PROTOCOL	2021-PT-01
TITLE:	Safety and Performance of POLYTHESE® vascular prosthesis
EFFECTIVE DATE:	1 July 2021

A Retrospective, Observational, Multicenter, Study to Collect Clinical Safety and Performance data of POLYTHESE® vascular prostheses

- Protocol 2021-PT-01

Version 1

Author		Location
Valerie LONGIN Clinical Trial Operations	Fait le 08/07/2021 Valerie Longin Signé par Valerie Longin Signé et certifié par yousign	ECLEVAR Tour Europlaza 20 avenue André Prothin 92927 La Défense Cedex
Mikaela DIMITRIU Head of RW solutions	Fait le 08/07/2021 Mikaela Dimitriu Signé par Mikaela Dimitriu Signé et certifié par yousign	ECLEVAR Tour Europlaza 20 avenue André Prothin 92927 La Défense Cedex
Verifiers		**Location**
Pascal CHABE R&D manager	Fait le 08/07/2021 Pascal CHABE Signé par Pascal CHABE Signé et certifié par yousign	PEROUSE MEDICAL Route du Manoir 60173 IVRY-LE-TEMPLE
Laura JULIEN Principal Regulatory Affairs Manager	Fait le 08/07/2021 Laura JULIEN Signé par Laura JULIEN Signé et certifié par yousign	PEROUSE MEDICAL Route du Manoir 60173 IVRY-LE-TEMPLE
Approvers		**Location**
Agnès JORDAN Regulatory Affairs DIRECTOR	Fait le 20/07/2021 Agnes JORDAN Signé par Agnes JORDAN Signé et certifié par yousign	PEROUSE MEDICAL Route du Manoir 60173 IVRY-LE-TEMPLE

PROTOCOL	2021-PT-01
TITLE:	Safety and Performance of POLYTHESE® vascular prosthesis
EFFECTIVE DATE:	1 July 2021

Study Product Name:	**POLYTHESE® vascular prostheses**
Sponsor/manufacturer:	**PEROUSE Medical**
	Route du Manoir,
	60173 Ivry-le-Temple
	France
Participating sites:	**To be detailed in separate document**

PROTOCOL	2021-PT-01
TITLE:	Safety and Performance of POLYTHESE® vascular prosthesis
EFFECTIVE DATE:	1 July 2021

CONTENTS

1. LIST OF ABBREVIATIONS

AAA	Abdominal aortic aneurysm
IAA	Ilia arterial aneurysms
FAA	Femoral arterial aneurysms
PAA	Popliteal arterial aneurysms
ADE	Adverse Device Effect
AE	Adverse Event
ABI	Ankle Brachial Index
AD	Aortic Dissection
CLTI	Chronic limb-threatening ischemia
MI	Myocardial Infarction
PAD	Peripheral arterial disease
PMCF	Post-Market Clinical Follow-up
SADE	Serious Adverse Device Effect
TASC	Trans-Atlantic Inter-Society Consensus
USADE	Unanticipated Serious Adverse Device Effect
aTAA	Ascending Thoracic aortic Aneurysm
dTAA	Descending Thoracic Aortic Aneurysm

PROTOCOL	2021-PT-01
TITLE:	Safety and Performance of POLYTHESE® vascular prosthesis
EFFECTIVE DATE:	1 July 2021

2. SYNOPSIS

Title:	**A Retrospective, Observational, Multicenter, Study to Collect Clinical Safety and Performance data on POLYTHESE® vascular prostheses**
Study Population :	Subjects who did receive **POLYTHESE®** at least one year ago for replacement or bypass of pathological arteries. 3 main sub-populations will be studied depending on location of surgery (thoracic or abdominal and peripheral), but data will be collected for all subjects who did receive **POLYTHESE®** vascular prosthesis.
Study Design:	Multi-center retrospective case series
Study Type:	PMCF
Number of subjects:	Data from a minimum of 300 subjects will be evaluated. A minimum of 200 subjects will be evaluated for thoracic location of surgery.
Follow-up	At least 1-year follow-up after surgery until a maximum of 5 years.
Study Product:	Any **POLYTHESE®** vascular prosthesis of following ranges: - **POLYTHESE® IC** - **POLYTHESE® ICT** - **POLYTHESE® IC-3GL**
Intended use:	**POLYTHESE®** vascular prostheses are indicated for replacement or bypass of arteries presenting aneurysm or arterial disease. Their indication is restricted to thoracic, abdominal and peripheral surgery not involving the crossing of the knee flexion crease.
Objectives:	• Describing safety and performance of **POLYTHESE®** throughout its expected lifetime
Performance primary endpoint:	Primary patency rate at 1 year after surgery using **POLYTHESE®**
Safety Primary endpoints:	• Mortality rate at 30 days after surgery using **POLYTHESE®**
Performance secondary endpoints:	• Procedural success rate • Primary patency rate at 30 days and 6 months after surgery using POLYTHESE® • Primary assisted patency rate at 30 days, 6 months and 1 year after surgery using POLYTHESE® • Secondary patency rate at 30 days, 6 months and 1 year after surgery using POLYTHESE®

	• Device failure during procedure or at discharge, at 30 days, 6 months and 1 year after surgery using POLYTHESE®
Safety secondary endpoints	• Mortality rate during procedure or at discharge, at 6 months and 1 year after surgery using POLYTHESE® • Limb salvage rate at 30 days, 6 months and 1 year after surgery using POLYTHESE® • Adverse event during procedure or at discharge, at 30 days, 6 months and 1 year after surgery using POLYTHESE®
Exploratory endpoints	• After 1 year until the end of follow-up (5 years) using POLYTHESE®: o Primary patency o Primary assisted patency o Secondary patency o Device failure o Mortality o Limb salvage o Adverse events o Identify possible systematic misuse or off-label use of POLYTHESE®, with a view to verifying that the intended clinical purpose is correct.
Inclusion criteria	Subjects who did receive POLYTHESE® (IC, ICT, IC-3GL) at least one year ago for replacement or bypass of arteries presenting aneurysm or arterial disease
Exclusion criteria	Patients who have objected to the collect of their data
Duration of the data collect:	6 months from first site operational to collect data until data delivery
Data to be collected (as far as available)	• **Identification and demographic data** o Patient characteristics o Indication and location of surgery o Patients demographics and risk factors o Summary of previous cardiovascular interventions o Relevant medications o Diagnosis • **Operative data** o Date of procedure

