medtronic or Competent Authority may decide to suspend or early terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, if interim analysis indicates that the results significantly differ from the study objectives or statistical endpoints). At these interim time points an independent DMC will review the safety data and according to the DMC charter determine whether study continuations is advisable. If the clinical study is terminated early or suspended, Medtronic shall promptly inform the investigators and the regulatory bodies of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC and the study subjects.

Early investigation site suspension or termination

Medtronic, EC, or Competent Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC, non-compliance to the Clinical Investigation Plan or lack of enrollment).

If an investigation site is suspended or prematurely terminated:

- Medtronic shall promptly inform the clinical investigator(s) of the termination or suspension and the reason(s) for this
- The investigator shall then promptly inform the reviewing EC
- The investigator shall then promptly inform study subjects
- The investigator agreement will be terminated
- The investigator will inform the institution (where required by applicable regulatory requirements)
- Medtronic will inform the Competent Authority(ies) (where required by applicable regulatory requirements)

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC, if applicable.

Subject follow-up in case of termination

If the study is terminated early, subjects will be followed as per routine standard of care by the investigational site or a treating physician.

After study termination relevant medical records may be made available by the investigational sites for the treating physician per local laws and regulations if needed for further subject treatment. As per local law and regulation the trial investigator may be contacted by the treating physician in case of questions related to the study device and treatment.

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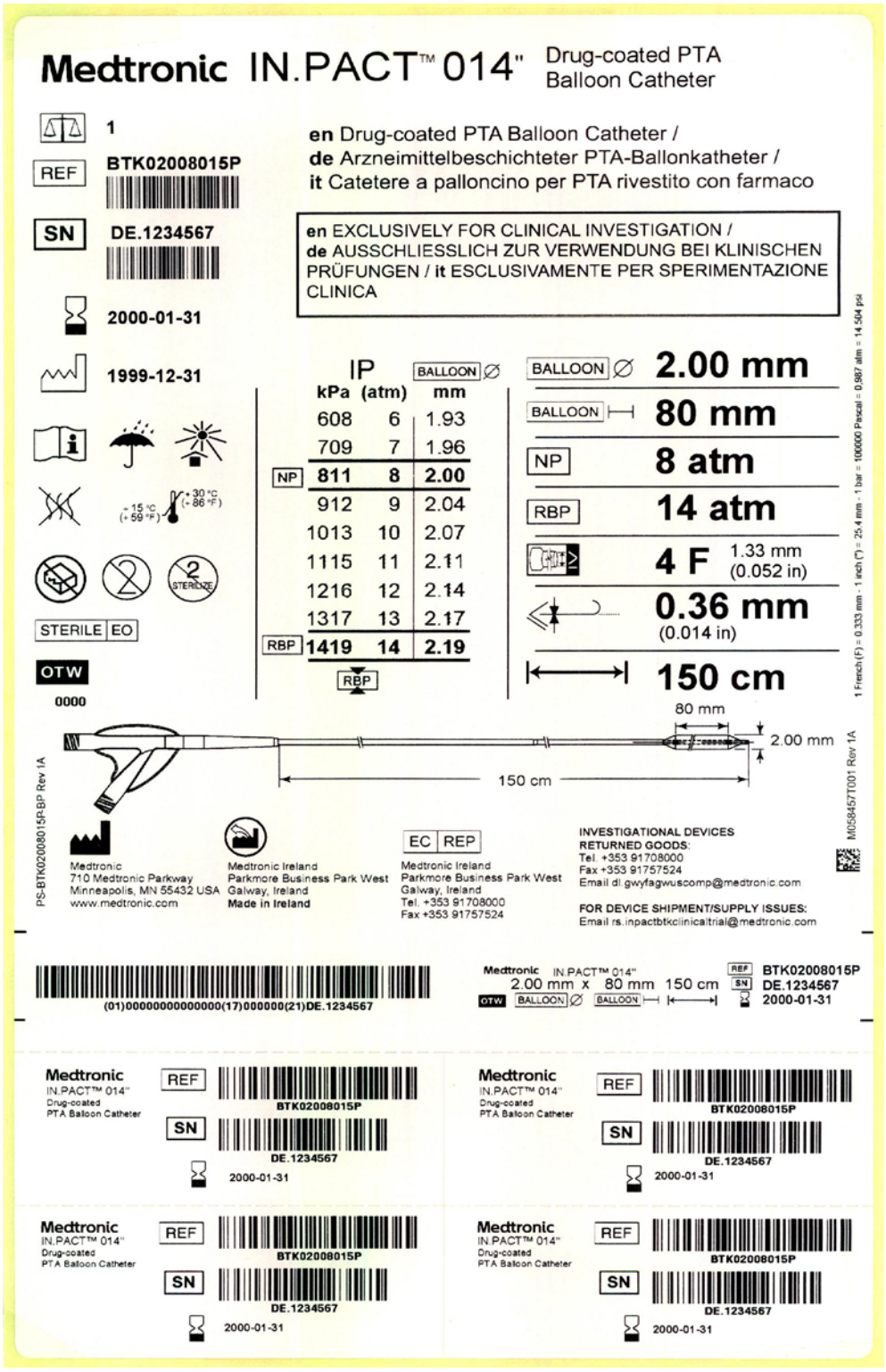
18. Appendices

