Post-Market Clinical Study Plan

Multicenter observational cohort study to evaluate Cerebral AneurysmFlow Results in Occlusion (CARO)

Security Classification: **Confidential**

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APPROVAL

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REVISION HISTORY

Date	Rev.	Author	Changes/Comments
2018 Jan 09	1.0	Joris AH de Groot	Initial version
2018 Mar 13	2.0	Joris AH de Groot	Removed 3 month follow-up to better resemble current clinical practice Updated approval status in participating countries Added extra motivation for the multicenter nature of the study Minor correction to Flowchart Updated Section 10 Compliance Statement to secure compliance for all participating centers.

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SUMMARY

Identification of study device

AneurysmFlow R1.0 is an approved (CE labeled, cleared in US, Canada and Argentina), software tool intended to provide relevant information on the blood flow in a cerebral aneurysm and its parent artery based on angiography. It provides color coded and vector field representation of a digital subtraction angiography (DSA). It can quantify blood flow rates in the artery based on DSA and 3-D Rotational Angiogram (3DRA) data. It can visualize blood flow patterns in an aneurysm based on DSA data. Specifically, it calculates the Mean Aneurysm Flow Amplitude (MAFA) ratio to measure the volumetric flow rate quotient before and after Flow Diverter Stent (FDS) implantation in the region of interest.
It is manufactured by Philips Medical Systems B.V., a Philips Healthcare company.

Study design

This is a prospectively planned, single arm, observational, multicenter cohort study to assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 12 months after flow diverter placement.

Objectives

Primary objective:

- To assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 12 months after flow diverter placement.

Secondary objectives:

- To assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 6 months after flow diverter placement.
- To determine optimal MAFA ratio threshold.
- To register (serious) adverse events (i.e. re-operations, ruptures and deaths).
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Exploratory objectives:

- To evaluate the potential value of additional AneurysmFlow parameters for predicting full aneurysm occlusion 6 and 12 months after flow diverter placement.
- To evaluate the potential value of additional clinical variables to predict full aneurysm occlusion 6 and 12 months after flow diverter placement using multivariate logistic regression.

Primary and secondary endpoints

The primary endpoint is the prognostic value (i.e. c-statistic including confidence intervals) of the MAFA ratio with respect to full aneurysm occlusion (i.e. using the Raymond-Roy Occlusion Classification I on standard-of-care head imaging) 12 months after Flow Diverter Stent placement. Secondary endpoints are the prognostic value (i.e. c-statistic including confidence intervals) of the MAFA ratio with respect to full aneurysm occlusion on standard-of-care head imaging 6 months after flow diverter placement, the optimal threshold for the MAFA ratio and the number of adverse events.

Main inclusion criteria

- Subject with unruptured, ≥5mm saccular aneurysm(s) located in the anterior intracranial circulation and suitable for an endovascular treatment with a Flow Diverter Stent
- Subject is 18 years of age or older, or of legal age to give informed consent per state or national law
- Subject is available for clinical follow-ups

Main exclusion criteria

- Non-saccular brain aneurysm(s) (i.e., dissecting, fusiform, atherosclerotic, mycotic, bifurcational) Prior aneurysm treatment with either endovascular (stenting, coiling) or surgical (clipping) techniques
- Endovascular treatment assisted with coils or intracranial stents
- Significant or severe allergy to intra-arterial contrast medium uncontrolled by pre-procedure medications
- Severe kidney disease (e-GFR < 60)

- Subjects not willing (or able) to attend post FDS insertion standard-of-care follow up clinic visits requiring DSA, head MRI or CTA imaging
- Subject participates in a potentially confounding drug or device trial during the course of the study.
- Subject meets an exclusion criteria according to national law (e.g. age, pregnant woman, breast feeding woman)

No. of subjects

In total 120 subjects will be enrolled in the study. The enrollment period is expected to last for 1 year.

Study procedures

Physician investigators participating in this study are expected to follow their normal clinical practice in enrolling, treating and following patients with intracranial aneurysms that are amenable to treatment with flow diverter stents. No additional procedures are required of patients in order to participate in this observational study.

Pre-Screening

Patients presenting with intracranial saccular aneurysm(s) will be evaluated by the neuro interventional team, in accordance with institutional practice, to establish an appropriate treatment plan based on the patient's medical condition and available diagnostic screening procedures prior to recruitment in the study. More than one aneurysm in a single patient may be treated, but only the target aneurysm(s) treated with FDS devices initially will be considered as part of this study. If treatment of the aneurysm with the FDS is deemed appropriate, the institution's guidelines regarding their ethics committee and informed consent process will be followed.

Screening

After obtaining the consent form(s) approved by the local research ethics board (REB), the principal investigator will screen the potential investigation subjects for the CARO study. The principal investigator or his delegates on the study team will enter data in a pre-designed e-CRF. This will include patient demographics, relevant past medical and surgical history, and specific target aneurysm data along with pre-procedural/screening imaging details.