	○ Identification data for the prosthesis ○ Information related to the surgical procedure ○ Relevant medication ○ Assessment of prosthesis function and mode of assessment if available ○ Device failure modes and documented adverse operative events • **Post-operative data (follow-up)** ○ Date of follow-up visits ○ Summary of vascular interventions, including minimally invasive procedures ○ Clinical evaluation ○ Relevant medications ○ Device failure modes and documented adverse events • **Any documented adverse events data (as far as available)** ○ Type of event, date of occurrence, severity, management, outcome ○ Any Documentation of probable causative factors (e.g. caused by the prosthesis, patient factors, technical factors)
Timepoints of collected data	- During procedure and at discharge (7-14 days) - 30-days after surgery ('peri-operative') - 6, 12 months - Annually up to 5 years post procedure

3. INTRODUCTION.

POLYTHESE® IC and ICT devices are CE-marked and were initially introduced in the international market in 1997, followed in 2003 and 2005 respectively by POLYTHESE® and POLYTHESE® devices. POLYTHESE® IC-3GL devices were then introduced in 2009.

Since January 2002, more than 60 000 single devices have been sold across various markets worldwide.

4. STUDY DEVICE

The studied device is POLYTHESE®, which consists in uniform straight or bifurcated tubular synthetic textile coated vascular grafts.

POLYTHESE® vascular prostheses are made by weaving of polyethylene terephthalate (PET – polyester) yarns and impregnated with collagen CXE® coating of bovine origin.

CXE® collagen impregnation of the POLYTHESE® vascular prostheses ensure water permeability of less than 10 ml/cm^2/min at a pressure of 120 mm of mercury (Hg) and allows direct implantation of the prosthesis without the need for pre-clotting.

4.1. Summary description of the device

The POLYTHESE® vascular prostheses are divided into 3 different ranges according to their configuration:

- POLYTHESE® IC

POLYTHESE® IC are straight tubes or bifurcated prostheses (*Figure **1***), with nominal diameters ranging from 6 to 28 mm, and usable length from 15cm to 100 cm.

- POLYTHESE® ICT

POLYTHESE® ICT are straight tubes with two equidistant longitudinal black guidelines over the entire length (*Figure **1***), with nominal diameters ranging from 30 to 38 mm, and usable length from 15cm to 60 cm.

- POLYTHESE® IC-3GL

POLYTHESE® IC-3GL are straight tubes with three equidistant longitudinal black guidelines over the entire length (*Figure **1***), with nominal diameters ranging from 20 to 38 mm, and usable length from 15cm to 60 cm.

A wide range of dimensions / references is available for each device listed in Appendix.

Straight POLYTHESE® IC/ICT | Bifurcated POLYTHESE® IC | POLYTHESE® IC-3GL

Figure 1: POLYTHESE® IC/ICT and POLYTHESE® IC-3GL vascular grafts

4.2. Intended purpose and patient population

4.2.1. Intended clinical purpose

POLYTHESE® IC, ICT and IC-3GL vascular prostheses ranges are indicated for replacement or bypass of arteries presenting aneurysm or arterial disease. Their indication is restricted to thoracic (POLYTHESE® ICT), abdominal and peripheral surgery not crossing the knee flexion crease.

POLYTHESE® IC-3GL prostheses are especially indicated in aortic root and ascending thoracic aorta surgery.

4.2.2. Patient population characteristics

Patient population conditions that may indicate abdominal, thoracic and/or peripheral vascular open surgical repair with implantation of a vascular graft include:

- Peripheral arterial diseases (PAD), characterized by reduced blood flow to the lower extremities, which may be categorized as:
  - Intermittent claudication (IC)
  - Chronic limb-threatening ischemia (CLTI)
  - Acute limb ischemia (ALI)
  - Chronic total occlusion (CTO)

- Arterial aneurysms, characterized by a permanent localized (i.e., focal) dilatation having at least a 50% increase in diameter, which may be categorized by location:
  - Thoracic aortic aneurysm (TAA)
    - Ascending thoracic aortic aneurysm
    - Aortic arch thoracic aortic aneurysm
    - Descending thoracic aortic aneurysm
    - Thoraco-abdominal aortic aneurysm
  - Thoracic aortic aneurysms
    - Ascending aorta
    - Descending thoracic aorta
  - Abdominal aortic aneurysms (AAA)
  - Peripheral arterial aneurysms
    - Ilia arterial aneurysms (IAA)
    - Femoral arterial aneurysms (FAA)
    - Popliteal arterial aneurysms (PAA)
- Arterial dissections are classified according to the location of the entry intimal tear and the extent of aorta involved in the dissection:
  - Stanford type A dissection
    - Type I Dissection (originates in the ascending aorta, extends through the aortic arch, and continues into the descending aorta and/or abdominal aorta).
    - Type II Dissection (originates in and is confined to the ascending aorta)

- Stanford type B dissection
  - Type IIIa Dissection (originates in the descending aorta and is limited to same)
  - Type IIIb Dissection (involves descending and variable extents of the abdominal aorta)
- Connective tissues abnormalities such as in Marfan Syndrome, Ehler-Danlos Syndrome, annulo-ecstasia disease, hereditary dysplasia, conjunctival elastic and media dystrophies

4.2.2.1. Peripheral arterial diseases (PAD)

Reported PAD risks factors are:

- History of cardiovascular disease
- Smoking
- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Obesity
- Age

Age is the strongest risk factor for PAD. The disease is rare in individuals younger than 40 years, rises in prevalence in the sixth to eighth decades, and may affect 25% or more of individuals 80 years and older.

4.2.2.2. Arterial aneurysms

Reported arterial aneurysms risks factors are:

- advanced age,
- gender,
- smoking,
- family history,
- obesity,
- hypertension,
- co-morbidities such as coronary heart disease, diabetes, atherosclerosis.

Although abdominal aortic aneurysms (AAAs) and ascending aortic aneurysms are more common, descending thoracic aortic aneurysms (TAAs) and thoracoabdominal aortic aneurysms (TAAAs) are not rare, with an estimated incidence of around 10 cases per 100,000 person-years.