18.1. IN.PACT 014 Device label



18.2. Definitions

ADJUNCTIVE THERAPY

A procedure performed after treatment with the protocol-defined treatment

AMPUTATION (TARGET LIMB)

Surgical removal of part of the limb anywhere from the toe to hip in the ipsilateral limb of the target segment. Amputations will be sub-classified as follows[68]:

- Major amputation: any procedure that results in an amputation at the level of the ankle or above;
    - below knee amputation – amputation affecting the tibia at any point below the knee and above the ankle;
    - above knee amputation – amputation above the knee, affecting the femur at any level.
- Minor amputation: any procedure that results in an amputation below the ankle, including the foot or toe(s).

ANKLE-BRACHIAL INDEX (ABI)

A ratio of the highest ankle systolic blood pressure in one leg, usually measured with a 10 cm cuff at the ankle and using a continuous wave Doppler to detect return of blood flow in the anterior tibial and posterior tibial arteries, to the highest of either arm systolic blood pressure. Performed at rest with subject in prone position.

CALCIFICATION, SCORING

No Calcification: No visual calcification present along the arterial wall of the artery.

Mild to Moderate Calcification: Calcium is visible along one side of the arterial wall in the area of the target lesion prior to injection of contrast. The calcium present encompasses < 50% of the total target lesion treatment area by visual estimate and/or the calcium is not circumferential (360°) in nature (i.e. on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophic calcification, no impedance of blood flow in the vessel.

Moderate to Severe Calcification: Calcium is visible along one or both sides of the arterial wall in the area of the target lesion. The calcium present encompasses ≤ 50% of total target lesion treatment area by visual estimate and/ the calcium is not circumferential (360°) in nature (i.e. on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophic calcification, and does not impede blood flow by more than 50%.

Severe Calcification: Calcium is visible along both sides of the arterial wall, covers 2 cm or greater of the target lesion area, encompasses greater than 50% of the total target lesion treatment area by visual estimate and/or the calcium is circumferential (360°) in nature (i.e. on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophic calcification, significantly impedes blood flow in the vessel.

CLAUDICATION

A pain, cramps, fatigue, or equivalent in leg muscles occurring during walking that results from inadequate blood supply, usually due to atherosclerotic arterial obstruction.

CLINICAL SUCCESS

Clinical success is defined as residual stenosis of ≤ 30% without procedural complications (death, major target limb amputation, thrombosis of the target lesion or Target Vessel Revascularization) prior to discharge.

CRITICAL LIMB ISCHEMIA

A clinical condition caused by chronically decreased perfusion of a leg that results in rest pain, ischemic tissue loss, or gangrene.

DEATH

Cardiovascular related death: Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death. Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

All deaths: are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (eg, cancer, infection) should be classified as cardiac.

DE NOVO LESION

A lesion in a native vessel that has not been previously treated.

DEVICE SUCCESS

Successful delivery, balloon inflation, deflation and retrieval of the intact study device without balloon burst under the rated burst pressure (RBP). Applicable to IN.PACT 014 study device only.

DISSECTION

Intimal disruption of the vessel wall with or without medial or adventitial contrast staining. See also NHLBI (National Heart, Lung, and Blood Institute) Classification of Dissection.

A Minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff

B Luminal flap that is radiolucent and that runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff

C Contrast appears outside of the vessel lumen as an "extraluminal cap". The staining appears even after contrast clears the lumen

D Spiral radiolucent luminal filling defects. Often persistent staining after contrast clears from the vessel.

E New and persistent filling defects in the vessel lumen.

F Lesions that progress to impaired flow or total occlusion.

ELECTRONIC DATA CAPTURE (EDC)

The tools that uses e-CRF to collect and manage subject data.

ELECTRONIC CASE REPORT FORM (eCRF)

A part of the EDC system used to store and manage the subject data.

HEALED WOUND:

A healed wound is defined as complete 100% epithelization of baseline ulcer(s) in the treated leg at a specified time point (all ulcers epithelialized)

INFLOW ARTERY

Target limb vessels including the ipsilateral iliac, SFA and popliteal arteries

LATE LUMEN LOSS

The difference between minimum lumen diameter (MLD) immediately after percutaneous balloon angioplasty PTA and MLD at follow up.

MAJOR ADVERSE EVENTS (MAE)

Composite of all-cause mortality, target limb major amputation and clinically-driven TLR

FUNCTIONAL FLOW ASSESSMENT

Absence of target lesion occlusion (no flow) assessed by duplex ultrasound

RELATEDNESS CATEGORIES FOR ADVERSE EVENT:

For the purpose of harmonizing reports, each AE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the adverse event to the investigational medical device and comparator, to Paclitaxel or procedures.

Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the event, it should not exclude the relatedness and classify the event as "possible".

PROTOCOL DEVIATION:

Any deviation from the Clinical Study Protocol (investigational plan).

RENAL INSUFFICIENCY

An acute or chronic reduction in kidney function, reflected by a serum creatinine greater than the upper limit of normal for the investigative site.

RE-OCCLUSION

Assessed through 30 days and defined as a re-blockage of the target segment resulting in re-intervention by either percutaneous or surgical methods.

RESTENOTIC LESION

A lesion in the vessel segment that has undergone a prior percutaneous treatment.

RUTHERFORD-BECKER SCALE (Clinical Category)

CATEGORY	CLINICAL DESCRIPTION
0	Asymptomatic-no hemodynamically significant occlusive disease
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss, focal gangrene with diffuse pedal ischemia
6	Major tissue loss-extending transmetatarsally; functional foot no longer salvageable

TARGET LESION (TL)

The lesion intended for treatment at the time of the index procedure that meets the inclusion criteria and none of the exclusion criteria will be considered the target lesion.

TARGET LESION REVASCULARIZATION (TLR)

Any repeat percutaneous intervention or bypass surgery performed on the TL.

CLINICALLY DRIVEN TARGET LESION REVASCULARIZATION (CD-TLR)

"Clinically driven TLR" is defined as any TLR of the target lesion with restenosis > 70% (confirmed by angiography) associated with at least one of the following:

- Reoccurence of ischemic rest pain
- worsening of pre-existing wounds
- Occurrence of a new wound(s)

MECHANICALLY DRIVEN TLR

Defined as any TLR due to a flow limiting dissection or flow limiting thrombosis at the target lesion that occurs within 37 days post procedure documented by a Peak Systolic Velocity Ratio (PSVR) >2.4.

TARGET EXTREMITY REVASCULARIZATION (TER)

Any repeated target extremity revascularization

TARGET VESSEL REVASCULARIZATION (TVR)

Any repeat percutaneous intervention or bypass surgery performed on the vessel in which the TL is located.

CLINICALLY DRIVEN TARGET VESSEL REVASCULARIZATION (CD-TVR)

"Clinically driven TVR" is defined as any TVR of the target vessel associated with at least one of the following:

- Reoccurence of ischemic rest pain
- worsening of pre-existing wounds
- Occurrence of a new wound(s)

THROMBOSIS:

The formation or development of a blood clot.

WIfI CLASSIFICATION:

The classification of the threatened lower extremity by the Society for Vascular Surgery (SVS) Lower Extremity Guidelines Committee. This classification is based on three major factors that impact amputation risk and clinical management: Wound, Ischemia and foot Infection (WIfI).

