CLINICAL EVALUATION REPORT

WIRION™ EMBOLIC PROTECTION SYSTEM

Document ID: TF015 Gardia Clinical Evaluation Rev 5.0, 15 June 2015

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HISTORY OF CHANGES			
REV	DESCRIPTION OF CHANGES	BY	DATE
1	Initial version	s22 [redacted]	15 Sep 2008
2	– Revised template according to MEDDEV2.7.1 Dec. 2009 requirements. – Updated Clinical Experience with the WIRION™ system. – Review and summary of relevant literature issued between *Jan 1st 2010 to July 25th 2012.*	s22 [redacted]	16 Aug 2012
3	– Added section 8.1.3: Summary of Comparison to conclude an outlined summary of the difference between the WIRION and comparable EPD systems. – Revised section 12: Conclusions	s22 [redacted]	04 Nov 2012
4	– Manufacturer address change – Added: Pivotal study interim results for Carotid Indication – PAD Clinical Study – Clinical Review: Peripheral Arterial Disease (PAD) – Updated relevant literature about EPDs	s22 [redacted]	19 June 2014
5	– Added: WIRION 510(k) submission (K143570) and FDA clearance – Updating WISE study results – Updating PAD Clinical Study plan – Updating relevant literature about EPDs – Added: SVG retrospective clinical trial – Updated market experience – Added: Clinical experience with atherectomy devices in lower extremity procedures – Updating journals impact factors	s22 [redacted]	15 June 2015

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1. Terms & Abbreviations

AE	Adverse Event
CAS	Carotid Artery Stenting
CE	Conformité Européenne
CEA	Carotid Endarterectomy
DPD	Distal Protection Device
EPD	Embolic Protection Device
HDL	High Density Lipoproteins
FDA	Food and Drug Administration
IFU	Instructions for Use
ISO	International Organization for Standardization
LE	Lower Extremities
MACE	Major Adverse Cardiac Event
MAE	Major Adverse Event
MDD	Medical Device Directive
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PAD	Peripheral Artery Disease
PCI	Percutaneous Clinical Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
QM	Quality Management
RAS	Renal artery stenosis
SOC	Standard of Care
SVG	Saphenous Vein Graft
TAVI	Transcatheter Aortic-Valve Implantation
TVG	Target Vessel Revascularization

2. General

2.1 Device Information

This updated clinical evaluation report pertains to the WIRION™ embolic protection device (EPD) System formerly named: SCORPIO, GARDEX and Gardia Medical EPD.

2.2 Manufacturer

Gardia Medical Ltd.
2 Ha'Eshel Street, South Industrial Park
Caesarea 3088900
Israel

2.3 Purpose

This document was issued to update the clinical evaluation for the WIRION™ Embolic Protection System. It contains clinical data obtained from clinical investigations with the WIRION and published/unpublished literature of the WIRION and equivalent devices between July 26th 2012 and Mar 25th 2014.

3. Description of the Technology

Embolic Protection Devices (EPDs) were developed in order to capture plaque material that may be dislodged during cardiovascular intervention. There are three main types of EPDs: (i) Filter (ii) Balloon Occlusion and (iii) Flow Reversal. [Note: applicable information for CAS procedures].

i. Filter EPDs: Filter EPDs are pre-mounted on a 0.014'' guide-wire platform and consist of a frame and membrane. The filters are delivered using a delivery system and deployed distal to the target lesion. When the filter EPDs are deployed, blood flows through the filter pores, and the filter membrane traps embolic debris. These devices do not interrupt blood flow and thus, angiography can be performed. The filter is removed at the conclusion of the procedure, along with the collected debris.

ii. Balloon Occlusion: Balloon occlusion techniques involve inflation of a balloon and interruption of flow distal to the stenosis for the duration of the stenting procedure. Aspiration is done prior to balloon deflation to remove embolic material. This type of EPD includes both distal and proximal occlusion balloons.

   The key disadvantages of balloon occlusion EPDs include the ischemic time that occurs during balloon inflation and poor visualization of the lesion during the procedure.

iii. Flow Reversal: The flow-reversal technique in CAS procedures involves placement of balloon in the ECA and CCA to interrupt flow in these vessels and cause retrograde flow in the ICA to prevent embolization into the intracranial circulation.

This document is an updated revision of report TF015 (2008), and thereby it will refer only to filter type embolic protection devices equivalent to the WIRION™ system. This report focuses mainly on the carotid application, as during this upcoming year carotid indication will be the company's primary focus.

4. Device Description

The WIRION™ system is a simple single use, single operator, rapid exchange distal Embolic Protection System.

The WIRION™ System is intended to be used as a system for embolic protection to contain and remove embolic material (thrombus/debris) during cardiovascular interventions.

WIRION™ is manufactured by Gardia Medical Ltd. (Caesarea, ISRAEL), and meets the provisions of the Council Directive 93/42/EEC and its 2007/47/EC amendment concerning medical devices. WIRION™ is a class III device under Annex IX, rule 8 and has a CE mark approval.

The WIRION™ System (catalog number P2-9-0705-S) consists of the WIRION™ Delivery Catheter and the corresponding WIRION™ Retrieval Catheter.

The **Delivery Catheter** contains and delivers a Filter Unit, delivers it to its working position, locks it onto the guide wire using the Activating Handle and deploys it in the target vessel (see Figure 1). The Delivery Catheter is compatible with standard work flow, and with any commercially available 0.014" guide wires.

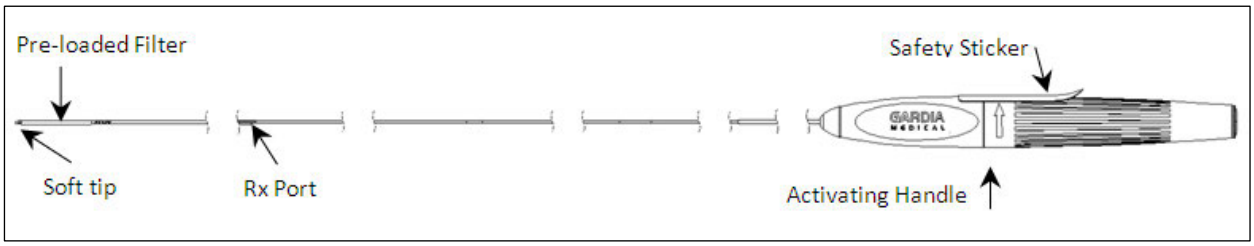


Figure 1: **WIRION Delivery Catheter**

The **Filter Unit** is responsible for the filtration of the blood. It comprises of a filter membrane and a filter frame. There are 3 marker bands on the frame for optimal visibility under fluoroscopy. A 5cc syringe with a soft needle is supplied for flushing the system prior to use.

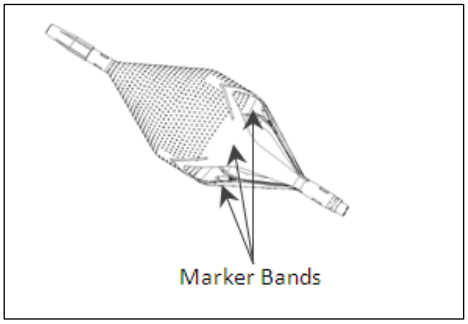


Figure 2: **WIRION - Filter Unit**

Activating Handle: User interface used by the physician to activate the lock of the Filter Unit onto the guide wire in the desired location within the artery (Figure 1).

The **Retrieval Catheter**: Retrieves the Filter Unit with the captured emboli and debris after the therapeutic procedure (Stent, PTCA) is completed (Figure 3).

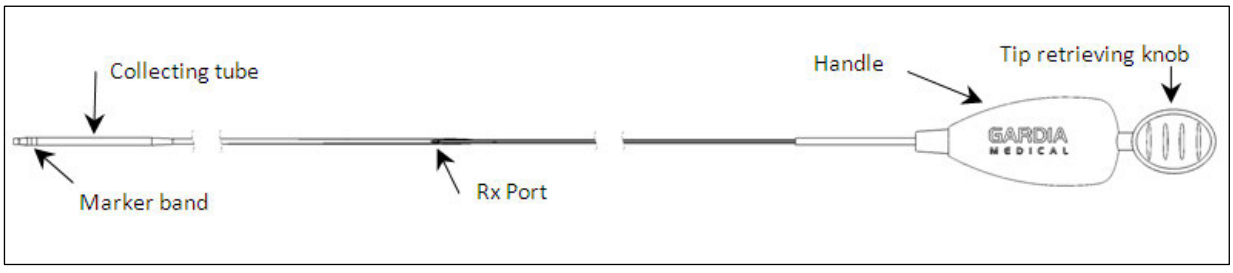


Figure 3: **WIRION Retrieval Catheter**

The WIRION system characteristics are given below (Table 1);

Target Blood Vessel Diameter	Filter Unit Length	Catheter Length
3.5-6.0 mm	22.5 mm	145 cm

Table 1: **WIRION System Characteristics**

The technique of advancing the WIRION Delivery Catheter is identical to a standard PTCA balloon or stent device and is performed as follows:

The WIRION delivery catheter is advanced over the guide wire in the target vessel under fluoroscopic imaging distal to the lesion. Placement should be done according to the landing zone recommendations given in the WIRION IFU.

Once the Delivery Catheter is placed in the required position, the Filter Unit can be locked on the guide wire by rotating the Activating Handle until a red marker becomes visible at the handle proximal end. Withdrawal of the Delivery Catheter will allow the filter to deploy.

During the intervention the guide wire is used according to normal workflow to track catheters and stent delivery systems to the target treatment site. After all interventional devices are removed, ensuring that the guide wire position is maintained, the WIRION Filter Unit is retrieved using the WIRION Retrieval Catheter.

4.1 Description of the Medical Method

The WIRION™ System is indicated for use as an embolic protection system to contain and remove embolic material during Cardiovascular interventions [3].

WIRION™ is deployed distal to the target lesion to capture plaque material (emboli) that may be dislodged during the procedure.

- Once the desired guide-wire is placed in the target vessel the delivery catheter is inserted onto the guide-wire.
- The catheter is than advanced on the guide wire (similar to PTCA balloon or stent device) until the later exits the Rx port about 38cm proximal to the catheter tip.
- Under fluoroscopic imaging, the Delivery Catheter is advanced to the target vessel and the Filter Unit is placed distal to the lesion. The filter unit and the marker bands are visible under fluoroscopic imaging.
- Once the Delivery Catheter crosses the lesion and is placed in the required position, a wire torque tool is slide along the guide wire and secures it against the hemostasis valve.
- The filter unit is now locked onto the guide wire by rotating the delivery catheter clockwise until a red indicator pops-up at the handle's proximal end.
- The filter unit is deployed by retrieving the delivery catheter while simultaneously holding the wire torque against the hemostasis valve.
- The guide wire is used according to normal practice to track catheters and stent delivery devices to the target site. The position of the filter should be carefully maintained, particularly during device exchange.
- Once the stent is placed at the target site and the procedure is finalized the filter unit is retrieved back by using the WIRION retrieval catheter.
- The retrieval catheter is flushed with saline and advanced over the guide wire while maintaining the guide wire position distal to the lesion. The retrieval catheter should pass the deployed stent until its tip reaches the filter unit.