TAAAs are primarily a disease of the elderly. The average age of patients with TAAAs is 65 years, with a male-female ratio of 1.7 : 1. TAAAs clearly have a genetic component, since more than 20% of patients will have a first-degree relative affected by aneurysm disease.

Aneurysms involving the aortic arch account for about 10% of the total cases of thoracic aorta aneurysms.

Prevalence of abdominal aortic aneurysms (AAA) 4 cm or larger is approximately 1% of men between the ages of 55 and 64 years and increases with advancing age by 2% to 4% by decade. Emergence of AAAs rises sharply in individuals aged ≥60 years old. It has also been consistently demonstrated that AAAs occur with greater frequency in men, smokers, and those with a family history of aortic aneurysm.

Data on prevalence of AAA varies between 1.3% and 12.5% in males, and between 0.0% and 5.2% in females. Overall prevalence varies from 4 to 8%.

Iliac artery aneurysms (IAAs) commonly occur concurrently with other more proximal arterial aneurysms. In contrast to generalized aorto-iliac aneurysms, isolated iliac aneurysms are prevalent in ≤ 2% of the general population.

Femoral artery true aneurysms are found predominantly in older men (70 years or older) and are associated with smoking and hypertension.

Popliteal artery aneurysms are rare in the general populations, although they are the most common peripheral artery aneurysms (70% of them). PAAs are exclusively found in men. A prevalence of around 1% in men has been reported in UK between 65 and 85 years.

4.2.2.3. Aortic dissections

Factors that predispose one to develop aortic dissection include:

- age,
- hypertension,
- structural abnormalities of the aortic wall

Incidence of acute aortic dissection ranges from 2 to 4 per 100,000 person-years. The incidence of type A dissection peaks between 50 and 60 years, while type B dissections occur more frequently between 60 and 70 years of age.

4.2.2.4. Connective tissue abnormalities including Marfan syndrome, Ehler-Danlos Syndrome, conjunctival elastic and media disorders

A connective tissue disease is a genetic disease in which the primary target is either collagen or elastin protein assembly, disruption of which leads to an inherent predisposition to degeneration, loss of structural integrity, and consequent aneurysm formation or spontaneous vascular dissection and rupture. These connective tissue abnormalities have severe vascular manifestations, and most commonly include Marfan syndrome (MFS), the vascular type of Ehlers-Danlos syndrome (EDS IV), Loeys-Dietz syndrome (LDS), and familial thoracic aortic aneurysm and dissection.

The vascular manifestations of Marfan syndrome invariably involve aortic root dilation, progressive root and ascending aortic aneurysmal degeneration, and potentially aortic dissection of variable extent. The incidence of Marfan syndrome (MFS) is about 2 to 3 per 10,000 individuals, with no gender predisposition. This genetic disorder is a dominant Mendelian trait in 75% of cases.

The prevalence of Ehler-Danlos Syndrom (EDS), with type III procollagen disorder, is currently estimated to be 1 in 50,000 to 90,000. Major complications in childhood are rare, even if 25% of the

subjects may present medical or surgical complications by the age of 20. By 40 years of age, major complications in the vascular or gastrointestinal systems or reproductive system (women) had developed in around 90 %.

4.3. Contra-indications

The use of any model of POLYTHESE® vascular prostheses is contra-indicated for:

- Coronary bypasses
- Patients with hypersensitivity to collagen

5. STUDY DESIGN

POLYTHESE® study is a retrospective, observational, multicentre, case series which examine short and long-term outcomes of using POLYTHESE®. This study will be done on Real World Data to describe the safety and performance of the device.

5.1. Summary of relevant Clinical data

Relevant clinical data on POLYTHESE® vascular prostheses consist in:

- 1 prospective randomized clinical trial (published data): Tofigh 2007 (52 patients)
- 1 prospective comparative non-randomized study (published data): Benetis 2014 (7 patients)
- 1 clinical non-comparative study (published data): Kaplan 2015 (12 patients)
- 1 multicenter retrospective study (unpublished data): Fabiani & Maiza 1996 (51 patients)
- 7 case reports (published data) – 15 patients:
    - Touati 2003 (n=6),
    - Colak 2012 (n=1),
    - Martens 2013 (n=1),
    - Baydar 2013 (n=1),
    - Yazici 2012 (n=1),
    - Alexoiu 2014 (n=1),
    - Kollias 2014 (n=4).

Prospective randomized clinical trial (published data)

A prospective randomized Clinical trial [Tofigh 2007] was performed to compare the outcome of the use of reversed saphenous vein and collagen impregnated woven polyester prosthesis. In a 3-year period, 103 above-knee femoropopliteal bypass graft operations were performed and followed in 85 patients (52 males, 33 female). The indication for operation was severe claudication in 74 cases, rest pain in 7 cases, and ulceration in 4 cases. For the bypass graft, a reversed saphenous vein was used in each of 51 cases, and a collagen impregnated woven polyester prosthesis was used in each of 52 cases. Preoperative risk factors were diabetes (24%), a history of myocardial infarction (23%), and current status with respect to smoking (74%). On a total of 85 patients, 103 operations were performed, 51 of

which used reversed vein and 52 of which used 6-mm **POLYTHESE® IC collagen prosthesis**. When collagen prosthesis was used, operating time was shorter than vein bypass graft (73±9.1 minutes vs. 105±8.8 minutes, p=0.002). Two cases with collagen prosthesis had superficial wound infection which did not require reoperation and result in graft loss. None of the patients who had collagen prosthesis were lost to follow-up. Primary patency rates of collagen prosthesis vs. vein bypass graft were 67% vs. 81% (p=0.065) at 2-year. After reintervention, the secondary patency rates of autogenous grafts vs collagen prosthesis were 81% vs. 77% (p=0.298) at 3-year. The difference between collagen prosthesis and bypass graft in terms of patency rates were not statistically significant due to short follow-up time and longer time is required to see a significant difference. Nevertheless, results suggest that collagen prosthesis can be safely used for femoropopliteal bypass grafting.