18.3. Version History

Version	Summary of Changes	Author(s)/Title
1.0 *(17 June 2016)*	Not Applicable, New Document	*Stijn Bollen* *Clinical Research Manager*
2.0 *(17 March 2017)*	"Standard Percutaneous Transluminal Angioplasty" has been updated to "Optimal Percutaneous Transluminal Angioplasty" throughout the document. Given multiple target lesions are allowed in this protocol, 'target lesion' has been updated to 'target lesion(s)' throughout the document. **7. Study design** • Randomization will be done by a web-based system only. A telephone option won't be available. • A blinding plan will be implemented according to 'Randomization and Blinding Plan'. Medtronic decision making stakeholders and those directly involved in the data analysis will remain blinded, until the primary endpoint analysis has been completed. Core lab and CEC will remain blinded until the end of the study. **8. Product Description** • Textual errors corrections. • Training of the implanting investigator will be documented prior to start of study activities. 8.6 Product Training Requirements. **9. Selection of Subjects:** Inclusion and Exclusion criteria have been updated to better identify the target patient population. • Inclusion criteria 7: RVD assessment needs to be based on visual estimation and confirmed by DUS assessment to make sure that the RVD assessment is accurate. • Inclusion criteria 11: Clarification to specify the presence of documented run-off to the foot: clearly visible dorsalis pedis, pedal arch or plantar arteries by angiography • Inclusion criteria 12: typo corrections: (≥ 50% stenosis as criteria for flow-limiting inflow lesions and a maximum residual stenosis of ≤ 30% per visual assessment. • Exclusion criteria 2: Clarifications on the index limb amputation criteria, including the metatarsal level. And the window for planned major surgery: 30 days pre or post-procedure. • Exclusion criteria 6: Updated to 6 months DCB procedure to allow for additional flexibility in patient enrollment. • Exclusion 15: WIfI classification, only Ischemia grade 1 is excluded. • Exclusion 17: Osteomyelitis excluding the phalanges. • Exclusion 18: type correction: Impaired renal function (GFR <20 mL/min) or patients on dialysis. **10. Study Procedures**	*Stijn Bollen* *Clinical Research Manager*

	• Schedule of Events, extension of the 9 months visit window to +/- 60 days. • DUS assessment RVD sizing is specified more clearly as part of the procedure. • Discharge DUS must be done according to protocol requirements. • Wound assessment and wound care is only applicable for subjects that present with wounds at baseline or for subjects who develop a new wound during the conduct of the study. • Correction of the selection angiography of the index limb to exclude the bilateral iliac and to include the pedal level. • Pre-dilatation must be at least 3 minutes. • In case of multivessel disease, all possible target lesions are to be evaluated according to the study eligibility criteria and treated accordingly. • Follow-up visit assessments can take place outside of the hospital setting if this is allowed per local regulations and if these are conducted according to the protocol. • Print outs of original electronic source documents must be signed and dated by a member of the investigation site team. • Given the study deviations are available to the site in the eCRF, wording regarding additional reporting is removed. **18.1 Definitions** • Calcification definitions added. • Definition for Mechanical Driven TLR updated Additional typo and grammatical corrections and clarifications throughout the document.	
3.0 *(09 May 2017)*	Updated number of sites and study duration. Additional specifications added to the definition for Mechanically Driven TLR.	*Stijn Bollen* *Clinical Research Manager*
4.0 *(21 Nov 2017)*	**4. Synopsis/7. Study Design/9.1 Study Population** • Revised wording around sample size: At a minimum 60 patients are planned for enrollment. **7. Study Design** • Revised wording around the enrollment cap per site. • One interventional operator per site is considered a preference rather than a requirement. • The study blinding setup is referred to in the blinding plan. **8.7 Product receipt and tracking** • The investigator or designee can be responsible for the Product Accountability Log. **9.3 Inclusion and 9.4 Exclusion Criteria have been updated per the Investigator Meeting on October 20th.**	*Stijn Bollen* *Clinical Research Manager*