- The retrieval catheter handle (retrieving knob) is rotated clockwise 90º and pulled back, until it reaches its final position. The distal tip slides backwards as its marker band passes the collecting tube marker in the proximal direction. The catheter is now ready for retrieval.
- A wire torque is slide along the guide wire and secures it against the hemostasis valve.
- The Filter Unit is retrieved slowly into the Retrieval Catheter collecting tube. The Filter Unit and Retrieval Catheter tip will be visible under fluoroscopic imaging.
- The Retrieval Catheter is carefully retracted through the guide catheter or sheath up to the hemostasis valve.
- The Retrieval Catheter is removed from the patient, ensuring that the hemostasis valve is sufficiently open prior to removal.

5. The WIRION™ System - Clinical Experience

CI-001: Safety and Performance Evaluation of SCORPIO™ Embolic Protection Device in patients undergoing Carotid Artery Stenting

(*December 2008 - September 2010*)

s22 [redacted]

Objectives: To assess the safety and performance of the Gardex EPD (Gardia Medical Ltd., Caesarea, Israel), during carotid artery stenting (CAS).

Methods: A total of thirty eight (38) patients underwent CAS with the Gardex EPD between December 2008 and September 2010, in two medical centers. The first 20 patients were treated as part of a first-in-man study and 18 patients were treated when CE-Mark was already approved. All patients were prospectively followed up for 30 days. Device performance and procedural details were collected and analyzed prospectively.

Results: All enrolled patients were successfully treated. There were one (2.6 %) minor periprocedural stroke and two (5.3 %) periprocedural TIAs that resolved within 24 hours. No additional complications were noted during the 30 days FU period. In this limited cohort, the 30 day stroke rate was therefore 2.6 % (one minor stroke, no major stroke). No deaths occurred until the 30 day follow-up.

Conclusions: In this first experience, CAS under cerebral protection with the Gardex EPD was safe and feasible. Our data suggests that the use of the Gardex EPD is simple, and shows high success rates even in challenging anatomies. No difficulties were observed in placing and retrieving the filter. The ability to cross the lesion over the guide wire of choice and then deploy the filter in any desired location across the wire creates a unique, natural and appealing advantage for all indications. Clinical outcomes appear to be favorable. The role of this new device in CAS needs to be further confirmed in a larger patient's population.

CI-003: Safety and Performance Evaluation of GARDEX™ Embolic Protection Device When Used During Saphenous Vein Graft (SVG) Interventions

(*January 2010 - November 2010*)

s22 [redacted]

Objectives: To demonstrate the safety and performance of the Gardex EPD when used during Percutaneous Coronary Interventions (PCI) of Saphenous Vein Graft (SVG) in a prospective, multi-center, non-randomized, open label single arm study.

Methods: A total of six (6) patients (of twenty (20), patients as approved by the ethic committee) underwent SVG intervention with the Gardex EPD between January 2010 and November 2010, in two medical centers. All patients were prospectively followed up for 30 days. Device performance and procedural details were collected and analyzed prospectively. The primary endpoint was a composite of major adverse cardiac events (MACE) at 30 days post procedure. Secondary endpoints included: device success, angiographic success, procedural success, TIMI flow grade and angiographically visualization of filling defect or thrombus occluding distally to the target vessel.

CL-002: Safety and Performance Evaluation of WIRION™ EPD in Patients Undergoing Carotid Artery Stenting

(*February 2013- April 2015*)

Pivotal study designed toward FDA approval.

s22 [redacted].

Objectives: The primary objective of the WISE study was to compare the safety and performance of WIRION™ in patients undergoing carotid artery stenting to a performance goal (PG) based on an analysis of the results of previous studies of five FDA-cleared distal embolic protection devices.

The study was performed on 120 high surgical risk patients candidate for catheter based therapy of a single stenosis located in the internal carotid artery or the carotid bifurcation, suitable for treatment with a single FDA cleared carotid stent. In the clinical study the WIRION™ system was used with the following FDA approved stents: ACCULINK™ (Abbott Vascular), PRECISE® Nitinol Self-Expanding Stent (Cordis Corporation), Wallstent® (Boston Scientific) and Xact® stent (Abbott Vascular).

Methods: Gardia Medical had completed the WISE pivotal clinical trial titled "Safety and performance Evaluation of WIRION™ EPD in patients undergoing carotid artery stenting" targeted towards obtaining FDA clearance for the WIRION™ system in carotid stenting procedure.

The study was prospective, multi-center, non-randomized, open label, single arm study, comparing the safety and performance of WIRION™ in patients undergoing carotid artery stenting to a performance goal based on an analysis of the results of previous US IDE carotid stent with embolic protection studies.

Subjects who met all the study's eligibility criteria and gave written informed consent were enrolled in the study. The study included a baseline visit, a treatment visit, first pre-discharge follow up (0-4 hours post procedure), second pre discharge visit (12-24 hours post procedure) and end of follow up visit (30±7 days post procedure). Adverse events were collected from intervention throughout the study follow-up period.

The primary safety endpoint was a composite of Major Adverse Cardiac and Cerebrovascular Events (MACCE), as determined by an independent Data Safety Monitoring Board (DSMB), including Death, Stroke and Myocardial Infarction (MI) occurring within 30±7 days post-procedure.

Results:

PATIENT DEMOGRAPHICS BASELINE AND INTERVENTION CHARACTERISTICS

One hundred and twenty (120) patients were included in the study. Mean age was 74.9±8.0 and 72.5% of the patients were males. 88.3% of the patients were asymptomatic. Tables 1 and 2 summarize the patients' demographics and baseline characteristics and intervention procedure characteristics respectively.

Comparing the demographic and baseline clinical characteristics of the study population to the US population undergoing carotid stenting procedures shows that the characteristics are highly similar. For example, the mean age in recent US carotid stenting studies ranges from 70.3 to 73.6 (with average of 72.0), which is similar to the mean age in the WISE study which is 74.9.

The baseline clinical characteristics are also similar. The most common comorbidities of those patients are hypertension, diabetes and heart failure. The mean percentage of hypertension patients in the US recent carotid stenting studies is 88.0% and that of the WISE study is 88.3%. The mean percentage of diabetes patients in recent US carotid stenting studies is 34.0% and that of the WISE study is 34.2%. The mean percentage of heart failure patients in recent carotid stenting studies is 19.1% and that of the WISE study is 18.3%. Therefore, it can be seen that the clinical characteristics in the WISE population are very similar to those of the US carotid stenting studies in which an EPD was used. Based on the similarities, it can be concluded that the results of the WISE study are applicable to the US population.

Table 1: Patients demographics and baseline characteristics

Patient Characteristic	ITT Population (n=120)
Age (years):	74.9 ± 8.0 (120)
Male:	72.5% (87/120)
BMI:	26.5 ± 3.9 (119)
History of Smoking:	47.5% (57/120)
Current Smoker	16.7% (20/120)
Ex-Smoker	30.8% (37/120)
Diabetes Mellitus	34.2% (41/120)
Hyperlipidemia	79.2% (95/120)
Hypertension	88.3% (106/120)
History of Peripheral Vessel Disease	36.7% (44/120)
History of TIA (within the past 6 months)	5.0% (6/120)
History of Stroke	10.8% (13/120)
Hemorrhagic	7.7% (1/13)
Ischemic	92.3% (12/13)
History of Congestive Heart Failure	18.3% (22/120)
History of Coronary Artery Disease	43.3% (52/120)
Previous CABG	8.3% (10/120)
Previous MI	14.2% (17/120)
Previous PCI	27.5% (33/120)
History of Cardiac Catheterization	12.5% (15/120)
Angina Pectoris	4.2% (5/120)
Acute Coronary Syndrome	4.2% (5/120)
Recent STEMI	0.0% (0/5)
Non-STEMI	40 0% (2/5)
Unstable Angina	60 0% (3/5)
History of Valve Disease	8.3% (10/120)
Recent or Recurrent Arrhythmia	12.5% (15/120)

Table 2: Patient intervention characteristics

Patient Characteristic	ITT Population (n=120)
Intervention Duration (minutes)	55.9 ± 25.9 (120)
Aortic Arch Abnormalities	7.5% (9/120)
Target Lesion Location	
Right	46.7% (56/120)
Left	53.3% (64/120)
Lesion Site	
ICA	83.3% (100/120)
Bifurcation	15.0% (18/120)
Other	1.7% (2/120)
Lesion Type	
De-Novo	87.5% (105/120)
Re-stenosis	12.5% (15/120)
Lesion Length (mm)	17.5 ± 15.3 (120)
Reference Diameter (mm)	5 31 ± 1.17 (118)
Involvement of the CCA	18.3% (22/120)
Proximal	13.6% (3/22)
Distal	86.4% (19/22)
Percent Diameter Stenosis of CCA (%)	50.7 ± 29.7 (22)
Percent Diameter Stenosis (NASCET) %	84.2 ± 7.8 (120)
Lesion Morphology	
Non calcified	21.7% (26/120)
Mild calcification	45.8% (55/120)
Moderate calcification	25.8% (31/120)
Severe calcification	6.7% (8/120)
Ulcerated Lesion	19.2% (23/120)
Visual Thrombus	0.0% (0/120)
Contralateral Disease	36.7% (44/120)

Previous Carotid Procedures	25.8% (31/120)
Baseline Carotid Disease:	--
Right	53.3% (64/120)
Left	46.6% (56/120)
Symptomatic	11.7% (14/120)
Patient Characteristic	**ITT Population (n=120)**
Ipsilateral Stroke	14.3% (2/14)
Ipsilateral TIA	28.6% (4/14)
Ipsilateral Amaurosis fugax	14.3% (2/14)
Retinal Infarction	0.0% (0/14)
Other	42.9% (6/14)
Asymptomatic	88.3% (106/120)

ICA	79.5% (35/44)
CCA	6.8% (3/44)
Bifurcation	9.1% (4/44)
Other	4.5% (2/44)
Balloon Size	5.3 ± 3.7 (119)
Patient Characteristic	**ITT Population (n=120)**
Max Inflation Pressure (atm)	10.0 ± 3.1 (118)
Stent Size (Diameter)	7.5 ± 1 2 (119)
Stent Size (Length)	32.7 ± 6.65 (120)
Stent Type	
ACCULINK	1.7% (2/120)
RX ACCULINK	0.0% (0/120)
PRECISE	42.5% (51/120)
WALLSTENT	24.2% (29/120)
XACT	30.8% (37/120)
Other	2.5% (3/120)
Post procedure residual stenosis (%NASCET)	7.3 ± 8 3 (120)

STUDY RESULTS

Following the completion of 120 patients with 30±7 days follow-up, analysis was carried out to evaluate the compliance with the PG. The results of the analysis showed that the device performance met the PG criteria. All MACCE were reviewed and adjudicated by the CEC and the DSMB.