Prospective non-randomized single-centre study (published data)

A prospective non-randomized single-centre study [Benetis 2014] was performed to compare the outcome of stent and surgery in terms of treatment success. Of 316 patients who underwent angiography, 101 consecutive patients treated for TASC II type B, C, and D iliac lesions were divided into two groups: (i) 54 patients (stent group) who underwent iliac endovascular procedures and (ii) 47 patients (surgery group) who underwent direct aortoiliac bypass reconstructions. All patients were followed up to assess the early, 1-year and 2-year stent and graft patency. Patients who underwent direct aortoiliac bypass reconstruction underwent either bilateral (n=7) or unilateral bypass (n=40) reconstruction, and collagen coated **POLYTHESE® IC** prostheses were used for bilateral reconstructions. Overall, 1- and 2-year prosthetic graft patencies were 97.1±2.9% and 97.1±2.9%, respectively. No perioperative mortality was observed in either of the groups. In the surgery group, 2 patients were lost to myocardial infarction (MI), one after 14 months and the other after 19 months following the surgery. Assisted primary patency rates of the surgery group were higher than the stent group. Complication rate was 7.4% in the stent group whereas it was 6.3% in the surgery group, which included pneumonia, wound complications and inguinal lymphorrhoea. Neither graft infection nor early mortality were observed in the surgery group, although this was attributed to the small number of patients undergoing above-knee femoropopliteal bypass procedures (n=7). In conclusion, both stent and grafting were found to be safe procedures for patients with severe aortoiliac occlusive disease.

Clinical non-comparative study

Kaplan et al. (2015) conducted a clinical non-comparative study with the aim to report the outcomes of patients who underwent proximal thoracic aortic aneurysm surgery with open distal anastomosis technique but without cerebral perfusion, instead under deep hypothermic circulatory arrest. A total of 30 patients (21 male, 9 female) with an average age was 60.2 ± 11.7 years (range, 30-74 years), with ascending aorta aneurysm associated with aortic valvular disease, coronary artery disease, or mitral valve disease were included. During this study, 12 patients were implanted with **POLYTHESE®** for proximal thoracic aortic aneurysm repair (other types of grafts were implanted).

There was one hospital death (3.3%) due to chronic obstructive pulmonary disease at postoperative day 22. No neurological dysfunction was observed during the postoperative period. Revision was required in 3 patients due to bleeding (10%) and wound side revision was required in another 2 (6.6%). Four patients had postoperative atrial fibrillation (13.3%) and sinus rhythm was reestablished with medical treatment in all patients.

Multicenter retrospective study (unpublished data)

A multicenter retrospective study was conducted (unpublished data) with the aim to report clinical and ultrasound results on the use of the POLYTHESE® IC Prosthesis in the treatment of infra-renal aortic lesions. Between 1993 and 1994, 26 patients (22 men and 5 women) were operated at Pr. Fabiani's unit (Centre 01) and 25 patients (22 men and 3 women) were operated at Caen Hospital (Pr. Maiza's unit, Centre 02). A total of 51 patients with infra-aortic lesions were included in the study, with an average age of 71 years in Centre 01, and 66 years in Centre 02. Overall, 41 cases of aneurysms, mostly aorto-iliac and infra renal aortic aneurysms, were operated during the study, in addition to 15 cases of occlusion / stenosis of femoral, iliac artery and the aortic bifurcation. Among the implanted prostheses, 41% of POLYTHESE® Grafts were tubular graft, mostly 20mmØ (11 cases) and 18mmØ (5 cases), and 59% were bifurcated grafts, mostly 16mmØ (8 cases) and 18mmØ (8 cases). Of note, length of prostheses was not measured per-operatively.

Postoperative permeability and stability were controlled by Doppler Ultrasound almost one year after implantation. Analysis of the Echo-Doppler results concluded that the one-year patency rate was 99.7%. Permeability of the prostheses was satisfactory.

Regarding safety, no death cases were associated to the prosthesis. Nonetheless, one patient developed a perioperative acute pulmonary oedema on day 2 with shock associated with ischemic heart disease and deterioration of renal failure requiring dialysis. Immediate post-operative complications were a bleeding case from the suture site, a Scarpa haematoma evacuated on D+7 and a retroperitoneal haematoma evacuated on D+1, leaving the complication of a reversible left femoral nerve paresis. Late postoperative complications related to surgery were a 16mmØ false aneurysm in the left prosthesis-femoral anastomosis and a graft occlusion detected by Doppler 19 months after the procedure. No infectious complications were reported during the study. Some other postoperative complications were reported but concluded not to be associated with the prosthesis or the procedure.

Case reports (published data)

A total of 7 case reports, describing the use of POLYTHESE® vascular prostheses in a limited number of patients (from 1 to 6 patients) have been identified, recording a total of 15 patients.

These case reports describe the use of POLYTHESE® vascular prostheses in the following procedures:

- Prosthetic graft replacement of the ascending aorta or aortic arch following an aneurysm (Touati 2003, Yazici 2012, Baydar 2013, Martens 2013, Alexoiu 2014, Kollias 2014)
- Prosthetic graft replacement of a descending aortic aneurysm (Colak 2012)

Touati et al. (2003) described six cases of patients (median age of 57.6±11 years) who were candidates for a new strategy of normothermic perfusion for replacement of the aortic arch to avoid the complications of profound hypothermic circulatory arrest. A POLYTHESE® vascular prosthesis was used in all patients. No patient died and all woke without neurologic deficit. No transient or permanent neurologic deficit was observed.

Colak et al. (2012) presented a case of 56-year-old woman with a history of prosthetic graft replacement of the ascending aortic and total aortic arch, using the elephant trunk technique 12 years previously for acute aortic dissection. Patient was admitted for surgical treatment of a descending

aortic aneurysm (6.8 cm in diameter) with the previously placed prosthetic graft detected in the aneurysm. Complete occlusion of the elephant trunk portion of the graft was achieved by inflating a compliant aortic occlusion balloon. A new graft, 28-mm diameter POLYTHESE® was placed with a polypropylene running suture to the elephant trunk. The prosthesis was then wrapped with the aneurysmal wall. The postoperative course was uneventful. She was discharged home on the fourth postoperative day in good condition.