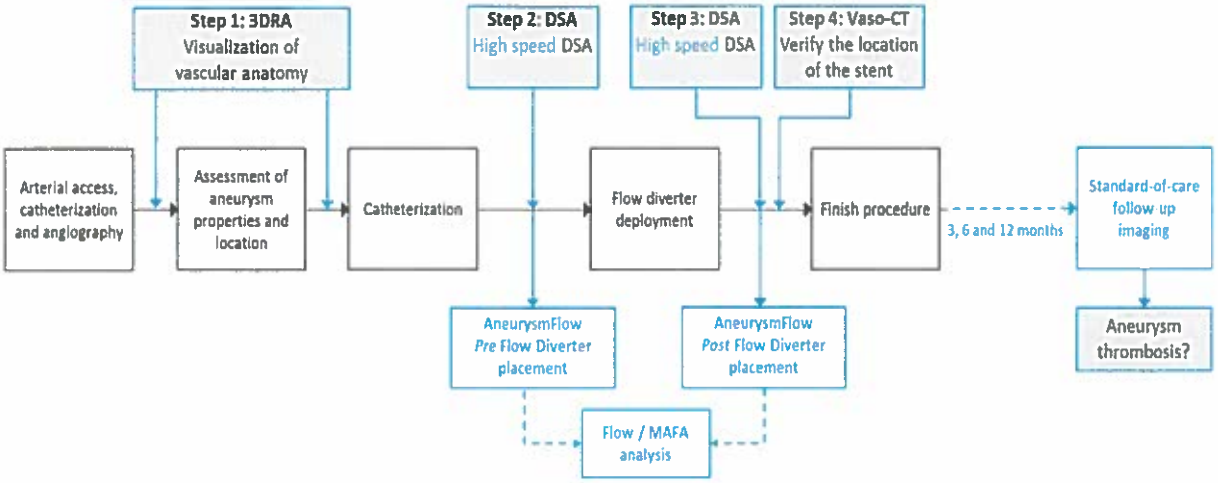
Only patients who meet all inclusion and none of the exclusion criteria will qualify for this study. The measurement and size of each aneurysm will be verified by the principal investigator. If the size of the aneurysm is acceptable, then it will be included in the study. It is recommended that this measurement should be done within 180 days before the procedure.

Index Procedure and Discharge

The investigator will proceed with standard of care procedures on the day of Index Procedure (i.e. FDS insertion) for the target aneurysm(s). Then, endovascular treatment procedure details should be provided under the "INDEX PROCEDURE & DISCHARGE" field for each eligible patient.
Blood flow velocity will be calculated using the dedicated software AneurysmFlow (Philips Healthcare, Best, The Netherlands), which will be installed on standard of care imaging equipment. For this purpose, digital subtraction angiograms will be acquired during the procedure; just before and right after placement of the FDS.

Calculation of blood flow velocity will be performed automatically on the AneurysmFlow software. The operator will have access to the results of the calculation in addition to all of the regular information that is at his/her disposal during routine clinical practice. There are no additional devices or medications required for the study. The AneurysmFlow software uses standard-of-care 2D DSA and 3D-RA image sequences to determine this flow information. All raw image sequences will be stored for future reference.

Figure 1 shows the workflow for using the AneurysmFlow software in this study.



In step 1 a 3D rotational angiogram (3D-RA) will be performed in the neuro-interventional suite with the x-ray C-arm to acquire a 3D image volume of the aneurysm anatomy to be treated. From this 3D-RA, an optimal viewing angle for the C-arm will be determined to obtain good flow information. This angle should show the parent artery, aneurysm neck and aneurysm itself clearly without any overlap. The 3D-RA will also help to determine a good C-arm viewing angle to help position and deploy the FDS across the aneurysm.

In Step 2 a 2D DSA x-ray run with contrast agent injection (i.e. advised injection rate 1.5 to 2 cc/s) will be acquired at the optimal C-arm viewing angle determined by the 3D-RA scan to obtain dynamic blood motion information before FDS deployment at the location of the aneurysm. If the initial contrast agent injection was insufficient, the injection will be altered and repeated with another DSA run to obtain high quality image information. The FDS will then be placed at the location of the aneurysm.

In Step 3, after FDS deployment, a second DSA run with contrast agent will be acquired (i.e. injection rate ≈1.5 to 2 cc/s) at the optimal C-arm viewing angle determined from the 3D-RA to qualitatively evaluate blood motion in the region of the aneurysm after deployment of the FDS. The C-arm angle and injection rate of this second DSA run (post FDS deployment) must be the same as the first DSA run (pre FDS deployment). The 2 DSA runs and the 3D-RA image volume will automatically be sent to the AneurysmFlow workstation right after they are acquired. If the FDS is ballooned after placement, the physician is asked to repeat Step 3 after ballooning.

In Step 4 a routine VasoCT scan, which is another 3D rotational x-ray C-arm scan, will then be performed with the x-ray C-arm in the neuro-interventional suite to evaluate the 3D apposition of the deployed FDS with respect the vessel wall.

The region of interest around the aneurysm and the corresponding arterial segment from which it has developed will be automatically segmented by the AneurysmFlow software, but manual controls are available in the software if modifications to the anatomical segment of interest are desired by the interventionalist. These modifications can be performed by an appropriately trained study member. The software will then automatically calculate the flow parameters of the aneurysm both before and after FDS deployment, along with the MAFA ratio.