From the results it can be shown that the WIRION system met the primary endpoint (safety) since only 4 patients had MACCE events which means MACCE rate of 3.3% accordingly the P-Value is 0.0008 which is less than the 0.0015 which is the performance goal as indicated in the study protocol (Table 3).

Table 3: Primary end point in the WISE study (WIRION) comparing to historic control

	Historical Control Group						Study Group
	ARCHeR 2	ARCHeR 3	BEACH	MAVERIC	CREATE	AVG	WISE
Any MACCE	24 (8.6%)	12 (8 3%)	24 (5.4%)	27 (5.4%)	26 (6.2%)	6.3%	4 (3.3%)
Death	6 (2.2%)	2 (1.4%)	7 (1.6%)	5 (1.0%)	8 (1.9%)	1.6%	0 (0%)
Stroke	15 (5.4%)	8 (5.5%)	20 (4 5%)	21 (4.2%)	19 (4.5%)	4.6%	3 (2.5%)
Ipsilateral	14 (5.0%)	7 (4.8%)	15 (3.4%)	17 (3.4%)	16 (3.8%)	3.9%	2 (1.7%)
Major	3 (1.1%)	2 (1.4%)	5 (1.1%)	13 (2.6%)	14 (3.3%)	2.1%	0 (0%)
Minor	11 (4.0%)	5 (3.5%)	10 (2 2%)	6 (1.2%)	2 (0.5%)	1.9%	2 (1.6%)
Contralateral	1 (0.4%)	1 (0.7%)	5 (1.1%)	5 (1.0%)	3 (0.7%)	0.83%	1 (0.8%)
Myocardial Infraction	8 (2.9%)	2 (1.4%)	5 (1.1%)	7 (1.4%)	4 (1.0%)	1.5%	1 (0.8%)
EPD System	Accunet (Abbott)		FilterWire (Boston Sci.)	GuardWire (Medtronic)	Spider (ev3)		WIRION (Gardia)

The historic controls average MACCE rate was 6 3%. Therefore it can be clearly shown that the WIRION system exceeded the safety results if values are compared.

All SAEs are detailed in table 4.

Table 4: Summary of SAEs

Event Type	ITT Population (n=120)
In-Hospital	
Any Serious Adverse Event	4.2% (5/120)
Serious Adverse Event Type	
Death	0.0% (0/120)
Cardiac Death	0.0% (0/120)
Myocardial Infarction	0.0% (0/120)
TIA	1.7% (2/120)
Stroke	0.8% (1/120)
Ipsilateral	0.8% (1/120)
Major Ischemic	0.0% (0/120)
Minor Ischemic	0.8% (1/120)
Hemorrhagic	0.0% (0/120)
Contralateral	0.0% (0/120)
Major Ischemic	0.0% (0/120)
Minor Ischemic	0.0% (0/120)
Hemorrhagic	0.0% (0/120)
Non-MACCE	1.7% (2/120)
Anytime through 30 Days follow-up (30 ± 7 days Post-PCI)	
Any Serious Adverse Event	9.2% (11/120)
Serious Adverse Event Type	
Death	0.0% (0/120)
Cardiac Death	0.0% (0/120)
Myocardial Infarction	0.8% (1/120)
TIA	1.7% (2/120)
Stroke	1.7% (2/120)
Ipsilateral	1.7% (2/120)
Major Ischemic	0.0% (0/120)
Minor Ischemic	1.7% (2/120)
Hemorrhagic	0.0% (0/120)
Non-MACCE	4.2% (5/120)

Secondary endpoint (performances) included device success, clinical success, access site complications, angiographic and procedural success rate. All functions had high success rate of more than 95%. The endpoints related to incidents and complications, were low resulting in 1.7% and 4.1% as summarized below:

- Device success: 99.2%
- Clinical success: 97.5%
- Angiographic success: 99.2%
- Procedural success: 98.3%
- Access site complications: 1.7%

- Neurological events: 4.1%

The study demonstrated safety and efficacy of the WIRION EPD. Results were similar to the performance of other embolic protection devices for carotid use as reported in the published literature.

On February, 2014 the study has reached the enrolment of half of the proposed sample size (240 patients) and had stopped for interim analysis. On December 14, 2014 WIRION 510(k) file was submitted to the FDA (K143570). In the meantime, Gardia had continued enrolment for the study. FDA response letter was sent to Gardia on February 14, 2015. Following, Gardia received a formal indication from the FDA that it met all clinical end-points of the clinical study. Thus, Gardia had decided to stop the enrolment. On 4 of June, 2015, Gardia received FDA clearance for the WIRION Embolic Protection System.

Post Marketing Surveillance (PMS) retrospective study of WIRION™ performance in patients undergoing saphenous vein graft (SVG) intervention

(September 2014 – on going)

s22 [redacted]

Objective: To collect data on the use of the WIRION system in Patients undergoing Percutaneous Intervention (PCI) of Saphenous Vein Graft (SVG).

Methods: From September 2014 to June 2015, patients underwent SVG stenting and/or balloon procedures, in which the WIRION™ system was used, were included in the study.

Results: Data was collected prospectively in patients (n=10) who underwent SVG intervention with the WIRION System in two medical centers. There were no anatomical or morphological exclusion criteria. The SVG were 13.5+/-1/2 years old. Average stenosis was 78%; mean baseline TIMI grade flow was 2.7. Lesion length was ≥15cm in 50% of the patients. Angiographically evident thrombi were identified in 30% of the cases. Moderate to severe tortuosity was found in 30% of treated vessels. Filter was successfully deployed in all patients. In one case retrieval catheter failure occurred, requiring the use of an alternative retrieval catheter. Angiographic success was obtained in all patients with mean residual stenosis of 3%. Mean final TIMI flow was 2.8. In one patient the final TIMI flow was 1, as well as at baseline. In the rest of the patients final TIMI flow was 3. MACCE (stroke, myocardial infarction, and death) was not observed during the procedure and at the 30-days follow-up period.

Conclusions: The use of the WIRION™ system for embolic protection during PCI of degenerated SVGs in a small patient cohort suggests that the use of WIRION™ system may be safe and effective during PCI of degenerated SVGs, even in challenging anatomies.

Evaluation of Safety and Effectiveness of the WIRION™ EPS in Lower Extremities arteries

(Expect to begin at *3Q 2015*)

s22 [redacted]

Objectives: To demonstrate the safety and performance of the WIRION™ EPS in in Lower Extremities arteries in patients suffering from Peripheral Arterial Disease (PAD).

Methods: Gardia Medical is planning a prospective, multi-center, non-randomized, open label, single arm study, in which forty five (60) patients undergoing lower limbs stenting procedure, in three medical centres.

Primary End Point: Freedom of in hospital device or procedure related SAE's such as death, unplanned amputation, unplanned urgent revascularization (interventional or surgical) and vessel perforation of the treated limb, as adjudicated by the Clinical Events Committee (CEC), after initial successful revascularization.

Secondary End Point:

Safety:

1. Assessment of in hospital device or procedure related AE's
2. Assessment of acute visible distal embolization by angiography and ultrasound Doppler

Performance:

1. A successful delivery, deployment and retrieval of the WIRION™ without complications
2. Angiographic assessment of the ability of the WIRION to prevent visible distal embolization, slow flow, and loss of distal tibial runoff with or without capturing visibly detected macrodebris
3. Microscopic assessment of debris in filter

To date, the WIRION Embolic Protection System of Gardia Medical was used in 20 clinical lower extremities procedures performed by s22 and s22 at University Clinic Leipzig, Germany and s22 at Carmel hospital in Israel. Patients were treated by atherectomy and by stenting without atherectomy. The following atherectomy devices, coupled with WIRION EPS were used: EXCImer (Spectranetics), RotaRex (Sraub Medical) and TurboHawk (ev3). Post-procedures, all filters were evaluated under microscope to evaluate emboli capture. In all cases of atherectomy debris were found in the filters. In some cases where no atherectomy was performed debris were found.

The physicians feedback was that the use of filter in lower extremities procedures in which atherectomy is performed is mandatory since during the atherectomy process a large volume of debris is released from the treated area and causes an embolic shower that may have undesired clinical effects such as distal blood vessels blockage. The WIRION is the most suitable system for the lower extremities since it is the easiest to use and the most versatile filter. The ability to cross relatively long and calcified lesions, with a crossing profile of a 0.014' naked guidewire, allows for an easy and safe maneuvering. In addition, the ability to place the filter anywhere along the wire allows positioning of the filter further downstream such that it will not compromise the stability achieved by the wire and will reduce the risk of damaging the artery wall.

Gardia plans to start a clinical study within the next few months on 60 patients in three European clinical sites performed atherectomy and/or angioplasty and/or stenting procedures in lower extremities arteries. The purpose of this study is to support submission of the WIRION system indicated for the lower extremities to the FDA.

6. Review of Relevant Literature

This report includes the following evaluations:

(1) **WIRION in Clinical Trials** - Summary of gained clinical experience with the WIRION system.
(2) **Equivalent Available EPDs**
(3) **Comparable EPDs in Clinical Practice** - include literature review of Carotid Artery Stenting Procedures (CAS), Saphenous Vein Graft Procedures (SVG), Transcatheter Aortic Valve Implantation procedures (TAVI) and Renal Artery Stenting.

6.1 Objective of the literature review

- The primary objective of the present literature review is to demonstrate compliance with the new directive for literature review (MEDDEV2.7.1 Dec. 2009) and to update the former Clinical Evaluation Report (TF015 Ver. 1, 2008).
- In addition, this report aims to demonstrate the conformity of the WIRION system with the relevant essential requirements, in particular:
  - The purpose and claims being made for the devices
  - The risk management assessment under normal conditions of use of the device
  - Evaluation of undesirable side-effects

This literature review demonstrates safety and effectiveness of the WIRION with respect to the following measures.

6.1.1 Safety and effectiveness of WIRION™

Safety Measures	Effectiveness Measures
Major Adverse Cardiac and Cerebral Events (MACCE): - Death - Stroke - Myocardial Infraction - Cardiovascular related SAEs	Device success Angiographic success Procedural Success

Table 4: **Safety and effectiveness measures**

These safety and effectiveness measures are in accordance to the objectives of on-going clinical trials, recent review articles and guidelines focusing on the use of embolic protection devices in cardiovascular interventions.