	• Upper age limit (85 years) has been removed. • lesion location specifications have been added. • Documented run-off to the foot criteria has been clarified. • Risk for major amputation criteria has been added for neurotropic ulcers, heel pressure ulcers and calcaneal ulcers. • Osteomyelitis exclusion criteria has been updated to active osteomyelitis only, excluding the phalanges and beyond cortical involvement of the bone per clinical judgement. • Subject with vasculitis, systemic Lupus Erythematosus or Polymyalgia Rheumatica will be excluded if on active treatment. • Systemic corticosteroid therapy has been specified as: expected dosage exceeding 5mg of prednisolone or equivalent, per day during the initial 9 months after procedure. • Exclusion criteria on the inability to tolerate concomitant antiplatelet therapy has been removed to support flexibility in the investigators choice of medication treatment. • Exclusion criteria regarding breast-feeding added per Competent Authority request in Switzerland. **10.1 Schedule of Events** • Specifications added for DUS prior to discharge. **10.3 Prior and Concomitant Medications.** • Clarification was added that the medication schedules specified in this section are per investigator's discretion and institutional standard of care should be followed. **10.6.5 Treatment of Target Vessels/Lesions** • CTO section length specification is aligned with inclusion criteria #8. **10.7.6 Wound Care Follow-up Assessments** • Flexibility in the schedule has been added to better accommodate daily practices. • Amputation and Skin graft were added to the wound status assessment options to allow for more detailed data collection. **10.11.4 Sponsor Reporting Responsibilities** • Final Report responsibilities have been corrected. **10.13.2 Lost-to-follow-up** • Additional specifications per Competent Authority request in Switzerland. **12.2 Reporting of Adverse Events**	

	• Updated reporting requirements for AEs and Device Deficiencies per ISO14155. **14.4.3 Analysis Method** • Additional interim analyses have been added.	
5.0 *(05 Nov 2018)*	**Front Page:** • Added Prof. Antonio Micari as Lead Principal Investigator. **4. Synopsis:** • **Secondary Objective(s):** The assessment of secondary objectives at the 36 month follow-up visit has been removed as the required subject follow-up will be reduced from 36 to 24 months. • **Study Design:** The 36 months follow-up visit has been removed as subjects will be followed until 24 months instead. • **Sample Size:** Reduction in the number of patients to be enrolled from "At a minimum 60 patients" to "At a minimum 50 patients" are planned for enrollment. • Study Procedures and Assessments: Removal of 36 months visit. **6.2.2 Secondary Endpoints(s):** • The assessment of secondary objectives at the 36 month follow-up visit has been removed as the required subject follow-up will be reduced from 36 to 24 months. **7. Study Design:** • Reduction in the number of patients to be enrolled from "At a minimum 60 patients" to "At a minimum 50 patients" are planned for enrollment. **7.1 Duration:** • Reduction in estimated study duration from approximately 60 months to approximately 48 months from the time of first enrollment to the last protocol-required follow-up contact. Each subject will be followed for 24 months instead of 36 months. **9.1 Study Population:** • Reduction in the number of patients to be enrolled from "At a minimum 60 patients" to "At a minimum 50 patients". **10.1 Schedule of Events:** • The 36 months follow-up visit has been removed as subjects will be followed until 24 months instead. **10.6.6 Adjunctive Therapies:**	*Stefanie Deckers* *Principal Clinical Research Specialist*

	• Figure 4: Randomization & Treatment Assignment Flow updated to reflect decrease in patient follow-up period. **10.7.6 Wound Care Follow-up Assessments:** • The requirement that pictures (digital format) must be taken and collected for source documentation (always with the same angulation and a reference tool to correctly assess the size of the wound(s)) has been removed. • The agreement on wound assessment between the interventionalist (Investigator that performs the endovascular procedure) and the wound care specialist will be documented has been removed. **14.3 Sample Size Consideration:** • Updated assumptions, expectations and precision. • Updated wording on sample to reflect the reduction in the number of patients from a sample of 60 to a sample of 50 subjects. **14.4.3 Analysis Method:** • Updated wording around the interim analysis to reflect reduction in sample size. **14.5.2 MAE Endpoint:** • The analysis of the MAE rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.3 Functional flow assessment:** • The assessment of the functional flow at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.4 Mortality Rate:** • The assessment of the mortality rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.5 Major Target Limb Amputation:** • The assessment of the major target limb amputation rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.6 Clinical-Driven Target Lesion Revascularization (CD-TLR):** • The assessment of the CD-TLR rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.8 Target Lesion Revascularization (TLR):**	