For this study, the operator will have the choice of selecting which target aneurysms are amenable to FDS treatment. Patients that have single or multiple target aneurysms that are suitable for FDS treatment as a first treatment step would be acceptable for this study. Each target aneurysm in the patient will have a separate CRF sub-form to fill out. Additionally, each target aneurysm sub-form can be further divided into several FDS sub-forms to account for multiple flow diverters, if needed. To summarize, if the patient has more than one target aneurysm and/or needs more than one flow diverter per aneurysm, then a sub-form on the CRF will need to be filled out for each aneurysm and for each FDS used.

As shown in Figure 1, if a target aneurysm is treated with a FDS (or more than one) initially, and is then treated using another approach (such as coiling) then this target aneurysm can remain included as part of the study. However, if a target aneurysm is treated using a non-FDS approach initially (such as with

coiling), followed by placement of an FDS or other approach, then the aneurysm will be excluded from the study.

The MAFA ratio will be calculated after the placement of each FDS. For each FDS, this ratio will be determined with the flow information before any stents were placed and also with the flow information after each FDS was placed. The final MAFA ratio will be calculated using the flow information before any FDS devices were placed and using the flow information after the last FDS was placed. Clinical and imaging outcomes of a procedure will be assessed using a combination of the flow metrics calculated by the AneurysmFlow software available to the operator during interventional treatment in addition to information that is routinely acquired during FDS placement. This information acquired across the patient population in the study will also contribute to determine more precise MAFA ratio thresholds to improve prediction of complete aneurysm occlusion after FDS placement. This study will not make any recommendation on patient management or on treatment strategy. Also, this software will not disrupt standard-of-care workflow for the interventionalist.

Follow-Ups (6 and 12 months)
All registry patients treated with FDS are expected to follow their routine post treatment clinical visits, which will include a standard-of-care head imaging (e.g. CTA, MRA and/or DSA) test to classify aneurysm occlusion (i.e. Raymond-Roy Occlusion Classification I (Roy *et al.*, 1997)) at 6 months (±49 days) and 12 months (±49 days). During the 6 and 12 month follow up visits, patient medical charts will be accessed to collect adverse events (if applicable) and document any post-treatment neurological deterioration (neurological assessment, mRs scale). De-identified data (i.e. clinical notes, imaging reports etc.) will be entered in the relevant e-CRF sections.

Follow-up visit	Start visit window (days post-procedure)	Target date (days post-procedure)	End visit window (days post-procedure)
6-months	134	183	225
12 months	316	365	414

Adverse Events
All (serious) adverse events (i.e. re-operations, ruptures and deaths) whether or not related to the investigational device will be collected and reported conform local rules and regulations.

Follow up

The subjects will be followed-up at 6 and 12 months according to regular clinical standard of care.

Duration of the study

The total duration of the study is expected to take approximately 2.5 years. Patient enrollment will take place between March 2018 and September 2019. Each subject will be in the study for 1 year (follow-up).

1. DEVICE DESCRIPTION

1.1. Summary description of the study device

AneurysmFlow R1.0 is an approved (CE labeled, cleared in US, Canada and Argentina), software tool intended to provide relevant information on the blood flow in a cerebral aneurysm and its parent artery based on angiography. It provides color coded and vector field representation of a digital subtraction angiography (DSA). It can quantify blood flow rates in the artery based on DSA and 3-D Rotational Angiogram (3DRA) data. It can visualize blood flow patterns in an aneurysm based on DSA data.
Specifically, it calculates the Mean Aneurysm Flow Amplitude (MAFA) ratio to measure the volumetric flow rate quotient before and after Flow Diverter Stent (FDS) implantation in the region of interest.
It is manufactured by Philips Medical Systems B.V., a Philips Healthcare company.

When treating intracranial aneurysms, neuro-interventionalists are interested in the flow patterns inside and around those aneurysms because these flow patterns are likely to impact the natural evolution of aneurysms, such as growth and risk of rupture. In order to evaluate the flow, physicians use high speed angiograms. By

observing and analyzing the displacement and dispersion of the injected contrast they develop an understanding and can measure the rate of the blood flow.

The Aneurysm Flow Visualization option serves to extract and enhance the flow patterns from those high speed angiograms, assisting the physician in the observation and analysis of these patterns.

Aneurysm Flow Visualization does not change the basic functionality of the Interventional Workspot and/or the interventional X-ray system. Users need to adhere to the normal handling and safety precautions as mentioned in the IFU.

The study device includes a software release number to permit full identification.

The manufacturer of the study device is:
Philips Medical Systems Nederland B.V.
Veenpluis 4-6
5684 PC Best
The Netherlands

1.2. Intended Purpose

AneurysmFlow is a software tool intended to provide relevant information on the blood flow in a cerebral aneurysm and its parent artery based on angiography.
AneurysmFlow is a software medical device and is intended to be used in combination with a Philips interventional X-ray system and 3D rotational angiogram (3D-RA) data.
AneurysmFlow is a software product (Interventional Tool) that provides color coded and vector field representation of a digital subtraction angiography (DSA). It can quantify blood flow rates in the artery based on DSA and 3D-RA data. It can visualize blood flow patterns in an aneurysm based on DSA data. It can also provide a side by side visual and quantitative comparison between two acquisitions.

1.2.1. Medical Purpose

AneurysmFlow assists during endovascular procedures for treating of saccular cerebral aneurysms, by:

- Visualization of blood flow patterns in the aneurysm and parent vessel, based on DSA.
- Quantification of the blood flow in the aneurysm parent vessel, based on DSA and 3D-RA.
- Comparison of blood flow, both visual and quantified between two acquisitions.