6.1.2 Safety Measures

We intend to list the following events in comparable follow up times: during the procedure and up to 30 days.

- ***Major Adverse Cardiac and Cerebral Events (MACCE)***

  Major adverse cardiovascular events summarize most relevant events and complications to facilitate the comparison of different studies. As defined in the literature and applicable regulations, the following MACCE events were included: death, stroke and MI. In this report, for each reviewed study we have counted the combined MACCE rate and the rate for each event separately.

- ***Potential Anticipated AE***:

  Complications associated with routine cardiovascular procedures and embolic protection devices, may include but are not limited to the following anticipated AEs:
  Angina, Bleeding Complications, Bradycardia or Arrhythmias including Ventricular fibrillation or Tachycardia, Congestive heart failure, Damage or Dislocation of the implanted stent(s), Death, Detachment and/or implantation of a component of the system, Drug reaction, allergic Reaction to contrast media, medications or device materials, Emergency surgery, Embolization of air, tissue, thrombus or other embolic debris, End Organ Ischemia vessel thrombosis or spasm, Hypotension / Hypertension, Infection (local or systemic), Myocardial Infarction (MI), No Reflow resulting from reduced blood flow through the WIRION™ system filter, Puncture site complications (e.g. vessel occlusion, Hemorrhage, hematoma, pseudoaneurysm or arteriovenous fistula), Renal Insufficiency, Kidney Failure, Hematuria, Stroke/ Cerebral Vascular Accident (CVA), Transient Ischemic Attack (TIA) or seizure, Vessel Damage, dissection, Occlusion, aneurysm, perforation, rupture or injury.

6.1.3 Performance Measures

The performance of the product can be measured in several ways

- ***Device Success***

  A successful delivery and deployment of WIRION™ distal to the intervention site without complications and a successful retrieval of WIRION™ following completion of the stenting procedure without complications.

  Device Failure: A device has failed if it does not perform according to labelling and negatively impacts the treatment while used according to the labelling.

  Device Malfunction: An unexpected change to the device that is contradictory to the labelling and may or may not affect device performance.

- ***Angiographic Success***

  Successful completion of the protected stenting procedure with a residual stenosis ≤30% and without angiographic complications e.g. Flow impairment, Dissection/perforation, intracranial vessel occlusion.

- ***Procedural Success***

  Defined as combined device and angiographic success

7. Identification of data

7.1 Considered clinical data and type of studies

To enable a comprehensive identification, selection and review of relevant sources of data, an extensive peer review literature search was performed. The selected references included studies of EPDs to which the WIRION™ system demonstrated equivalence.

We considered within this literature review all published and unpublished data of clinical investigations of the WIRION™ system and assessed all data about safety and effectiveness, which were gained under normal conditions of use as intended for the product including evident studies which demonstrate the safety and effectiveness of substantially equivalent devices.

Not included are reports lacking sufficient details to permit scientific evaluation and unsubstantiated opinions.

Criteria for including or excluding of particular study with equivalent devices are determined in section 9.2.

7.2 Recognized scientific data

Sources of data

Different sources of information were considered within this literature review to identify clinical data and studies of interest, substantially equivalent devices, adverse events and field safety corrective actions.

a) Substantially equivalent devices were identified by means of:
   - Information of manufacturers (labelling, prospects, instructions for use, manufacturers homepages)
   - Literature and review articles

b) Databases referring to English literature were used to identify studies of interest; in particular:
   - Pubmed database

c) Finally, vigilance systems of European and US Health Authorities were used to identify reported recalls, in particular:

- Germany (BfArM)
- Switzerland (SwissMedic)
- United Kingdom (MHRA)
- USA (MAUDE and FDA vigilance system)

7.3 Rationale for the selection/relevance of the literature

As this is the second revision of Gardia Medical's clinical evaluation we have conducted more specific literature search to include only literature of stenting procedures using distal filter type embolic protection devices for demonstrating the safety and effectiveness of the WIRION™ system.

The selected literature included procedural data about the device application which indicates the effectiveness, in particular device success, procedural success or information about the safety of the procedure including at least one safety parameter of the table in section 6.1.1.

8. Equivalent Available EPDs

8.1 Identification of equivalent EPDs

The literature review discusses clinical studies were embolic protection devices with similar essential characteristics; i.e. clinical condition, patient population, intended use, clinical effect, and similar technical parameters, to the WIRION™ system were used.

The data selected were found to be relevant to the clinical safety and efficacy of the WIRION™ system as it refers to the following aspects:

- Safety of distal filter EPDs in CAS, SVG, TAVI and Renal procedures.
- Efficacy of distal filter EPDs in capturing debris during the indicated clinical interventions
- Device success in terms of delivery, deployment and retrieval
- Clinical outcome of protected procedures

The studies included in the literature database refer to a variety of commercially available distal filter protection devices; all, share similar intended use as well as common fundamental technological features. Distal embolic filters are intended to trap plaque-derived emboli during interventions and prevent embolization into distal vascular bed. Filter protection devices are wire-based (usually a 0.014" wire) devices, consisting of a filter made of a polymer filter membrane and a metallic frame, placed distal to the site of intervention. Such devices contain radiopaque markers intended to assist in visualization during device positioning, deployment and retrieval, and allow contrast injection during the procedure for lesion and arterial visualization. Following debris capture, the filter and the trapped particles are withdrawn from the body by the retrieval catheter.

8.1.1 Relation to specific characteristics of the device in question

The literature review considers the following relevant device properties:

- Use as embolic protection device in cardiovascular procedures
- Serves as distal embolic protection
- Filter type EPD

The properties provide identification of devices which are equivalent with respect to clinical, technical and physical properties.

Clinical

Clinical equivalence is determined by looking at the clinical condition or purpose, the site in the body, the relevant characteristics of the population and performance according to expected clinical effects.

Selected literature and devices assumed to be clinically equivalent to the WIRION have to fulfil:

a) **Clinical condition or purpose**: *Indication for use*

b) **Site**: *Position relevant to the lesion / treatment site*

c) **Population**: *Treated patients*

d) **Performance**: *Emboli capture principle*

Technical

Technical equivalence is determined by looking at the condition for use, specification, design, deployment method and principle of operation.

Each aspect is considered as follows:

a) **Condition for use**: *Clinical application*

b) **Specification and design**

c) **Deployment method**: *Principle of operation*

8.1.2 Appraisal of data

The following identified devices for embolic protection are accordant to their equivalence to the WIRION™ system assessed and due to their characteristics sorted in equivalence classes.

The classification is shown in Table . The classification is divided into application, construction and indication.

The equivalence of products in Class A and B is high. The products in Class C and D have low equivalence and they will be excluded for the analysis of safety and effectiveness. A special attention was given to protection devices most frequently used in clinical studies. Cited in this review:

s22

Equivalence of EPDs		
Equivalence class	Description of the EPD	Inclusion
A	Same design appearance, comparable size, same application technique, same indication	Yes
B	Comparable design appearance, comparable size, comparable application technique, same indication	Yes
C	Comparable design appearance, comparable size, different application technique, same indication	No
D	No comparable design, different application technique, same indication	No

Table 5: **Equivalence of EPDs**

The equivalent devices, Class A-B, have a comparable outer appearance as the WIRION™ system and are based on a similar indications and comparable application technique as described for WIRION™.

The filter unit includes the nitinol frame and the delivery catheter is intended for the delivery of the filter unit to the target site.

Evaluation of manufacturers' homepages and review articles results in embolic protection devices as listed below. Most relevant differences between these devices and their relation to WIRION™ are listed in Table .

Identified EPDs of Equivalent Classes (A-D)		
Product Name and Manufacturer	**Equivalence Class**	**Specification**
WIRION™ System (Gardia Medical Ltd Caesarea, Israel)	NA	The WIRION Embolic Protection System is indicated for use as an embolic protection system to contain and remove embolic material during cardiovascular interventions
s22		

Identified EPDs of Equivalent Classes (A-D)		
Product Name and Manufacturer	Equivalence Class	Specification
s22		

Table 6: **Competitive EPDs**

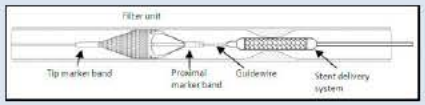
As mentioned above, for the following analysis we included only products of the equivalent Classes A and B.

Therefore, to expose the characteristics of these products, demanded in section 8 for stenting procedures, we search for according information on the manufacturers, homepages and adequate literature references. The following references were used to find out data for equivalent product characteristics, listed in Tables 9, 10 and 11.

Clinical Equivalence			
Product	**Clinical Use or Purpose**	**Location of Use**	**Capability Characteristics**
WIRION™ System (Gardia Medical Ltd Caesarea, Israel)	The WIRION Embolic Protection System is indicated for use as an embolic protection system to contain and remove embolic material during cardiovascular interventions	Any cardiovascular intervention	One size fits all. Vessel diameter: 3.5-6.0mm
s22			

Clinical Equivalence			
Product	Clinical Use or Purpose	Location of Use	Capability Characteristics
s22			

Table 7: **Clinical Equivalence**

Technical Equivalence			
Product	**Application Rules**	**Specification & Design**	**Operational Principle**
WIRION™ System	1. Carefully insert the Delivery Catheter onto the guidewire. 2. Advance the catheter on the guide wire until the guide wire exits the Rx port. 3. Under fluoroscopic imaging, advance the Delivery Catheter to the target vessel and place the Filter Unit distal to the lesion. 4. Once the Delivery Catheter crosses the lesion and is placed in the required position, slide a wire torque tool along the guide wire and secure it against the hemostasis valve. 5. Hold the Activating Handle and peel away the safety sticker. 6. Rotate the rotating section of the handle clockwise, until a red indicator becomes visible at the handle proximal end. The Filter Unit is now locked to the guide wire. 7. Deploy the Filter Unit by holding the guide wire in place with the guide wire torque tool pressed against the hemostasis valve while simultaneously retracting the Delivery Catheter. The three marker bands in the center of the Filter Unit will expand and indicate filter sealing position. 8. Continue retracting the Delivery Catheter, until the Rx port appears at the hemostasis port. 9. Remove the wire torque tool and carefully remove the distal segment of the Delivery Catheter from the wire while maintaining guide wire stability and Filter Unit position	The WIRION™ system consists of the following components: **Delivery Catheter**: A catheter arranged in a form of a rapid exchange catheter. It contains the Filter Unit, delivers it to its working position, locks it onto the guide wire and deploys it. The Activating Handle is the interface used by the physician to activate the lock of the Filter Unit onto the guide wire in the desired location within the artery. **Retrieval Catheter**: The part in the system used to retrieve the Filter Unit, with the trapped emboli and debris, after the therapeutic procedure (Stenting, PTCA) is completed. 	The WIRION Embolic Protection System is a temporary embolic protection system, filtering distal to the intervention site. It is provided sterile and for single use. The system is a rapid exchange, pre-loaded filter that can be used with commercially available 0.014" guide wires. After the guidewire of choice is properly located in the target vessel, the filter is delivered, locked and deployed on the wire, at any location according to physician's discretion. The locking mechanism is remotely activated, allowing the stand-alone filter unit to be positioned in any location along the vessel without compromising wire performance and support. At the end of the procedure, the filter is retrieved along with the wire