Yazici et al. (2012) presented a case of 66-year-old male who had an intimal flap in the ascending aorta with a diagnosis of type A aortic dissection. A hemiarch replacement was therefore performed with a 30 mm diameter POLYTHESE®. Early postoperative course was uneventful, but, an acute renal failure was developed in day 3 and treated medically. No other complications occurred. Patient was discharged in Day 16, and was well during the 15-months follow up.

Baydar et al. (2013) reported a case of a 41-year-old woman who had a left ventricular outflow tract pseudoaneurysm following aortic valve replacement, which was reconstructed with a 24 mm diameter POLYTHESE®. The patient's postoperative course was uneventful, and a control transthoracic echocardiography evaluation showed a good surgical repair. She was discharged on the sixth postoperative day. Currently, the patient is under follow-up without any problem (no further detail).

Martens et al. (2013) described a case report of a 32-year-old male who was initially diagnosed with a saccular aneurysm (maximal diameter of 69 mm) of the right common iliac artery and a partially thrombosed left common iliac artery aneurysm. Patient was treated with an aortobifurcated graft in an end-to-end confirguration to both internal and external iliac arteries, without complications. A diagnostic workup revealed a dilated aortic root of 49 mm at the level of the sinuses of Valsalva. A second procedure was conducted to replace the dilated aortic root with reimplantation of the aortic valve and the coronary buttons in a 28 mm diameter POLYTHESE®. The postoperative recovery was uneventful and the patient was discharged on postoperative day 7 with good outcome.

Alexoiu et al. (2014) reported a case of a 73 year-old male who had communication between aortic aneurysm and the origin of the left pulmonary artery (aorto-pulmonary fistula). Total aortic arch replacement was conducted with short elephant-trunk extension into the ascending aorta using a 24 mm diameter POLYTHESE®. The left subclavian artery was reimplanted into the ascending aorta using a Gelweave graft and the expected 8-mm fistula was obliterated through the inside aneurysmal sac using small Gore-tex patch. Postoperative CT scan control at 3 months confirmed satisfactory exclusion of the aortic aneurysm, closure of the fistula and decompression of the left pulmonary artery. This case report did not describe complication.

Kollias et al. (2014) presented cases report of 4 patients with atherosclerotic aortic arch and descending thoracic aorta (DTA) aneurysms where a hybrid repair surgery technique was performed. All patients were assessed to be at high risk for conventional open repair. This technique employs surgical debranching and revascularization of the aortic arch, and placement of endovascular stent-grafts within the ascending aorta, the aortic arch and the DTA. Surgical procedure used the proximal end of a bifurcated POLYTHESE® vascular graft which was stitched by an end-to-side technique the rest of the vasculature except the last anastomosis with the left carotid artery done by an end-to-end anastomosis. There were no strokes or spinal cord ischemic injuries, even in the cases with extensive DTA stent-grafting.

5.2. Rationale for PMCF study

Available evidence confirms acceptability of performance and side effects related to POLYTHESE®; however, intended claims on clinical safety and performance are not sufficiently supported with existing clinical evidence, especially for long term assessment and thoracic use. In order to keep POLYTHESE® in European market, a post-market clinical follow-up (PMCF) study is needed.

5.3. Subjects

The participating hospitals will screen all potential subjects and will select those who are appropriate for study inclusion, i.e. subjects implanted with POLYTHESE® for at least one year, or with complete data to death. As the study explores real world data, there is no exclusion criteria for subjects and all subjects with POLYTHESE® implanted for at least one year and have not objected to the collect of their data will be included in the study.

All data will be retrieved from medical charts for each patient from time of surgery (considered as index date) until a maximum of 5 years after surgery.

Data from a minimum of 300 from 3 to 8 different sites in France will be evaluated. A minimum of 200 subjects with thoracic location of surgery will be evaluated.

Not more than 50% of study total enrolled subjects shall pertain to one unique centre.

5.3.1. Inclusion criteria

Patients must meet the following inclusion criteria in order to be eligible for inclusion in the study:

- Patient has a minimum of 1-year post-operative follow-up data available, or complete data to death

5.3.2. Exclusion criteria

There are no exclusion criteria apart from patients who have objected to the collect of their data.

6. RISKS AND BENEFITS OF THE DEVICE

6.1. Anticipated clinical benefits

There is no clinical benefit expected from the study as the evaluated device is already commercially available and used in routine, and as there will be no extra procedure for subjects who have been already implanted and followed. The study will only analyse already collected data.

There is no anticipated additional clinical benefit expected from the use of POLYTHESE® devices rather than other commercially available similar devices with same indications for use.

Anticipated clinical benefits of the device are thus equivalent to anticipated clinical benefits of open surgical vascular repair of thoracic, abdominal and peripheral arteries.

Replacement or bypass of arteries presenting obliterative arterial disease is required to restore the function of the artery: restore the blood flow to distal tissues. Anticipated clinical benefits may consist in patient's symptoms relief, improved quality of life and reduced tissular ischemia, amputation and mortality risks.

Replacement or bypass of arteries presenting dissection and/or aneurysmal disease is required to exclude the false lumen entry tear(s) and/or aneurysmal part without compromising the blood flow to distal tissues. Anticipated clinical benefits may consist in reduced risks of dissection and/or aneurysm associated complications and reduced risk of aneurysm rupture and mortality.

6.2. Anticipated risks

There is no risk either associated to the study as there is no procedure performed in the scope of the study. The risks listed below are those related to revascularization surgery and use of grafts and will be the ones monitored

The type and rate of anticipated risks may differ according to indication and location of the surgical procedure, and may result in:

- Medically important event or reaction
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Re-intervention and re-hospitalization or prolongation of existing hospitalization
- Life-threatening event, reaction up to death.

Early (peri-operative) and late adverse events of abdominal aortic and peripheral arteries open vascular repair with POLYTHESE® devices include (but are not restricted to):

- Bleeding
- Hematoma
- Adherence to surrounding tissues
- Allergic reaction
- Inflammatory reaction / oedema
- Seroma / lymphorrea formation
- Wound complications: infection (superficial or deep), revision
- Graft infection
- Graft dilatation
- Pseudo aneurysm / false aneurysm (para-anastomotic aneurysm; non-anastomotic aneurysm)
- Graft stenosis / occlusion
- Limb occlusion
- Amputation (major or minor)
- Secondary aorto-enteric fistula
- Renal dysfunction
- Neurologic deficit
- Pericardial effusion

- Pulmonary complication (pneumonia, perioperative acute pulmonary oedema)
- Cardiac complications (myocardial infarction or arrhythmia, ischemic heart disease, atrial fibrillation)

7. OBJECTIVES AND ENDPOINTS

The principal objective of the POLYTHESE® study is to describe safety and performance of POLYTHESE®.