	• The assessment of the TLR rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.9 Clinical-Driven Target Vessel Revascularization (CD-TVR):** • The assessment of the CD-TVR rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.10 Target Vessel Revascularization (TVR):** • The assessment of the TVR rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.11 Status of Wound Healing:** • The assessment of the wound healing status at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months. **14.5.12 Thrombosis:** • The assessment of the thrombosis rate at 36 months has been removed as the required subject follow-up will be reduced from 36 to 24 months.	
6.0 *(15 Mar 2019)*	**4. Synopsis:** • Updated CIP template A has not been implemented for CIP6.0 update to avoid confusion during the course of the study. A gap analysis was performed; Clinical Study Type updated following guidance CIP template A Clinical Study Type: First in Human, Interventional • Secondary Objective(s): The assessment of secondary objectives at the 36 month follow-up visit has been added as the required subject follow-up will be updated from 24 to 36 months. • Study Design**:** The 36 months follow-up visit has been added as subjects will be followed until 36 months instead. • Study Procedures and Assessments: Addition of 36 months visit. **6.2.2 Secondary Endpoints(s):** • The assessment of secondary objectives at the 36 month follow-up visit has been added as the required subject follow-up will be updated from 24 to 36 months. **7.1 Duration:** • Update in estimated study duration from approximately 48 months to approximately 60 months from the time of first enrollment to the last protocol-required follow-up contact. Each subject will be followed for 36 months instead of 24 months. **10.1 Schedule of Events:**	*Wendy Moeyersons* *Clinical Research Specialist*

	• The 36 months follow-up visit has been added as subjects will be followed until 36 months instead. **10.6.6 Adjunctive Therapies:** • Figure 4: Randomization & Treatment Assignment Flow updated to reflect update in patient follow-up period. **14.5.2 MAE Endpoint:** • The analysis of the MAE rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.3 Functional flow assessment:** • The assessment of the functional flow at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.4 Mortality Rate:** • The assessment of the mortality rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.5 Major Target Limb Amputation:** • The assessment of the major target limb amputation rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.6 Clinical-Driven Target Lesion Revascularization (CD-TLR):** • The assessment of the CD-TLR rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.8 Target Lesion Revascularization (TLR):** • The assessment of the TLR rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.9 Clinical-Driven Target Vessel Revascularization (CD-TVR):** • The assessment of the CD-TVR rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.10 Target Vessel Revascularization (TVR):** • The assessment of the TVR rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **14.5.11 Status of Wound Healing:** • The assessment of the wound healing status at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months.	

	14.5.12 Thrombosis: • The assessment of the thrombosis rate at 36 months has been added as the required subject follow-up will be updated from 24 to 36 months. **17. References: reference 68 has been added** **18.2 Definitions:** • Amputation (Target Limb) has been updated to reflect the PARC definition and ensure consistency across trials. • Major amputation: any procedure that results in an amputation at the level of the ankle or above; • Below knee amputation – amputation affecting the tibia at any point below the knee and above the ankle; • Above knee amputation – amputation above the knee, affecting the femur at any level. • Minor amputation: any procedure that results in an amputation below the ankle, including the foot or toe(s). • Functional Flow Assessment has been corrected to remove freedom from CD-TRL component: • Absence of target lesion occlusion (no flow) assessed by duplex ultrasound.	
7.0 (11 Jun 2020)	**Overall:** • Language update per the latest version of ISO14155 and EU MDR. • Page footer: Replaced "Medtronic Confidential" by "Medtronic Business Restricted" **Second Page:** • "Document reference Number" replaced by '"Version date". • Added "EUDAMED generated unique identifier" **3. Glossary:** • Removed "PIC, Patient Informed Consent" • Removed "UADE, Unanticipated Adverse Defice Effect" **4. Synopsis:**	*Giulia Gatta* *Clinical Research Specialist*