Technical Equivalence			
Product	Application Rules	Specification & Design	Operational Principle
s22			

Technical Equivalence			
Product	Application Rules	Specification & Design	Operational Principle
s22			

Technical Equivalence			
Product	Application Rules	Specification & Design	Operational Principle
s22			

Technical Equivalence			
Product	Application Rules	Specification & Design	Operational Principle
s22			

Technical Equivalence			
Product	Application Rules	Specification & Design	Operational Principle
s22			

Table 8: **Technical Equivalence**

Physical Equivalence					
Product	Filter Size (mm)	Vessel Diameter (mm)	Pore Size (µm)	Retrieval Device Profile	Regulatory Status
WIRION™ System	One Size	3.5 – 6.0	120	4.9F	CE Mark
s22					

Table 9: **Physical Equivalence**

8.1.3 Summary of comparison

The WIRION system has the following features:

(1) The ability to apply the filter on ANY commercially available 0.014" guide wire per physicians discretion

(2) The user can place the filter ANYWHERE along the positioned guide wire, ANYWHERE along the vessel

(3) Ease of use; the WIRION delivery catheter is a 'stent like' system, rapid exchange with a pre-crimped filter; intuitive for the user and requires no preparation phase.

These features make the WIRION unique and novel. The system allows the physician to choose his preferable tools for the procedure and place the filter unit in the optimal position anywhere along the wire, anywhere along the vessel, with maximal support and optimal branch protection.

To the best of our knowledge, WIRION is the only EPD system that can be placed on ANY commercially available 0.014'' guide wire. The physician can select his guide wire for the procedure among the variety of 0.014" guide wires available in the cathlab, according to the anatomical challenge and lesion morphology, experience and preference. This, presumably, allows for the best wire selection and thereby easier lesion crossing with higher success rates.

The WIRION system is introduced into the target vessel after the selected guide wire is optimally positioned distal to the lesion site. The physician can lock the filter ANYWHERE along the guide wire, ANYWHERE along the vessel with optimal branch protection and without compromising wire support and stability throughout the procedure. This feature is unique to the WIRION system.

The WIRION RX Delivery catheter with its pre-crimped filter is introduced in a similar way as all stent/balloon systems, with no need for any special preparation steps. Hence is easy to use and significantly reduces user's learning curve.

Review of available EPDs in the market for clinical, technical and physical equivalence as summarized above demonstrate that [redacted] s22 and the s22 [redacted] are claiming to have an "over the wire" capability:

- The Emboshiled cannot be used with commercially available standard 0.014" guide wires. Its' kit includes a choice of 4 dedicated guide wires (differ in lengths and stiffness) having a 0.019" diameter stopper at the distal tip of the wire. Their design is different than standard guide wires and most likely represents diminished wire functionality, maneuverability and trackability characteristics. The four guide wires included in the Emboshield kit are still limiting in choice and characteristics and are not similar to the available guide wires in the physician's toolbox. Furthermore, the pre-positioned stopper at the distal end

of the dedicated wire does not allow positioning of the filter anywhere along the wire anywhere in the vessel and thereby may compromise filter positioning, wire support and branch protection.

- The s22 [redacted], which also considered as an over the wire device, allows initial step with a wire of choice, however, after crossing the lesion, the initial wire is replaced - using a dedicated exchange catheter and an additional exchange step - removing the initial wire and introducing the Spider fixed on a wire filter. The rest of the procedure, in this case, is done without the wire of choice.

The WIRION is the only system that is a true and fully "over the wire". The technique used by the operator is identical to common PCI workflow.

9. Selection of Literature

9.1 Selection of relevant literature about EPDs

At first the terms and the literature describing the device in question and medical method were generally limited to references describing studies which:

- English language
- Human subjects / clinical trial
- Publication date from *01/01/2010 to 10/06/2015*

Terms	Hits
1. Embolic Protection and Filter and Carotid	22
2. Embolic Protection and Filter and TAVI	3
2.1 Embolic Protection and TAVI	4
3. Embolic Protection and Filter and SVG	3
3.1 EPD and SVG	7
4. Embolic Protection and Filter and Renal	1
5. Embolic Protection and Filter and Peripheral Arterial Disease	4
TOTAL	44

Table 10: **Terms and hits for selection of relevant literature**

The selected terms were used to search in Pubmed database on 10 of June 2015. Thereby the present evaluation considers literature published from *01/01/2010 to 10/06/2015*. The selected terms were linked appropriately by use of the Boolean Operators AND or OR. At the end of this selection 44 articles were screened. Additional limitations were considered as suitable:

- Total number of patients <25
- Equivalent intended use
- Absence of the term "embolic protection" in the abstract or title
- Technical / Non-relevant use

According to this described search strategy there are 13 articles which will be taken into account in the current literature evaluation.

The results were merged to avoid listing twice.

Included were the references which

- address at least one primary or secondary endpoint according to the objective of section 6.1.1, for effectiveness or safety
- address effectiveness for the interventional procedure itself and the follow-up

Thus, in the following literature evaluation 11 references were considered.

9.2 Criteria for exclusion of particular references

a) **Excluded EPD devices:** included only filter-type EPDs with similar intended use and comparable design and technical features to the WIRION™ system.

b) **Excluded literature**: This evaluation does not make use of literature which describes: In-vitro or in-vivo trials in animals; use of embolic protection devices others than filter type; Clinical trials with devices which are not substantially equivalent to the device in question.

c) **Adequacy of exclusion criteria:** Studies with insufficient statistical power and studies which are not in accordance to medical and scientific requirements were excluded.

9.3 Sufficiency of references according to the objectives

We believe that the referenced published literature is able to prove clinical safety and performance of the device in question due to following reasons:

- References within the identified original articles point to articles, also identified by our search, which meets our conclusion to have identified relevant literature.
- The search criteria do not distinguish between favourable and unfavourable publications.
- Selection and evaluation of literature is performed according to MEDDEV 2.7.1. rev.3 [1].

Therefore, from current point of view we believe to have evidence that sufficient references were identified. In particular safety and effectiveness of the device in question is provided by the selected literature.

9.4 Adequacy of data according to the objective

According to section 7 the present evaluation considers all data on safety and effectiveness available for the substantially equivalent embolic protection devices. With respect to the objective of this clinical evaluation in the literature, the sources of interest were identified.

Sufficient evidence for substantially equivalence to the device in question was shown. Consequently the data of these devices were regarded as relevant. Finally, adequacy of data according to the objective is demonstrated.

Moreover, as shown in sections 10 and 11 the data are capable to demonstrate that the device in question complies with the relevant essential requirements.

10. Assessment of Clinical Data

Data on safety and effectiveness of substantially equivalent devices are available in the references 8-13; 17-21; 22-28.

10.1 Authors Background

Data from publications were collected by physicians and researchers in Europe and US. The authors work at medical facilities and universities mainly in the field of cardiovascular interventions.

10.2 Substantiation of Conclusions by Data

The data were collected in studies which endpoints, designs and methods were described. In this connection they deal with compare studies as well as application studies.

The data provide evidence for conclusions of authors in all cases.

10.3 Recognition of Publications

All References were published in scientific evident peer reviewed journals and classified by the pubmed database as "core clinical journals".

The impact factors (IF, 2015) are as follows:

Reference	Journal (alphabetical order)	IF 2015
[12;15;17;21]	Catheterization and Cardiovascular Interventions	2.396
[8]	Journal of the American College of Cardiology	16.503
[9]	Journal of Vascular Surgery	3.021
[10]	American Journal of Neuroradiology	2.928
[11]	Journal of Interventional Cardiology	1.318
[13]	Cerebrovascular Diseases	3.70
[18;19;20]	Euro-Intervention	3.769

Table 11: **Impact factors (IF)**

10.4 Scientific Principles

The publications from [9] describe clinical trials performed in Europe and US according to current guidelines.

The selected studies were conducted with at least 15 patients. The reviewed studies were all prospective [8-13]. Some were multicenter studies [9; 11; 12] and some included single center experience [8; 10; 13]. Furthermore, some were randomized [8; 13] to either comparison between different embolic protection techniques [8] or for CAS without protection [13].

In particular end points, inclusion and exclusion criteria, number of patients, complication and success rate and statistical methods were determined.

If the complication or success rate was not explicitly listed it was calculated from given criteria, whereas the complication rate was the added number of all complications which were life threatening and needed further treatment. The success rate was the rate of successful procedure.

In case of no unique identification of the data, we classified them to the more critical one, to not overestimate the positive impact.

Ref.	End points	Inclusion Criteria	Exclusion Criteria	Sample Size	Complications Rate (%)	Procedural Success Rate (%)	Stat. Analysis
[8]	√	√	√	31[(1)]	0%	NA	√
[9]	√	√	√	220	NA	96.8%	√
[10]	√	√	√	65	4.6%	96.9%	√
[11]	√	√	√	160	NA	97.5%	√
[12]	√	√	√	237	NA	97.5%	√

Ref.	End points	Inclusion Criteria	Exclusion Criteria	Sample Size	Complications Rate (%)	Procedural Success Rate (%)	Stat. Analysis
[13]	√	√	√	30	NA	NA	√
[17](2)	√	NA	NA	113	2.65%	81.6%	√
[18]	√	NA	NA	50	NA	NA	√
[19]	√	√	√	15	0%	100%	√
[20](3)	√	√	√	40	0%	1st gen: 60% 2nd gen: 87%	√
[21]	√	√	√	20	0%	100%	√

Table 2: **Scientific principles of references**

(1) Half of the study sample size (n=31) was treated with filter EPD the other half was treated with proximal balloon occlusion EPD.

(2) Refers to Ostial SVG

(2) Include two generations (first and second) of the EPD

11. Critical evaluation of the literature

11.1 Filter EPD in Carotid Artery Stenting (CAS)

Distal embolization remains the most feared complication of carotid artery stenting (CAS), although its incidence can be reduced by proper technique, adequate antithrombotic therapy and the use of EPD. Virtually any step of the procedure may be associated with debris formation. The two most critical steps in this respect are the engagement of the common carotid artery with the guiding catheter and the post-inflation of the stent [29]. A systematic review including 2357 patients undergoing CAS and 839 patients stented with adjunctive EPD documented a 30 day death and stroke rate of 5.5% and 1.8% ($p<0.001$) respectively [30] A German prospective CAS registry assessing 1483 procedures detected an in-hospital death or stroke rate of 2.1% among 666 patients underwent CAS with EPD and an event rate of 4.9% among 789 patients treated without EPD [31]. Similarly, in a multicentre feasibility study of CAS performed in 261 patients with and without EPD the one year major ipsilateral stroke rate was significantly lower among patients underwent CAS with EPD (0% Vs. 2.3%)[32].