1.2.2. Patient Population

AneurysmFlow is suitable for use with patients who were elected for a cerebral endovascular aneurysm treatment procedure using fluoroscopy.

The study device manual contains safety precautions and handling of the study device.

1.2.3. Clinical Environment

AneurysmFlow is intended to be used in the control room and in the exam room of an interventional suite or hybrid operating room. The system is connected to a Philips Interventional X-ray system.

1.3. Necessary training and experience needed to use the research device

The Intended Operator profile is a clinical specialist who is fully skilled and responsible for sound clinical judgment and for applying the best clinical procedure, for example (but not limited to): interventional neuroradiologists, skilled radiology technicians (or nurses) assisting the physician, vascular/endovascular/neuro surgeons.

1.4. Materials that will be in contact with tissues or body fluids

No materials of the study device will be in contact with tissue or body fluids.

1.5. Device Traceability

The study device includes a name, including software version and accessories to permit full identification. Device traceability will be maintained by Philips. Records shall be kept to document when the device is received, installed or uninstalled at the hospital.

2. JUSTIFICATION FOR THE DESIGN OF THE STUDY

Intracranial aneurysms IA(s) are a prevalent medical condition for which their rupture can produce a major impact in a patient's life and also in society because of collective costs associated with disability recovery, treatment and rehabilitation (Bruno *et al.*, 1998). The physiopathology of IA(s) is still undefined and there is no corresponding animal model to better study and understand the disease (Bruno *et al.*, 1998). Treatment of IA(s) progressed over the years with advances in the surgical field and the development of minimally invasive techniques (Krings *et al.*, 2011). This progress generated a major impact on clinical practice such as the development of coil embolization with or without balloon remodeling, intracranial stent assisted coiling and more recently, implantation of flow diverting stent (FDS) devices (Pereira *et al.*, 2013). An FDS is an endoluminal prosthesis that changes the intra-aneurismal flow and progressively replaces it with thrombosis until the whole aneurysm is excluded from blood circulation, along with parent vessel remodeling (Lylyk *et al.*, 2009). This technology brought a significant advance to the neuroradiology field and some important questions started to be raised concerning its mode of use, efficacy, procedural risks, post procedural bleeding risk and time taken to complete aneurysm thrombosis after treatment (Lylyk *et al.*, 2009). The evaluation of this new technology remains uncertain, but over the past years, many discussions and meeting sessions have been dedicated to intracranial hemodynamics and aneurysmal flow.

A new method to determine intracranial flow from x-ray digital subtracted angiography (DSA) images during endovascular treatment procedures has been developed. This method forms the basis of the new Philips AneurysmFlow visualization software used for the proposed research in this protocol. The method is based on optical flow analysis to estimate velocity vectors from both temporal and spatial variations of contrast agent density, measured from 2D time-series DSA images (Bonnefous *et al.*, 2012).

2.2 Data from Pre-Clinical Studies

The technique behind the AneurysmFlow software is based on the acquisition of 2D DSA sequences, in combination with a 3D rotational angiography (3D-RA) acquisition. These image acquisitions are already part of routine, standard-of-care imaging for brain aneurysm patients. Using the AneurysmFlow software, the proposed technique measures the flow values from an angiographic DSA sequence. It exploits the transportation of contrast agent injected into the arterial blood stream. Due to the pulsatile character of the blood flow, contrast media patterns are created that propagate in the vascular network. Using image processing techniques, velocity profiles are obtained from the motion of these patterns. Finally, the velocity profiles are converted into flow values. To validate the approach described above, it has been tested using vascular phantoms. In an in vitro setup, X-ray based flow estimations were compared to flow values recorded by flow meters. Furthermore, various contrast medium injection protocols were explored to determine the appropriate injection parameters. The results of the in vitro tests suggested that the proposed technique can be used in routine clinical conditions with standard image acquisition protocols (Bonnefous *et al.*, 2012).

2.3 Clinical Experience

The clinical feasibility of the technique mentioned above using AneurysmFlow was previously evaluated using several clinical cases acquired during interventional procedures. This work compared Doppler ultrasound flow measurements with X-ray based flow measurements. The outcomes of these tests suggested that the use of the AneurysmFlow software is feasible during interventional procedures (Bonnefous *et al.*, 2012). Further validation of the technique was performed on a set of 22 clinical cases (Pereira *et al.*, 2014). During that study, blood flow velocity in the internal carotid artery measured using AneurysmFlow was validated with Doppler sonography. Mean flow rates measured with the AneurysmFlow method significantly matched Doppler sonography measurements (slope regression coefficient, $b=0.83 \pm 0.19$, $P=0.05$). These initial results proved that blood flow velocity measurements can be measured reliably and accurately using the AneurysmFlow software.
The AneurysmFlow software has also been used for patients presenting with saccular unruptured IAs, to assess both flow modification after FDS implantation and correlation with aneurysm thrombosis. A metric has been defined, the Mean Aneurysm Flow Amplitude (MAFA) ratio, to measure the volumetric flow rate quotient before and after FDS implantation in the region of interest. Though preliminary, this MAFA ratio

index predicted thrombosis accurately with commercialized flow diverter stents. This was the first time blood flow could be appraised in in-vivo intracranial vessels during endovascular procedures (Pereira *et al.*, 2013). Recently, a larger study conducted by the coordinating investigator confirmed these results (not yet published).