Identification and analysis of potential emergent risks will be performed according to the availability of the collected adverse events.

Identification of possible systematic misuse or off-label use of POLYTHESE®, with a view to verifying that the intended purpose is correct, will also be performed according to the availability of the data.

The following table summarizes the performance and safety endpoints and timeframe after surgery.

		Time period following surgery			
Study endpoints	**At surgery**	**30 days**	**6 months**	**1 year**	**>1 year until 5 years of follow-up**
Performance endpoints					
Primary patency rate*	---	X	X	**X***	X
Primary assisted patency rate	---	X	X	X	X
Secondary patency rate	---	X	X	X	X
Device Failure	X	X	X	X	X
Procedural success rate	X	---	---	---	---
Safety endpoints					
Mortality rate*	X	**X***	X	X	X
Limb salvage rate	---	X	X	X	X
Adverse events **	X	X	X	X	X

** Primary endpoint*

*** Listed in section 6.2*

7.1. Performance endpoints

Primary performance endpoints are **primary patency rate at 1 year** after surgery using POLYTHESE®.

The others effectiveness endpoints are:

- Procedural success rate, *defined as:*
    - *Ability to use with no need for replacement by another device and,*
    - *Effective vascular flow restoration after procedure and,*
    - *In case of aneurysm, exclusion of aneurysmal portion after procedure.*

- Primary patency rate, *defined as rate patency of the bypass graft without procedure or intervention of the conduit itself (except for occlusion)*
- Primary assisted patency rate, *defined as rate patency of the bypass graft with or without procedure or intervention of the conduit itself (except for occlusion) after device implantation*
- Secondary patency, *defined as rate patency of the bypass graft with or without procedure or intervention of the conduit itself for occlusion after device implantation*
- Device Failure, *defined as:*
    - *Uncontrolled blood leakage from device*
    - *Loss of structural integrity, e.g. rupture and/or exaggerated dilation (> 50 %)*
    - *Occlusion of the device*
    - *Total or partial replacement of the device required*

7.2. Safety endpoints

Primary safety endpoint is **mortality rates at 30 days** after surgery using POLYTHESE®.

- Others study safety endpoints are:
    - *Mortality rate, defined as freedom % from death*
    - *Limb salvage rate, defined as freedom % from target limb amputation*
    - *Adverse events, defined as any documented adverse events, including anticipated (as listed in section 6.2) and non-anticipated adverse events.*

8. STATISTICAL CONSIDERATIONS

8.1. Statistical design, method and analytical procedures

All patients participating in the study who met the eligibility criteria will be included in the study population.

A descriptive analysis with clinical characteristics of all patients included in the study will be performed at the index date.

Exploratory analyses will be conducted globally and stratified by sub-populations. Sub-populations will be defined according to the three main areas of surgery:

- Thoracic
    - Ascending aorta and/or aortic arch and/or descending thoracic aorta and/or thoraco-abdominal aorta
- Abdominal
    - Aorto-aortic and/or aorto-iliac and/or aorto-femoral repair
- Peripheral

- Peripheral artery repair and extra anatomic bypasses not crossing the knee flexion crease

Since no hypotheses will be tested, study objectives will be addressed using descriptive statistics only. Given the real-world nature of the data, the use of multiple imputation methods for missing data would introduce bias as missing data cannot be considered completely at random (MCAR) or at random (MAR). Variables will not be imputed, with the exception of dates in which the exact day is missing: the missing day will be replaced by the middle day of the month.

Continuous variables will be described with number of patients with valid / missing observations, mean and its 95% confidence interval (95%CI), standard deviation (SD), median, 25 and 75 percentiles (P25 and P75, respectively), minimum and maximum. For non-normally distributed continuous variables geometric mean and its 95%CI will be reported too.

For categorical variables counts and percentages per category will be presented. Missing observations (including invalid or outlier observations) will be tabulated as a separate category. The calculation of proportions will not include the missing/invalid category in the denominators.

P-values will be presented in the summary tables, in association with the descriptive statistics. In addition, 95% confidence intervals (95%CI) will be presented when considered convenient or relevant. Results will be graphically represented when appropriate to make interpretation easier.

The two-sided level of significance will be set at 0.05 for all the statistical tests performed.

Statistical calculations will be carried out by using R software. More details on the statistical analysis will be provided in the Statistical Analysis Plan.

8.1. Sample size justification

Data from a minimum of 300 subjects will be evaluated. A minimum of 200 subjects will be evaluated for thoracic location of surgery. The number of patients has been chosen in accordance with the realistic number of operated patients in the involved hospitals.

9. DATA MANAGEMENT

9.1. Data sources

Real World Data sources used to generate Real World Evidence are:

- Data derived from Electronic health Record
- Medical claims and/or billing data
- Product and/or disease registry data

9.2. Data to collect

As mentioned previously considering study is retrospective and considering that every site can have different ways to follow their patients after surgery, data will be collected as much as possible in order to determine the clinical safety and performance.

The following data will be collected, when available according to participating site available data.