Distal protection filters have been an accepted standard of care for the CAS procedures. Filters are metallic baskets coated by a membrane made by polyethylene. The membrane has pores with a diameter ranging from 80 to 220µm. Filters are usually mounted on a 0.014'' guidewire generally 30mm proximal to a flexible tip and are delivered through a 3F profile catheter. Once the lesion is crossed the filter should be opened in a straight portion of the ICA, at least 2cm above the target lesion. At the end of the stenting procedure a retrieval catheter is inserted to recapture the filter and remove it. Where the stenosis is very tight or the anatomy very tortuous, the passage of the delivery catheter through the lesion may be difficult or impossible. In such cases pre-dilation of the stenosis must be performed using a very small balloon to neither fracture the plaque nor the vagal sinus reflex. The diameter of the filter must be selected on the basis of the calibre of the ICA segment where the filter is to be placed. Generally 1mm oversize is required to get the correct wall apposition reducing the possibility of failure to capture the emboli [33].

11.1.1 Summary of safety data from literature

The following Tables indicate the procedural safety. We summarized all complications indicated within 24 h up to 30 days as procedure related.

Potential anticipated AEs are defined as complications associated with routine cardiovascular interventions. They included but are not limited to the following anticipated AEs: [6]. **Note**: The anticipate AE rate presented in Table 3 below, is a composite of all reported Anticipated AEs including MACE (MI, Stroke and Death), TIA, Amaurosis Fugax and Bleeding complications.

The data, listed in Table 3 and Table 14 are expressed in % referred to the absolute amount of patients.

	[8]	[9]	[10]	[11]	[12]	[13]
Death	0 %	0.5%	0%	2.5%	0.4%	NA
Stroke	3.2%	1.8%	1.5%	5.0%	2.1%	3.33%
Major Stroke	*0%*	*0.5%*	*1.5%*	*3.1%*	*1.3%*	*3.33%*
Minor Stroke	*3.2%*	*1.4%*	*0%*	*1.9%*	*0.8%*	*0%*
MI	NA	0.5%	0%	0.6%	0.8%	NA
TIA	NA	3.6%	3.1%	NA	2.1%	33.3%
Amaurosis Fugax	NA	0.5%	NA	NA	NA	13.3%
Overall MACE Rate	3.2%	2.3%	1.5%	5.6%	3.0%	3.33%
Bleeding / Vascular Complications	0%	NA	3.1%	1.9%	NA	NA
Overall Anticipated AEs	NA	6.9%	7.7%	23.8%	18.5%	50%
EPD Related complications	NA	0.9%	4.6%	NA	NA	NA
Sample Size	**31**	**220**	**65**	**160**	**237**	**30**

Table 3: **Procedural safety; up to 30 days FU post procedure**

11.1.2 Summary of Effectiveness data from literature

Table 14 indicates the success rates within the first day and 30-day follow up time after intervention.

Reference	Sample Size	Device Failure [%]	Procedural Success [%]	Evidence of debris in Filter	Operation time reduction [min]
[8]	**31**	3.2%	NA	NA	8min compared with prox. balloon EPD
[9]	**220**	2.7%	96.8%	NA	NA
[10]	**65**	3.1%	96.9%	NA	NA
[11]	**160**	2.5%	97.5%	36%(1)	NA
[12]	**237**	2.53%	97.5%	90.9%(2)	NA
[13]	**30**	NA	NA	NA	NA

Table 14: **Effectiveness data from literature**

(1) Gross Observation
(2) Microscopic evaluation

Only one reference [10] provided information on angiographic success (residual stenosis ≤30%) with success rate of 97.2%.

11.2 Fulfilment of the Intended Purpose

The intended purpose of the equivalent devices covers WIRION™ intended use. Also the applied procedures comply with current practice. Particularly, claims and purpose of the WIRION were considered while excluding literature referring to other devices, intervention of other anatomic structures, compared to section 7.

11.2.1 Population

The following Table 14 contains relevant information about the population participate in the clinical trials with equivalent devices. This includes data regarding demography (Table 14a) and lesion characteristics (Table 14b).

Reference	Mean age [Years]	Male [%]	Diabetes	Hypertension	Symptomatic	Sample Size
[8]	71.7±10.4	77.4%	25.8%	96.8%	38.7%	**31**
[9]	72.5±9.7	63.6%	30.9%	88.6%	12.8%	**220**
[10]	69±9	73.9%	38.5%	81.5%	41.7%	**65**
[11]	73.5±9	69%	35%	91.3%	15%	**160**
[12]	73.9±8.3	62.4%	39.7%	92.8%	20.3%	**237**
[13]	70±9.7	60%	40%	73%	NA	**30**

Table 14a: **Study population - Demographics**

Reference	[8]	[9]	[10]	[11]	[12]	[13]
Lesion Length (mm)	18.4±5.1	18.0±5.6	NA	16.8±8.6	14.3±6.8	NA
Lesion Location *CCA* *ICA* *Bilateral*	 NA 54.8% 25.8%	 NA 15.2% 84.8%	 *4.2%* *95.8%* *10.8%*	 6.3% 82.5% 11.3%	 5.9% 83.1% 11.0%(1)	NA
Eccentric Lesion	87.1%	15.1%	NA	77.5%	52.6%	NA
Calcified Lesions	61.3%	46.1%	NA	58.8%	65.5%	NA
Ulcerated Lesions	29.0%	16.1%	NA	40.6%	43.8%	NA
Thrombotic Lesions	0%	0.5%	NA	0.6%	0%	NA
Mean Stenosis	88.2%	73.5±9.4%	82±9%	82.6±8.6%	NA	NA

Table 14b: **Study population - Lesion Characteristics**

(1) Lesion located in the bifurcation

In the patient populations the majority of the patients were of male sex.

The mean age of the included patient population in the reviewed papers was approximately 72 years.

According to the safety data the most feared potential anticipated AEs were peri- and post-interventional stroke, myocardial-infraction, TIA, Hyperperfusion, bleeding, Renal insufficiency and mortality.

The procedure duration was not applicable in most articles.

Due to the inclusion and exclusion criteria, the population characteristics (age, gender, medical history) as well as lesion characteristics (lesion length, location, stenosis rate) are comparable to the population expected to be treated by the WIRION™ system. Therefore similar results in safety and effectiveness are expected.

11.2.2 Conclusion of equivalence

The clinical data were collected in populations with high risk for carotid endarterectomy undergoing carotid artery stenting procedure with distal filter-type embolic protection systems. Similarly, The WIRION™ System is intended for use as a system for embolic protection to contain and remove embolic material (thrombus/debris) during cardiovascular interventions.

The clinical and technical equivalence of the WIRION™ and the comparable devices, determined as equivalence classes A and B in section 8.1.2. Table 5 Equivalence of EPDs, has been demonstrated.

The lesion site may be very challenging or impossible to cross with available guide-wires carrying the embolic protection device. The availability of an embolic protection system that allows the physician to use his guidewire of choice, most suitable to the challenging anatomy or lesion morphology, we believe, will reduce the risk of debris prior to deployment of the filter and will allow the physician to better deal with challenging cases (i.e. anatomy) with protected CAS.

We believe that the analyzed literature covers the properties, study results are assignable and the studied population are all applicable to the WIRION system.

11.3 Market Experience

Gardia Medical Ltd. has gained market experience with WIRION™ in Europe (Poland, Nether Land and England) and in Israel (Bnai-Zion, Elisha, Belinson and Assuta). Gardia Medical Ltd. plans to conduct additional studies as part of its PMS activities.

11.3.1 Corrective actions and recalls

The vigilance systems of FDA, BfArM and SwissMedic were analyzed for corrective actions and recalls. The databases cover data to July 2012. We included clinical equivalent devices.

We used competing equivalent devices names as search term, and found no recalls in the past 3 years.

We used '*Embolic protection*' and '*stent*' as search terms and found the following recalls related to one embolic protection device (Angioguard™) and applicable stents.

We have decided to include stents as well as due to usage in similar interventions it may provide relevant safety information.

	Product	Date	Notice No	Reason for Recall
1	[redacted]			
2				
3				
4				

Table 15: **Identified corrective actions and recalls**

No entries were found at BfArM.

11.4 Identified Hazards

In the analyzed literature which contained articles on embolic protection for CAS, SVG, TAVI and Renal procedures, the following hazards occurred:

- Death
- Stroke (Major and Minor)
- Myocardial Infraction
- TIA
- Amaurosis Fugax
- Hyperperfusion
- Vasospasm
- ICA Dissection
- Intracranial hemorrhage
- Access site complications
- Stent thrombosis
- Renal insufficiency
- Anemia
- Severe hypotension/hypertension
- Contrast nephropathy
- GI Bleeding

Hazards related to the use of devices equivalent to WIRION™ included

- Asymptomatic dissections of the ICA
- Symptomatic spasm of the ICA

All these terms are presently represented in the WIRION™ IFU as anticipated AEs.

11.5 Risk Analysis

The prospective risk analysis has to regard the identified risks of this clinical evaluation according to ISO 14971. No intolerable risk is allowed to persist.

We claim the risks that were found in the literature search conducted for this clinical evaluation were all considered by Gardia and are all presented in Gardia's Risk analysis document number REA PD 01 named Risk management WIRION and were all mitigated during the verification and validation process of the WIRION system. We have listed all those risks in the IFU [3].

The referenced published literature includes angioplasty procedures related adverse events. These hazards should be assessed with respect to WIRION™ within the risk management.

The main identified risks are as follows:

- Angina
- Bleeding complications
- Bradycardia or arrhythmias, including ventricular fibrillation or tachycardia
- Congestive heart failure
- Damage to or dislocation of the implanted stent(s)
- Death
- Detachment and/or implantation of a component of the device
- Drug reaction, allergic reaction to contrast media, medications or device materials
- Emergent surgery
- Embolization of air, tissue, thrombus or other embolic debris
- End organ ischemia, vessel thrombosis or spasm
- Hypotension/hypertension
- Infection (local or systemic)
- Myocardial infarction
- No-reflow resulting from reduced blood flow through the Filter Unit
- Puncture site complications (i.e., vessel occlusion, hemorrhage, hematoma, pseudoaneurysm or arteriovenous fistula)
- Renal insufficiency, kidney failure, hematuria
- Stroke/cerebrovascular accident (CVA), transient ischemic attack (TIA) or seizure
- Vessel damage, dissection, occlusion, aneurysm, perforation, rupture or injury

Those risks were assessed for the WIRION system during the bench, animal and clinical studies. A large clinical study named WISE pivotal study was performed in order to assess the WIRION safety and performance. During this study no un-anticipated device or procedure related AE's that were listed above were found.