2.1. Clinical study Justification

Previously published data has indicated that blood flow changes measured by the AneurysmFlow software predicted thrombosis accurately with commercialized Flow Diverting Stents (FDS).(Pereira *et al.*, 2014) The purpose of the clinical study in this protocol is to investigate the ability of the intra-operative, intra-aneurysmal flow evaluation to assist with the treatment of intracranial aneurysms ≥ 5mm using FDS.

The clinical hypothesis of this protocol to be tested is that by knowing the potential aneurysm occlusion rates by calculation of the MAFA ratio during a procedure, one might be able to adapt the therapeutic strategy intra-operatively to maximize the flow diverting effect for inducing complete aneurysm occlusions. Different strategies can be used to accelerate the aneurysm occlusion such as the addition of another stent layer or stent-assisted coiling with a jailed micro-catheter. Current treatment strategies are based on personal physician preferences or on subjective evaluation of aneurysm stagnation.
In this protocol, we propose to test a more quantitative assessment of the intra-aneurysmal flow, which may be able to support intra-operative clinical decisions which improve the occlusion rate of IA(s) after FDS treatment. Additionally, data collected in this proposed study will further expand the body of clinical knowledge concerning the relationship between blood flow metrics (including but not limited to the MAFA ratio) as determined by the AneurysmFlow software and clinical outcome in patients undergoing treatment for intracranial aneurysms with FDS.

3. OBJECTIVES AND HYPOTHESES

3.1. Primary objective

The primary objective of this clinical study is:

- To assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 12 months after flow diverter placement.

3.2. Secondary objectives

The secondary objective are:

- To assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 6 months after flow diverter placement.
- To determine optimal MAFA ratio threshold.
- To register (serious) adverse events (i.e. re-operations, ruptures and deaths).

3.3. Exploratory objectives

The exploratory objectives are:

- To evaluate the potential value of additional AneurysmFlow parameters for predicting full aneurysm occlusion 6 and 12 months after flow diverter placement.
- To evaluate the potential value of additional clinical variables to predict full aneurysm occlusion 6 and 12 months after flow diverter placement using multivariate logistic regression.

4. STUDY DESIGN

4.1. General

This is a prospectively planned, single arm, observational, multicenter cohort study to assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 12 months after flow diverter placement.

A prospective observational multi-center study has been chosen to observe standard of care with the study device. The multi-center nature of the study will not only enable more efficient patient enrollment and thus a

shorter study duration, but it will also provide information on heterogeneity between centers and enable (cross) validation of study results.

4.2. Study device exposure

This is an observational study, in which data is collected during the regular clinical procedure: a treatment of an aneurysm with (a) flow diverter(s). During this procedure, high-speed angiograms will be made before and after placement of the flow diverter device. Clinical decision making is not affected by this study.

There are no additional devices or medications required for the study.

4.3. Subjects

4.3.1. In- and exclusion criteria

Subjects participating in the study will be carefully selected based on the next inclusion and exclusion criteria.

4.3.1.1. *Inclusion criteria*

- Subject with unruptured, ≥5mm saccular aneurysm(s) located in the anterior intracranial circulation and suitable for an endovascular treatment with a Flow Diverter Stent
- Subject is 18 years of age or older, or of legal age to give informed consent per state or national law
- Subject is available for clinical follow-ups

4.3.1.2. Exclusion criteria

- Non-saccular brain aneurysm(s) (i.e., dissecting, fusiform, atherosclerotic, mycotic, bifurcational) Prior aneurysm treatment with either endovascular (stenting, coiling) or surgical (clipping) techniques
- Endovascular treatment assisted with coils or intracranial stents
- Significant or severe allergy to intra-arterial contrast medium uncontrolled by pre-procedure medications
- Severe kidney disease (e-GFR < 60)
- Subjects not willing (or able) to attend post FDS insertion standard-of-care follow up clinic visits requiring DSA, head MRI or CTA imaging
- Subject participates in a potentially confounding drug or device trial during the course of the study.
- Subject meets an exclusion criteria according to national law (e.g. age, pregnant woman, breast feeding woman)

4.3.2. Enrollment and duration

Subjects are considered to be enrolled in the study after they have signed the informed consent form. The subjects will be followed-up at 6 and 12 months according to regular clinical standard of care.

The total duration of the study is expected to take approximately 2.5 years. Patient enrollment will take place between March 2018 and September 2019. Each subject will be in the study for 1 year (follow-up).

4.3.3. Number of subjects

In total 120 subjects will be enrolled in the study. The enrollment period is expected to last for 1 year.

See section 5 Statistical considerations for more details on the number of subjects.

4.3.4. Subject withdrawal or discontinuation

Subjects can withdraw informed consent at any time during the clinical investigation. There are no specific criteria for subject withdrawal or discontinuation.

4.4. Procedures

Physician investigators participating in this study are expected to follow their normal clinical practice in enrolling, treating and following patients with intracranial aneurysms that are amenable to treatment with flow diverter stents. No additional procedures are required of patients in order to participate in this observational study.