	• Funding source added • External Organizations added • Secondary Objective(s): The assessment of secondary objectives at 48 and 60 months follow-up visit have been added as the required subject follow-up will be updated from 36 to 60 months. • Study Design**:** The 48 and 60 months follow-up visit have been added as subjects will be followed until 60 months instead. • Study Procedures and Assessments: Addition of 48 and 60 months visit; addition of Upon Early Termination Phone Calls • Statistics: replaced "standard error" by "standard deviation" **6.2.2 Secondary Endpoints(s):** • The assessment of secondary objectives at 48 and 60 months follow-up visit have been added as the required subject follow-up will be updated from 36 to 60 months. **7.1 Duration:** • Update in estimated study duration from approximately 48 months to approximately 60 months from the time of first enrollment to the last protocol-required follow-up contact. Each subject will be followed for 60 months instead of 36 months. **8.6 Product Training Requirements:** • Added that training requirements for clinical site Personnel is documented in the study training plan and based on a risk assessment **10.1 Schedule of Events:** • The 48 and 60 months follow-up visit have been added as subjects will be followed until 60 months instead. • Addition of collection of vital health status. **10.4.1 Consent Materials:** • Removed "patient" and/or "PIC" and spelled out "Informed consent" or "Informed consent form". **10.4.2 Informed consent process:** • Removed "patient" and/or "PIC" and spelled out "Informed consent" or "Informed consent form". **10.4.4 Subject Accountability for Follow-up Extension:** • Added section to define accountability of subjects during the follow-up period, up to 60 months. **10.6.6 Adjunctive Therapies:** • Figure 4: Randomization & Treatment Assignment Flow updated to reflect update in patient follow-up period.	

	10.7.3. Follow-up phone calls: • Added section describing follow-up phone calls at 48 and 60 months post-procedure. **10.11.4 Sponsor reporting responsibilities:** • "MDD 93/42/EEC and MEDDEV 2.7/3 and additional applicable local requirements" replaced by "local legislation". • Added "serious health threat" **10.11.1 Investigator records** • Removed "PIC" and spelled out "Informed consent". **10.12 Deviation handling:** • Removed "UADE" **10.13 Subject Exit, Withdrawal or Discontinuation:** • Added information about subject's (vital) health status collection until 60 months after index procedure. **10.13.2 Study completed** • Added section to define completion of the study **10.13.3 Lost-to-follow-up** • Added information to describe healthcare arrangements for subjects unable to complete the study follow-up period **11.1 Potential risks** • The analysis process for the IN.PACT 014 DCB is being performed in accordance with ISO 14971 **11.1.1 Risks associated with the use of the study product** • Updated language on potential risks due to the use of Paclitaxel. **12.1.1 Definitions /Classifications** • Removed "UADE, Unanticipated Adverse Defice Effect" • Added "Serious Health Threat" • Updated other definitions per latest ISO14155. **12.1.2 Recording and reporting of Adverse Events:** • Added language to specifiy details in the process for reporting adverse events **12.3 Subject Death** • Added section per latest CIP template **14.1 General considerations** • Added language on how to handle deviations from the Statistical Plan **14.3 Sample size consideration**	

	• Randomization will be done in a 1:1 fashion, and precisions numbers are updated **14.4.3 Analysis Method** • After primary endpoint analysis, additional analysis may be performed upon discretion of the sponsor • Replaced "standard error" by "standard deviation" **14.5.2 MAE Endpoint:** • The analysis of the MAE rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.4 Mortality Rate:** • The assessment of the mortality rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.5 Major Target Limb Amputation:** • The assessment of the major target limb amputation rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.6 Clinical-Driven Target Lesion Revascularization (CD-TLR):** • The assessment of the CD-TLR rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.8 Target Lesion Revascularization (TLR):** • The assessment of the TLR rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.9 Clinical-Driven Target Vessel Revascularization (CD-TVR):** • The assessment of the CD-TVR rate at 48 and 60 months has been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.10 Target Vessel Revascularization (TVR):** • The assessment of the TVR rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **14.5.12 Thrombosis:** • The assessment of the thrombosis rate at 48 and 60 months have been added as the required subject follow-up will be updated from 36 to 60 months. **15.1 Statement(s) of Compliance:** • Added language to reflect compliance to EU MDR 2017/745, and te latest version of ISO 14155.	

	16.7 Data Management: • Added language to define data storage upon study completion **16.8. Direct Access to Source Data/Documents:** • Reference to the monitoring plan for source data verification requirements **16.12 Publication and use of information:** • Added language that the clinical investigation will be registered in a publicly accessible database and the results will be made publicly available. **17 References:** • Added reference #69.	