To summarize, all risk identified in the literature and disclosed in this clinical evaluation document were considered in Gardia's risk analysis and were mitigated. Furthermore the WISE clinical study did not reveal any new and un-anticipated risks.

11.6 Discussion

The outcomes of safety and effectiveness from current reviewed studies show relation to the used method. No differences in the outcomes of the studies related to the used product can be found.

The adverse events within the procedure sorted in Table 12 show Death as MACCE only in 0.84% of the cases. Information about device failures was very limited and device malfunctions were not mentioned in anyone of the reviewed papers. The usually observed peri- and post-procedural AEs were as follows: Death, Stroke (Major and Minor), Myocardial Infraction, TIA, Amaurosis Fugax, Hyperperfusion, Vasospasm, ICA Dissection, Intracranial hemorrhage, Access site complications, Stent thrombosis, Renal insufficiency, Severe hypotension/hypertension, Contrast nephropathy and GI Bleeding [8-13].

The chosen follow-ups in the reviewed papers were as follows: 3 h, 24 h; 7 days, 30 days, 180 days; 1, 2 and 3 years.

Study endpoints included: mainly MACCE rate as primary end point. One article [13] referred to the number of new lesions 1-3 hours, 24 h and 30 days post procedure as the primary end point. Secondary end points included device/technical success and procedural success. One article [9] also included the composite rate of 'TIA and Amaurosis Fugax' and 'Target lesion revascularization (TLR) rate' as secondary assessments as well.

The main conclusions which can be made from the reviewed papers can be described as follows:

- Using embolic protection in CAS procedures is essential and may significantly reduce procedural complications.
- Age ≥80 years old were associated with more clinical complications.
- Challenging anatomies and lesions morphologies may be very challenging and even impossible to be crossed with applicable distal protection devices.

11.7 Filter EPDs in TAVI Procedures

Minimally invasive cardiovascular interventions with EPDs have progressed into the area of heart valve repair (e.g., valvuloplasty) and valve replacement of dysfunctional valve structure (e.g., implantation of prosthetic valves for replacement of the native, diseased aortic, mitral, tricuspid or pulmonary valves). Perhaps the most prevalent of these procedures is transcatheter aortic-valve implantation (TAVI), but minimally-invasive techniques have also been developed for repair and replacement of the other heart valves.

Due to the size of the prosthetic heart valve and the delivery catheter required, aortic valve replacement is typically performed by catheterization using the femoral artery approach, traversing the aortic arch to access the native valve (i.e., progressing in the direction from the left atrium to the left ventricle). More recently it has become possible to introduce a replacement aortic valve by exposing the heart in a minimally-invasive manner and entering the heart through the apex to access the native valve (i.e., progressing in the direction from the left ventricle to the left atrium).

Such minimally-invasive heart valve replacement procedures also pose considerable risk of complications due to embolization, and generally warrant similar preventative measures being taken with adjunctive embolic protection. The most critical anatomical location requiring embolic protection during such procedures is the ascending aorta immediately above the heart, and more particularly with respect to the series of aortic branches located at the aortic arch (i.e., brachiocephalic trunk or innominate artery (BA) which further branches into the right subclavian artery and the right common carotid artery; left common carotid artery (LCA); and left subclavian artery (LSA)). With these aortic branches the primary objective is to prevent embolic debris from entering either the carotid or vertebral arteries thereby causing neurovascular events.

Previously, it has been proposed to use various tubular filters or curved shields as embolic protection devices within the aorta. Typically, these deflectors are deployed adjacent the internal upper wall of the aortic arch and are positioned to overlie the respective ostium of the aortic branches. Unfortunately, these devices are difficult to deliver, and they may not fully achieve and maintain sufficient apposition with the upper wall of the aortic arch during the interventional procedure. Additionally, such deflectors are susceptible to being dislodged during deployment of valve delivery catheters and prosthetic implants which are being introduced by femoral artery approach. Consequently, these devices might only reduce, but will likely fail to altogether eliminate, the ultimate migration of embolic debris into the aortic branches. It is therefore believed that the most effective and safe embolic protection would be utilizing filters which are directly inserted into the ostium of each aortic branch.

Alternatively, embolic protection devices have been developed for delivery by brachial or radial artery approach. However, these devices require accessing additional patient vasculature in support of a filter delivery already utilizing the femoral artery approach. Statistics indicate that such brachial or radial artery approaches may introduce further complications than the femoral artery approach. Access to the brachial or radial arteries carries not only a higher risk of complications, but the complications are generally more severe than those associated with femoral access. The arteries of the upper extremity have an enveloping fascial sheath. Therefore when a hematoma does occur, brachial plexopathies are more common. In addition, upper extremity vessels tend to spasm more frequently during manipulation, making access more challenging. Brachial access also carries the added risk of distal ischemia and embolization over radial access. Finally, although guiding sheaths up to 6 or 7 French may be percutaneously placed in either vessel; radial access should be preferred over brachial because of a lower complication profile. While others have previously proposed deployment of multiple embolic filters during cardiac catheterization, with the objective that each aortic branch independently receives an embolic filter, none of these embolic protection systems have been adjunctively sufficient to address all of the following clinical problems associated with TAVI, for example:

- Accurate embolic filter delivery and stable deployment within each aortic branch (i.e., embolic filters being firmly deployed within each ostium at the appropriate orientation);
- Safe and effective embolic protection for every aortic branch being filtered (i.e., deflectors may not prevent entry of all embolic debris);
- Minimal clinical complications by avoiding multiple vascular access sites (i.e., avoiding additional, unnecessary access, such as brachial or radial artery approach, while supporting valve delivery utilizing femoral artery approach);
- Presenting minimal structural interference with the therapeutic catheter procedure (i.e., the deployed embolic protective system posing minimal physical obstruction to subsequent delivery of the valve replacement catheter, such as by sequentially deploying multiple, self-locking embolic filters over a single guidewire); and
- Ease of retrieval (i.e., a single retrieval catheter capable of retrieving all deployed filters).

It is thus desirable to provide an improved embolic protection system, including delivery and retrieval catheters and associated filter elements, which can provide an accurate and safe deployment and retrieval of multiple embolic filters within the aorta in support of minimally invasive cardiac valve repair and replacement procedures

11.8 Filter EPDs in Renal Procedures

Renal artery stenosis (RAS) is the most common cause of secondary hypertension, with an estimated incidence of 5% in the hypertensive population. Atherosclerosis is by far the most common cause of RAS. Atherosclerosis affecting the renal artery is a progressive disease that most often results from encroachment of aortic plaque into the renal ostium. Endovascular management of RAS is the primary modality of treatment with a very high success rate, low complication rate, and acceptable long-term patency. Nonetheless, renal artery percutaneous treatment is not universally accepted as safe and effective. This lack of acceptance mainly stems from post-procedural temporal deterioration of renal function and variable long-term improvement in blood pressure control in this patient population. Post-procedural deterioration in renal function may occur in 20% to 40% of cases and is an important limitation of this technique.

Deteriorating renal function may occur either due to deleterious effects of contrast media or atheroembolization during percutaneous intervention. Like many other vascular beds, such as the carotids, saphenous vein grafts, and certain coronary lesions, atheroembolization may occur during any renal artery

intervention. Most patients undergoing renal endovascular revascularization have clinically silent renal atheroembolization. Patients with baseline renal insufficiency or poor functional reserve may have clinical expression of renal atheroembolization. Although it is logical that embolic protection devices are needed during renal artery intervention, very limited data exist in the literature to support its use. Moreover, many technical and device design issues are unresolved.

In an attempt to better understand the current objective evidence regarding renal protection efficacy we reviewed contemporary literature and summarize the findings herein. There is increasing observational data suggesting the use of embolic protection devices decrease the risk of continued decline in renal function after renal artery stenting.

Atheroembolization is probably a clinical or subclinical complication of renal artery intervention. Deterioration in renal function after the procedure may occur due to contrast-induced nephrotoxicity, progression of concomitant nephrosclerosis, restenosis and, most importantly, atheroembolism. The importance of careful patient selection, appropriate guide catheter and guidewire selection, and meticulous technique cannot be stressed enough. An atherosclerotic fragments released during renal intervention are of sufficient size to create vascular occlusion and ischemic renal parenchymal damage. Every step of the procedure including wire passage, balloon angioplasty, and stent placement may be associated with the release of embolic debris.

For renal artery stenting procedures, there are currently no well controlled prospective trials to conclude the added risk and expense of renal protection by proven clinical benefit. Based on the literature compiled in this report we do believe EPDs should be considered in some high-risk patients.

11.9 Filter EPDs in Lower Limbs Procedures

Peripheral Arterial Disease (PAD) is a highly prevalent atherosclerotic syndrome that affects approximately 8-12 million individuals in the US and is associated with significant morbidity and mortality. Because of its high prevalence, high rates of non-fatal cardiovascular ischemic events, increased mortality and diminution of quality of life the consequences of PAD in US communities are significant [34].

The femoral and popliteal arteries are affected in 80% to 90% of symptomatic PAD patients, the tibial and peroneal arteries in 40% to 50%, and the aortoiliac arteries in 30%. The goals of PAD management are limb salvage, symptom relief, improving functional status, and preventing cardiovascular events. Limb revascularization procedures are offered to select patients indicated. The absolute indications for lower extremity revascularization are for acute limb ischemia, critical limb ischemia (usually manifested as rest pain, nonhealing lower extremity ulcers), or lifestyle-limiting claudication [35].

Plaques in the femoropopliteal arteries and bypass grafts can be eccentric, ulcerated, calcified, and/or composed of soft tissue. These lesions can be affected by instrumentation, resulting in debris embolization. The incidence of embolic debris following routine angioplasty and stent placement can vary from 0% to 25% [36].

In a study by Matchett et al. [37], a cohort of 80 patients with threatened limbs was treated with stent placement. Of this group, 15 developed blue toes; 4 (27%) of these patients incurred amputations. It is still difficult to know whether the embolization was the deciding factor in causing these patients to lose a limb. However, the goal of a lower limb intervention should be the preservation of the limb.

Matsi et al. [38] assessed the incidence and types of complications. During 410 Balloon Angioplasties (BA) in 295 patients, the complication rate was 10.5% (43/410), a subgroup analysis revealed the greatest rate of complications occurred in occlusions (18%) versus stenosis (7%, p=0.002). The rate of distal embolization was 2.7% (11/410).

In addition to stenting and BA procedures, high-embolic-risk femoropopliteal interventions include thrombolytic therapy, mechanical thrombectomy, extirpative atherectomy, and stent-graft insertion, as well as treatments involving friable atheroma and unstable plaque. The rate of embolization from thrombolytic therapy varies from 3.8% to 37%. For rheolytic thrombectomy devices, the incidence of embolization can vary from 25% to 56%.