Pre-Screening
Patients presenting with intracranial saccular aneurysm(s) will be evaluated by the neuro interventional team, in accordance with institutional practice, to establish an appropriate treatment plan based on the patient's medical condition and available diagnostic screening procedures prior to recruitment in the study. More than one aneurysm in a single patient may be treated, but only the target aneurysm(s) treated with FDS devices initially will be considered as part of this study. If treatment of the aneurysm with the FDS is deemed appropriate, the institution's guidelines regarding their ethics committee and informed consent process will be followed.

Screening
After obtaining the consent form(s) approved by the local research ethics board (REB), the principal investigator will screen the potential investigation subjects for the CARO study. The principal investigator or his delegates on the study team will enter data in a pre-designed e-CRF. This will include patient demographics, relevant past medical and surgical history, and specific target aneurysm data along with pre-procedural/screening imaging details.

Only patients who meet all inclusion and none of the exclusion criteria will qualify for this study. The measurement and size of each aneurysm will be verified by the principal investigator. If the size of the aneurysm is acceptable, then it will be included in the study. It is recommended that this measurement should be done within 180 days before the procedure.

Index Procedure and Discharge
The investigator will proceed with standard of care procedures on the day of Index Procedure (i.e. FDS insertion) for the target aneurysm(s). Then, endovascular treatment procedure details should be provided under the "INDEX PROCEDURE & DISCHARGE" field for each eligible patient.
Blood flow velocity will be calculated using the dedicated software AneurysmFlow (Philips Healthcare, Best, The Netherlands), which will be installed on standard of care imaging equipment. For this purpose, digital subtraction angiograms will be acquired during the procedure; just before and right after placement of the FDS.

Calculation of blood flow velocity will be performed automatically on the AneurysmFlow software. The operator will have access to the results of the calculation in addition to all of the regular information that is at his/her disposal during routine clinical practice. There are no additional devices or medications required for the study. The AneurysmFlow software uses standard-of-care 2D DSA and 3D-RA image sequences to determine this flow information. All raw image sequences will be stored for future reference.

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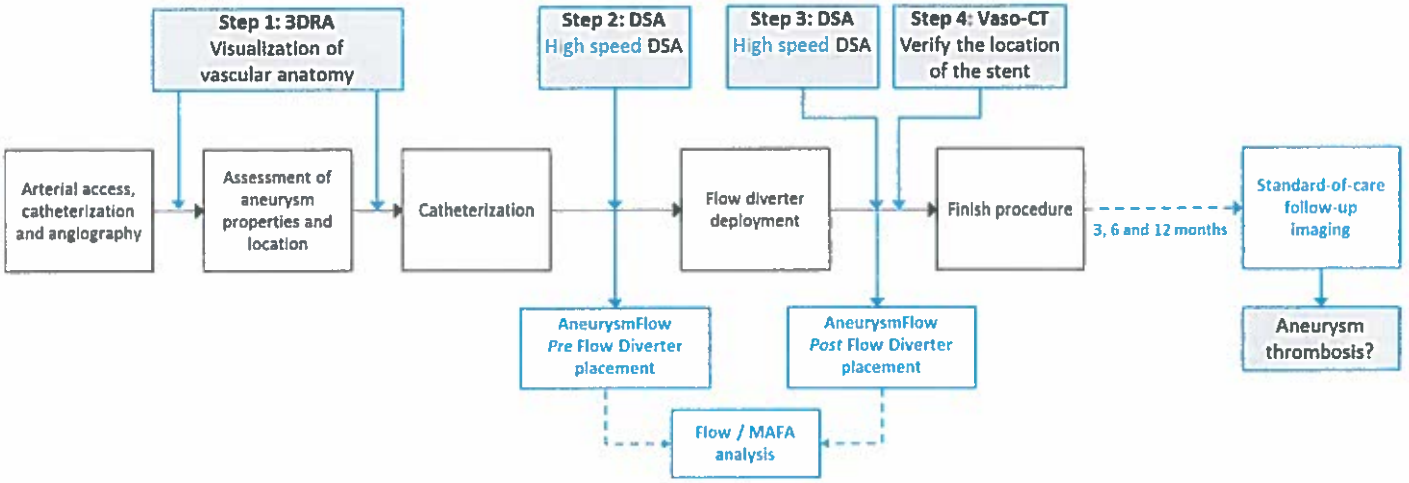

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In Step 3, after FDS deployment, a second DSA run with contrast agent will be acquired (i.e. injection rate ≈1.5 to 2 cc/s) at the optimal C-arm viewing angle determined from the 3D-RA to qualitatively evaluate blood motion in the region of the aneurysm after deployment of the FDS. The C-arm angle and injection rate of this second DSA run (post FDS deployment) must be the same as the first DSA run (pre FDS deployment). The 2 DSA runs and the 3D-RA image volume will automatically be sent to the AneurysmFlow workstation right after they are acquired. If the FDS is ballooned after placement, the physician is asked to repeat Step 3 after ballooning.

In Step 4 a routine VasoCT scan, which is another 3D rotational x-ray C-arm scan, will then be performed with the x-ray C-arm in the neuro-interventional suite to evaluate the 3D apposition of the deployed FDS with respect the vessel wall.

The region of interest around the aneurysm and the corresponding arterial segment from which it has developed will be automatically segmented by the AneurysmFlow software, but manual controls are available in the software if modifications to the anatomical segment of interest are desired by the interventionalist. These modifications can be performed by an appropriately trained study member. The software will then automatically calculate the flow parameters of the aneurysm both before and after FDS deployment, along with the MAFA ratio.