- **Identification and demographic data**
    - Patient identification
    - Indication and location of the treatment
    - Location of the surgery
    - Patients demographics
        - Year of birth
        - Sex
        - Mass
    - Identification of implanting physician
    - Name of the institution
- **Pre-operative data**
    - Risks factors, such as hypertension, diabetes, coronary artery disease, hyperlipidaemia, tobacco use, obesity, anaesthesia risk and any cardiovascular risk factor.
    - Summary of previous vascular interventions at the same or other relevant vascular sites, including non-surgical interventions and previously implanted vascular devices (e.g. stents, endovascular prostheses, surgically placed vascular grafts)
    - Relevant medications
    - Diagnostic criteria
        - Clinical assessment (e.g. non-invasive hemodynamic assessment);
        - Objective assessment (e.g. C.T. scanning, magnetic resonance imaging, ultrasonography, arteriography, duplex Doppler)
- **Operative data**
    - Date of procedure
    - Identification data for the vascular prosthesis including configuration (e.g. straight uniform or bifurcated) and diameter
    - Information regarding the procedure:
        - Identity of native vessel treated

        - Details of anastomoses (e.g. type (end-to-end), location
        - Length of prosthesis implanted (if available)
        - Adjunctive vascular procedures
    - Relevant medication (e.g. heparin, other anticoagulants)
    - Assessment of prosthesis function and mode of assessment if available (e.g. intraoperative angiography, intraoperative Doppler)
    - Failure modes and adverse operative events
- **Post-operative data**
    - Interval of follow-up (e.g. discharge or 7 d to 14 d after surgery, 30 days, 6 and 12 months after surgery, up to 5 years for exploratory time points)
    - Date of follow-up visits
    - Summary of vascular interventions, including minimally invasive procedures
    - Clinical evaluation:
        - Clinical assessment (e.g. non-invasive hemodynamic assessment)
        - Objective assessment of prosthesis (e.g. C.T. scanning, magnetic resonance imaging, ultrasonography, arteriography, duplex Doppler)
    - Relevant medications (e.g. anticoagulants or antiplatelets)
    - Any documented adverse events including the events listed in section 6.2 anticipated risks and any events that lead to the patient's death

- **Any documented adverse events data**

  As far as available the following data will be collected per adverse event:
    - Type of event, date of occurrence, severity, management (e.g. none, medical treatment, endovascular procedure, open surgery), outcome (e.g. continuing, resolved, unknown, death)
    - Any Documentation of prosthesis involvement
    - Any Documentation of probable causative factors (e.g. caused by the prosthesis, patient factors, technical factors)
    - Explant data:
        - Date
        - Whether the subject is living or deceased
        - Reason for explant, if applicable

- Relevant observations (e.g. device integrity, device positioning, tissue incorporation, vascular tissue erosion), if available

A separate document with all available data to collect will be produced in a second time to add further details depending on the level of details available.

9.3. Data consistency

Data consistency will be verified for each variable. Harmonization of units (conversion), categorical variables consistency and ranges of numerical variables will be also verified. This step will be proceeded before database freezing and analyses. If inconsistencies are noticed, monitoring and checks will be asked from the sites.

9.4. Missing data

Some endpoints can be missing for some subjects. Endpoints proportions will be calculated on the number of non-missing observations. No imputation method is planned.

9.5. Database structuration

After data consistency step, databases will be compiled to one database frozen for analyses. Variables might be created for the analyses.

10. ADVERSE EVENTS DEFINITIONS

An Adverse Event (AE) is 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 studied medical device.

11. SAFETY REPORTING PROCEDURES

Considering the nature of this PMCF study (retrospective study), only Vigilance reporting applies. Any event that meets the vigilance criteria as per MEDDEV 2.12-1 and that would not have already been reported to the Authorities will be reported in accordance to manufacturer and hospital/manufacturer standard procedures.

12. REGULATORY CONSIDERATIONS

This PMCF study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and any regional or national regulations applicable in France.

This PMCF study will be conducted in compliance with GDPR and by following the Methodology of Reference MR-004 developed by CNIL (French Data Protection Agency).

The principals set forth in the ISO14155:2011 will be followed as far as possible considering the nature of this PMCF study (retrospective collect of data).

13. INFORMED CONSENT PROCESS

An information letter explaining the purpose of this PMCF study will be sent to patients who meet the inclusion criteria. In accordance with the MR-004, the collection of data of patients who have not objected this collect will be initiated.

The completion of this process will be recorded in study documentation.

14. MONITORING OF THE STUDY

The conduct of this retrospective study will be monitored by the sponsor to ensure that it is conducted, recorded and reported in accordance with this protocol and the applicable regulatory requirements. A centralized visit (phone call) will be performed at the start of the study, during the study to oversee its progress and at the end of the study.

15. CONFIDENTIALITY OF THE STUDY

Subjects will be identified by a study number and subject identification code. Subject ID log will be maintained in a secure storage facility and archived for at least 2 years after study completion or for a longer period as required by the local regulations. Study records will not be destroyed without authorisation from the Sponsor.

16. PUBLICATION POLICY

16.1. Multicentre Publication

The sponsor may invite the participating hospitals to take part to a multicenter publication of the study results, in which case it will be ensured that the documents submitted for publication comply with the publisher's requirements for authors and contributors. Also, the sponsor will select a publisher based on mutual agreement with the participating hospitals, who are invited to participate in the publication.

16.2. Publication

The participating hospitals may publish his/her own data subject to the following restrictions:

- the multicenter manuscript must be published prior to each participating hospital publishing their own data;
- the manuscript shall be submitted to the Sponsor for review prior to submitting the manuscript for publication;
- the manuscript must reference the study multicenter manuscript.

17. CLINICAL STUDY REPORT

The Sponsor will prepare a Clinical Study Report that will comprehensively describe study findings. Before finalization, a draft will be circulated to the participating hospital physician for review and endorsement.