In studies involving a small number of patients in whom a distal protection filter was used during superficial femoral artery (SFA)/popliteal interventions, the rate of visual embolic debris in the filter following the procedure was high, ranging from 63% to 100% [36].

Konig et al. [39] performed an evaluation using a filter for protected infrainguinal BA in 11 patients with femoropopliteal lesions (6 stenoses, 3 occlusions, 2 controls); they observed macroembolization in all patients with concentric stenoses, but in none of those with chronic occlusion. Based on these limited data, they concluded that microembolization of fibrin aggregates is a common event in BA of femoropopliteal stenoses.

Siablis et al. [40] used the SpiderFX filter in 17 patients with acute and subacute ischemic limbs; macroscopic particulate debris consisting of fresh thrombus, calcification minerals, cholesterol, and fibrin was extracted from all the filters.

Karnabitidis et al. [41] used distal protection filters in 48 patients with lower extremity disease. They found particles with a major axis >1 and >3 mm in 58% (n=29) and 12% (n=56), respectively, of the examined filters. Collected particles consisted primarily of platelets and fibrin conglomerates, trapped erythrocytes, inflammatory cells, and extracellular matrix. Increased lesion length, increased reference vessel diameter, acute thromboses, and total occlusions were positively correlated with higher amounts of captured particles ($p<0.05$).

Shammas et al. [42] reported the results of 40 patients from the single-center prospective PROTECT (Preventing Lower Extremity Distal Embolization Using Embolic Filter Protection) registry established to evaluate the safety and effectiveness of EPDs in reducing distal embolization during percutaneous lower extremity interventions. Patients undergoing angioplasty, stenting, or SilverHawk atherectomy and adjunctive BA for infrainguinal occlusive disease were eligible. They treated lesions with moderate or severe calcification of any length, total occlusions of any length, filling defects, and suspected ulcerations. SpiderFX and EmboShield were used in 2 patients groups: 29 BA/stenting patients with 43 lesions (group A) or 11 SilverHawk atherectomy procedures (group B). Macroembolization occurred in 22 (55.0%) patients: 11 (37.9%) in group A and 11 (100%) in group B ($p<0.001$). Clinically significant (≥2 mm in diameter) macrodebris was found in 18 (45.0%) patients: 8 (27.6%) in group A and 10 (90.9%) in group B ($p<0.001$). All filters were retrieved successfully with no complications, indicating that the filter technology they used is safe. The authors proved that macroembolization is very frequent in patients undergoing lower extremity interventions, particularly with atherectomy.

Table 16 summarize the number of tapped debris in the various studies is presented below.

Embolic Protection Devices (EPDs) in Peripheral Interventions

	N	Procedure	EPD Type	Visible Trapped Debris	Particle Size, µm
König[23]	11	FP PTA (occlusions, stenoses)	s22	5/9	NA
Siablis[6]	16	FP PTA (occlusions)		17/17	1702
Wholey[22]	5	FP PMT (occlusions)		5/9	NA
Karnabatidis[8]	48 (50 limbs)	FP PTA (occlusions, stenoses)		35/50	NA
Shammas[25]	40	A: FP PTA/stent; B: atherectomy (occlusions, stenoses)		18/45 27.6% (A) 90.0% (B)	>2 mm

FP: femoropopliteal, PTA: percutaneous transluminal angioplasty, PMT: percutaneous mechanical thrombectomy, NA: not available.

Table 16: **EPDs in Peripheral Interventions [36]**

As seen in the table in all presented procedure significant amount of debris was found on the filter indicating that EPD are useful for peripheral applications.

Roberts et al [43] presented last year (2014), the results of the DEFENITIVE Ca^{++} trial performed to evaluate the safety and effectiveness of directional atherectomy and distal embolic protection, used together to treat moderate to severely calcified femoropopliteal lesions. A total of 133 patients with 168 moderate to severely calcified lesions were enrolled. Lesions were treated with directional atherectomy devices, coupled with distal embolic protection. The 30-day freedom from MAE rate was 93.1%. Per angiographic core laboratory assessment, the primary effectiveness endpoint (50% residual diameter stenosis) was achieved in 92.0% (lower confidence bound of 87.6%) of lesions. By core lab analysis, these results did not achieve the success criteria (90%) for the primary effectiveness objective. Per site assessment, the objective was met with the endpoint

being achieved in 97.0% (lower confidence bound 93.8%). A mean residual diameter stenosis of 33.3% was achieved with the directional atherectomy device. This was further decreased to 24.1% with the use of adjunctive therapy. The proportion of asymptomatic subjects [Rutherford Clinical Category (RCC) = 0] increased from 0% at baseline to 52.3% at the 30-day follow-up visit. In total, 88.5% of subjects experienced an improvement of one or more Rutherford categories. The results of the DEFINITIVE Ca^{++} study demonstrate that the s22 and s22 atherectomy devices are safe and effective in the endovascular treatment of moderate to severely calcified lesions in the superficial femoral and/or popliteal arteries when used with the s22 distal embolic protection device.

These studies and more demonstrates that distal emboli are very common during lower extremity percutaneous peripheral interventions (PPI) and that use of an embolic protection system appears safe and at least feasible during lower extremity PPI.

12. Conclusions

Based on the clinical data of competitive devices the effectiveness and safety of these devices were proved. Therefore, the available literature contains sufficient data to determine the expectation of safety and effectiveness of the device in question.

This literature search showed that challenging anatomies and lesions morphologies may be very difficult and even impossible to be crossed with applicable distal protection devices. In some of these cases the procedure was done without protection, suggesting that a standard guidewire was used to cross the lesion, thus supporting the benefit of the use of the WIRION system.

The WIRION™ IFU is adequate. The IFU and the risk management assessment include the identified hazards and inform the user adequately about residual risks.

In addition , the adverse events stated in the WIRION™ IFU is considered adequate and will be revised as needed as per additional input to be gained by clinical experience.

As already mentioned under section 3 description of the device, the application of the WIRION™ system differs from the comparable devices. Its filter is free to be locked on any 0.014'' guidewire of choice. Most available filter EPDs in the market are pre-mounted over the guidewire. The WIRION™ system is easy to use and requires no preparations.

12.1 Regulatory Requirements

The essential requirements of the MDD regarding the clinical aspects pertaining to the safety and the performance of WIRION™ is covered by a compilation of information collected from literature, preclinical studies and bench studies. Post market data will further support safety and performance of the WIRION™.

Design, endpoints and duration of the intended clinical investigation were able to address the safety and effectiveness measures according to section 5. Therefore, the essential requirements of the MDD regarding clinical aspects were further covered.

The review of the literature verifies equivalence of WIRION™ with the competitor products and therefore WIRION™ meets the minimum requirements of clinical safety and performance.

Keeping in mind the technical innovation of WIRION™ the compatibility between WIRION™ and the equivalent EPDs, in terms of application technique, is limited.

In our opinion clinical data collected so far with the WIRION™ system, is sufficient to prove that the device is safe. Additional post marketing data will be generated to further substantiate safety and performance.

12.2 PMS Activities

The WIRION™ system and Gardia Medical are engaged in the process of post marketing surveillance (as required per MEDDEV 2.12). Applicable information on device performance, user experience, device malfunctions and complaints are collected and analyzed by the company management. Relevant information derived from PMS activities will contribute to the continuous assessment of the device and will be incorporated into this report.

12.3 Device Design and Clinical Indications

Currently device is clinically used in cardiovascular procedures. Company is concentrating at this stage, for marketing reasons, in the carotid and SVG applications where more data is generated.

12.4 Risks Vs. Benefits

Based on literature review and following successful completion of clinical investigation, we believe that the safety of the WIRION™ system is acceptable and risks are tolerable. Therefore, per company assessment, the benefits outweigh the risks for the WIRION™ system.

Appendix A: Claims made for the device

Indications, contraindications and potentially *adverse* effects of WIRION™ are as follows:

Indications

The WIRION™ Embolic Protection System is indicated for use as an embolic protection system to contain and remove embolic material during cardiovascular interventions.

Contraindications

- Do not use laser devices with the System.
- Any contraindication for PCI.

Potential adverse events

Based on the literature, and on clinical and commercial experience with the use of available comparable embolic protection systems, the following list includes possible adverse events associated with the use of EPDs:

- Access site adverse events (e.g. fistula, hematoma, hemorrhage, pseudoanneurysm, puncture site infection)
- Adverse reaction to antiplatelet/anticoagulation agents or contrast media
- Allergic reaction to device materials
- Amaurosis Fugax (CAS indication only)
- Aneurysm
- Angina (coronary indication only)
- Arrhythmia
- Arterial dissection
- Cardiac tamponade (coronary indication only)
- Death
- Device deformation, collapse, fracture or rapture
- Device thrombosis (acute and subacute)
- Embolization of air, debris, plaque or thrombus from mechanical disruption by the intervention, resulting in TIA or stroke
- Embolization or migration of the interventional device
- Emergency surgery
- GI bleeding due to anticoagulation
- Hemodynamic compromise (e.g. prolonged hypotension requiring treatment with intravenous medications)
- Infection
- Intimal falp
- Intracereberal bleed (CAS indication only)
- Ischemia
- Myocardial infarction (MI)

- Renal failure / insufficiency
- Restenosis of stented / dilated vessel
- Seizure
- Significant cardiac arrhythmia requiring treatment with medications and/or transvenous pacing
- Stent / filter entanglement / damage
- Stroke / cerebrovascular accident (CVA)
- Thrombosis
- Vasospasm
- Vessel dissection, perforation, or rupture

Additionally the IFU of the WIRION™ EPS stated the following adverse events:

- Angina
- Bleeding complications
- Bradycardia or arrhythmias, including ventricular fibrillation or tachycardia
- Congestive heart failure
- Damage to or dislocation of the implanted stent(s)
- Death
- Detachment and/or implantation of a component of the device
- Drug reaction, allergic reaction to contrast media, medications or device materials
- Emergent surgery
- Embolization of air, tissue, thrombus or other embolic debris
- End organ ischemia, vessel thrombosis or spasm
- Hypotension/hypertension
- Infection (local or systemic)
- Myocardial infarction
- No-reflow resulting from reduced blood flow through the Filter Unit
- Puncture site complications (i.e., vessel occlusion, hemorrhage, hematoma, pseudoaneurysm or arteriovenous fistula)
- Renal insufficiency, kidney failure, hematuria
- Stroke/cerebrovascular accident (CVA), transient ischemic attack (TIA) or seizure
- Vessel damage, dissection, occlusion, aneurysm, perforation, rupture or injury

Appendix B: Curriculum vitae of the authors

s22 [redacted]

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