For this study, the operator will have the choice of selecting which target aneurysms are amenable to FDS treatment. Patients that have single or multiple target aneurysms that are suitable for FDS treatment as a first treatment step would be acceptable for this study. Each target aneurysm in the patient will have a separate CRF sub-form to fill out. Additionally, each target aneurysm sub-form can be further divided into several FDS sub-forms to account for multiple flow diverters, if needed. To summarize, if the patient has more than one target aneurysm and/or needs more than one flow diverter per aneurysm, then a sub-form on the CRF will need to be filled out for each aneurysm and for each FDS used.

As shown in Figure 1, if a target aneurysm is treated with a FDS (or more than one) initially, and is then treated using another approach (such as coiling) then this target aneurysm can remain included as part of the study. However, if a target aneurysm is treated using a non-FDS approach initially (such as with coiling), followed by placement of an FDS or other approach, then the aneurysm will be excluded from the study.

The MAFA ratio will be calculated after the placement of each FDS. For each FDS, this ratio will be determined with the flow information before any stents were placed and also with the flow information after each FDS was placed. The final MAFA ratio will be calculated using the flow information before any FDS devices were placed and using the flow information after the last FDS was placed. Clinical and imaging outcomes of a procedure will be assessed using a combination of the flow metrics calculated by the AneurysmFlow software available to the operator during interventional treatment in addition to information that is routinely acquired during FDS placement. This information acquired across the patient population in the study will also contribute to determine more precise MAFA ratio thresholds to improve prediction of complete aneurysm occlusion after FDS placement. This study will not make any recommendation on patient management or on treatment strategy. Also, this software will not disrupt standard-of-care workflow for the interventionalist.

Follow-Ups (6 and 12 months)
All registry patients treated with FDS are expected to follow their routine post treatment clinical visits, which will include a standard-of-care head imaging (e.g. CTA, MRA and/or DSA) test to classify aneurysm occlusion (i.e. Raymond-Roy Occlusion Classification I (Roy *et al.*, 1997)) at 6 months (±49 days) and 12 months (±49 days). During the 6 and 12 month follow up visits, patient medical charts will be accessed to collect adverse events (if applicable) and document any post-treatment neurological deterioration (neurological assessment, mRs scale). De-identified data (i.e. clinical notes, imaging reports etc.) will be entered in the relevant e-CRF sections.

Follow-up visit	Start visit window (days post-procedure)	Target date (days post-procedure)	End visit window (days post-procedure)
6-months	134	183	225
12 months	316	365	414

Adverse Events
All (serious) adverse events (i.e. re-operations, ruptures and deaths) whether or not related to the investigational device will be collected and reported conform local rules and regulations.

4.5. Monitoring Plan

Monitoring will be performed by a trained person appointed by Philips to ensure compliance with the investigation plan, applicable national regulations and international standards, patient safety and data validity. The Sponsor may designate one or more individuals to monitor the progress of a clinical study. The Sponsor may also delegate the monitoring responsibilities to a third party. However, the Sponsor remains ultimately responsible for the conduct of the study. The Institution is responsible for the appropriate de-identification of subject data. The investigational site should provide access to the source data of the subjects.

All regulatory documents (e.g. MEC/IRB approval, contracts, etc.) will be reviewed for each actively participating center.

The first visit will occur as soon as possible after the first subject is enrolled at each study site. The monitoring schedule is based on the following considerations: enrollment rate, study compliance at the center, magnitude of data corrections required, study stage (e.g. start-up or follow-up), complexity of the investigation, IRB/MEC request, audit/inspection.

Critical data and processes will be monitored for this study prior to clinical report completion based on a risk based monitoring approach. Dependent on the risk a high or lower sample will be monitored.
The monitor will review critical clinical data that effect study endpoints. Data collection for reasons other than to support the protocol-defined endpoints will not be monitored.
A close-out visit for sites that have enrolled subjects will be conducted once the site has completed collecting data for the study.

Names of the monitor(s) can be found in Appendix II of this protocol. An update of this list can be provided to the site under separate cover.

5. STATISTICAL CONSIDERATIONS

Baseline patient characteristics and follow-up results will be summarized descriptively using frequencies and percentages or summary statistics like means and medians (including confidence intervals and interquartile ranges). Multiple imputation methods will be used to correct for missing data (Rubin, 1987).

5.1. Sample Size Justification

The total sample size for this study was calculated using the following formulas for Receiver Operating Characteristics Studies (Obuchowski, 2000):

$$n_D = \frac{[z_\alpha \sqrt{0.0792 \times (1 + 1/\kappa)} + z_\beta \sqrt{V(\hat{\theta})}]^2}{(\theta - 0.5)^2}$$

where V(θ̂) is the variance function of θ̂, given by:

$$V(\hat{\theta}) = (0.0099 \times e^{-A^2/2}) \times ([5A^2 + 8] + [A^2 + 8]/\kappa)$$

i.e., the variance of θ̂ is equal to V(θ̂)/nD; A = Φ−1(θ) × 1.414; Φ−1 is the inverse of the cumulative normal distribution function; κ is the ratio of the number of control patients (nC) to the number of diseased patients (nD) in the study sample (i.e., κ = nC/nD); θ is the conjectured area under the ROC curve (under the alternative hypothesis); zα is the upper αth percentile of the standard normal distribution, where α is the type I error rate (usually α = 0.05); and zβ is the upper βth percentile of the standard normal distribution, where β is the type II error rate (often β = 0.10 or 0.20).