18. BIBLIOGRAPHY

1. Tofigh, A. Mohammadi; Warnier De Wailly, G.; Rhissassi, B. (2007) Comparing vein with collagen impregnated woven polyester prosthesis in above-knee femoropopliteal bypass grafting. In : International journal of surgery (London, England), vol. 5, n° 2, p. 109–113. DOI: 10.1016/j.ijsu.2006.07.003.
2. Alexoiu, Valerica Lenuta; Ou, Phalla; Messika-Zeitoun, David; Jacob, Brice Lortat; Kirsch, Matthias (2014) Post-Traumatic Aortic Arch Aneurysm Complicated by Aorto-Pulmonary Fistula. In : Aorta (Stamford, Conn.), vol. 2, n° 6, p. 293–295. DOI: 10.12945/j.aorta.2014.14-035.
3. Baydar, Onur; Coşkun, Ugur; Balaban, Betul; Cetin, Gurkan; Firatli, Inci; Ersanli, Murat Kazim; Kucukoglu, Mehmet Serdar (2013) Cardiac tamponade due to left ventricular pseudoaneurysm after aortic valve replacement. In : The heart surgery forum, vol. 16, n° 1, E49-51. DOI: 10.1532/HSF98.20121083.
4. Benetis, Rimantas; Kavaliauskiene, Zana; Antusevas, Aleksandras; Kaupas, Rytis Stasys; Inciura, Donatas; Kinduris, Sarunas (2016) Comparison of results of endovascular stenting and bypass grafting for TransAtlantic Inter-Society (TASC II) type B, C and D iliac occlusive disease. In : Archives of medical science : AMS, vol. 12, n° 2, p. 353–359. DOI: 10.5114/aoms.2016.59261.
5. Colak, Necmettin; Nazli, Yunus; Kirbas, Ismail; Cakir, Omer (2012) Transbrachial endoclamping of the graft for descending aortic aneurysm after the elephant trunk procedure. In : The Annals of thoracic surgery, vol. 93, n° 3, p. 1004–1006. DOI: 10.1016/j.athoracsur.2011.10.071.

6. Kaplan, Mehmet; Temur, Bahar; Can, Tolga; Abay, Gunseli; Olsun, Adlan; Aydogan, Hakki (2015) Open distal anastomosis technique for ascending aortic aneurysm repair without cerebral perfusion. In : The heart surgery forum, vol. 18, n° 4, E124-8. DOI: 10.1532/hsf.1284.
7. Kollias VD (2014) Single-stage, off-pump hybrid repair of extensive aneurysms of the aortic arch and the descending thoracic aorta. In : Hellenic J Cardiol., 55(5):355-60.
8. Martens, Thomas; van Herzeele, Isabelle; Ryck, Frederic de; Renard, Marjolijn; Paepe, Anne de; François, Katrien et al. (2013) Multiple aneurysms in a patient with aneurysms-osteoarthritis syndrome. In : The Annals of thoracic surgery, vol. 95, n° 1, p. 332–335. DOI: 10.1016/j.athoracsur.2012.05.085.
9. Touati, Gilles D.; Roux, Nicolas; Carmi, Doron; Degandt, Alexandra; Benamar, Amar; Marticho, Paul et al. (2003) Totally normothermic aortic arch replacement without circulatory arrest. In : The Annals of thoracic surgery, vol. 76, n° 6, p. 2115–2117. DOI: 10.1016/S0003-4975(03)00739-2.
10. Yazici, Pinar; Oz, Kursad; Celik, Omer; Erek, Ersin (2012) Extensive anterior chest wall ecchymosis as a sign of subacute type A aortic dissection. In : Interactive cardiovascular and thoracic surgery, vol. 15, n° 4, p. 797–799. DOI: 10.1093/icvts/ivs204.

19. APPENDIX

Table 1: POLYTHESE® IC CE-marked straight tube reference

Reference	Diameter (mm)	Length (cm)	MD Class
1201 0600	6	60	III
1201 0601	6	100	
1201 0602	6	15	
1201 0603	6	70	
1201 0700	7	60	
1201 0701	7	100	
1201 0702	7	15	
1201 0703	7	70	
1201 0800	8	60	
1201 0801	8	100	
1201 0802	8	15	
1201 0803	8	70	
1201 1000	10	60	
1201 1001	10	100	
1201 1002	10	15	
1201 1003	10	70	
1201 1200	12	60	
1201 1202	12	15	
1201 1203	12	70	
1201 1400	14	40	
1201 1401	14	60	
1201 1402	14	15	
1201 1600	16	40	
1201 1601	16	60	
1201 1602	16	15	
1201 1800	18	40	
1201 1801	18	60	
1201 1802	18	15	
1201 2000	20	40	
1201 2001	20	60	
1201 2002	20	15	
1201 2200	22	40	
1201 2201	22	60	
1201 2202	22	15	
1201 2400	24	40	
1201 2401	24	60	
1201 2402	24	15	
1201 2600	26	40	
1201 2601	26	60	
1201 2602	26	15	
1201 2608	26	8	
1201 2800	28	40	
1201 2801	28	60	
1201 2802	28	15	
1201 2808	28	8	

Table 2: POLYTHESE® IC CE-marked bifurcated references

Reference	Diameter (mm)	Length (cm)	MD Class
1202 1206	12 x 6	45	III
1202 1407	14 x 7	45	
1202 1608	16 x 8	45	
1202 1809	18 x 9	45	
1202 2010	20 x 10	45	

1202 2211	22 x 11	45	
1202 2412	24 x 12	45	

Table 3: POLYTHESE® ICT CE-marked straight bifurcated references

Reference	Diameter (mm)	Length (cm)	MD Class
1301 3000	30	30	III
1301 3001	30	60	
1301 3002	30	15	
1301 3008	30	8	
1301 3200	32	30	
1301 3201	32	60	
1301 3202	32	15	
1301 3400	34	30	
1301 3401	34	60	
1301 3402	34	15	
1301 3600	36	30	
1301 3601	36	60	
1301 3602	36	15	
1301 3800	38	30	
1301 3801	38	60	
1301 3802	38	15	

Table 4: *POLYTHESE® IC-3GL CE-marked references*

Reference	Diameter (mm)	Length (cm)	MD Class
PT3GL020015	20	15	III
PT3GL020030	20	30	
PT3GL020060	20	60	
PT3GL022015	22	15	
PT3GL022030	22	30	
PT3GL022060	22	60	
PT3GL024015	24	15	
PT3GL024030	24	30	
PT3GL024060	24	60	
PT3GL026015	26	15	
PT3GL026030	26	30	
PT3GL026060	26	60	
PT3GL028015	28	15	
PT3GL028030	28	30	
PT3GL028060	28	60	
PT3GL030015	30	15	
PT3GL030030	30	30	
PT3GL030060	30	60	
PT3GL032015	32	15	
PT3GL032030	32	30	
PT3GL032060	32	60	
PT3GL034015	34	15	
PT3GL034030	34	30	
PT3GL034060	34	60	
PT3GL036015	36	15	
PT3GL036030	36	30	
PT3GL036060	36	60	
PT3GL038015	38	15	
PT3GL038030	38	30	
PT3GL038060	38	60	