Assuming k=0.25 (i.e., 4 times as many occluded aneurysms than non-occluded aneurysms after 1 year), a fair AUC of 0.70, a type I error of 0.05 and a type II error rate of ≤0.10 (power ≥0.90), a total of 100 subjects should be included in the study. This total number of 100 subjects also accommodates the pre-planned explorative multivariate analysis allowing inclusion of 8 candidate predictors including AneurysmFlow (Peduz *et al.*, 1996). Allowing for an expected drop-out rate of 15% we aim to include a total of 120 patients into the study.

Any deviation from the planned analysis described below will be documented with justification in the final clinical end report.

5.2. General Consideration

The primary analysis of the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 12 months after flow diverter placement will be performed including all subjects who underwent treatment. Baseline patient characteristics and follow-up results will be summarized descriptively using frequencies and percentages or summary statistics like means and medians (including confidence intervals and interquartile ranges). Multiple imputation methods will be used to correct for missing data (Rubin, 1987). All statistical analysis will be performed using R statistical software (www.https://www.r-project.org)

5.3. Subject disposition

Subject disposition, including the total number of subjects evaluated will be presented. In addition, a listing will be provided with the reasons for why the subject was not evaluated.

5.4. Primary objective

Objective
To assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 12 months after flow diverter placement.

Endpoint

The primary endpoint is the prognostic value (i.e. c-statistic including confidence intervals) of the MAFA ratio with respect to full aneurysm occlusion (i.e. Raymond-Roy Occlusion Classification I (Roy *et al.*, 1997)on standard-of-care head imaging) 12 months after flow diverter placement.

Experimental design
We will use logistic regression analysis to evaluate the univariate predictive association between the index test (i.e. the MAFA ratio) and complete aneurysm occlusion (i.e. complete occlusion yes/no) at 12 months (Moons *et al.*, 2012). All subjects with complete follow-up will be included in this analysis.

Presentation format
The primary endpoint will be presented using an ROC curve including the c-statistic and confidence intervals.

5.5. Secondary objectives

5.5.1. Secondary objective: Predictive value at 6 months follow-up

Objective
To assess the prognostic value of the MAFA ratio for predicting full aneurysm occlusion 6 months after flow diverter placement.

Endpoint
The secondary endpoint is the prognostic value (i.e. c-statistic including confidence intervals) of the MAFA ratio with respect to full aneurysm occlusion (i.e. Raymond-Roy Occlusion Classification I (Roy *et al.*, 1997) on standard-of-care head imaging) 6 months after flow diverter placement.

Experimental design
We will use logistic regression analysis to evaluate the univariate predictive association between the index test (i.e. the MAFA ratio) and complete aneurysm occlusion on standard-of-care head imaging at 6 months (Moons *et al.*, 2012). All subjects with complete follow-up will be included in this analysis.

Presentation format
This secondary endpoint will be presented using a ROC curves including the c-statistic and confidence intervals.

5.5.2. Secondary objective: Optimal MAFA ratio threshold

Objective
To determine optimal MAFA ratio threshold.

Endpoint
The endpoint for this secondary analysis is the optimal threshold to make treatment decisions.

Experimental design
To determine the optimal threshold for the MAFA ratio, ROC analysis will be performed. The optimal threshold for clinical decision making will be determined using net-benefit analysis (Mallett *et al.*, 2012). Net benefit incorporates estimates of prevalence and misclassification costs, and it is clinically interpretable since it reflects changes in correct and incorrect diagnoses when a new diagnostic test is introduced.

Presentation format
This secondary analysis will be presented within (the legend of) the various ROC curves composed for the primary and secondary objectives.

5.5.3. Secondary objective: Adverse events

Objective
To register (serious) adverse events (i.e. re-operations, ruptures and deaths).

Endpoint

The endpoint fort his secondary analysis is the (total) number of adverse events.

Experimental design
The number of adverse events will be described using frequencies and percentages

Presentation format
The (total) number of adverse events will be presented in tabular format.

5.6. Exploratory objectives

5.6.1. Exploratory objective: Potential value additional AneurysmFlow parameters

Objective

- To evaluate the potential value of additional AneurysmFlow parameters for predicting full aneurysm occlusion 6 and 12 months after flow diverter placement.

Endpoint
The endpoint of this exploratory objective is the identification of one or more additional AneurysmFlow parameters for predicting full aneurysm occlusion 6 and 12 months after flow diverter placement.

Experimental design
To explore which additional AneurysmFlow parameters (e.g. maximum inflow, number of jets) independently contribute to the prediction of, i.e., are associated with, full aneurysm occlusion 6 and 12 months after flow diverter placement predictor finding methods will be used. These methods will be applied to the raw imaging data, collected during the study.

Presentation format
The identified additional AneurysmFlow parameters for predicting full aneurysm occlusion 6 and 12 months after flow diverter placement will be presented in a tabular form, including the strength of the association.

5.6.2. Exploratory objective: Potential Value of Adding Clinical Variables

Objective

- To evaluate the potential value of additional clinical variables to predict full aneurysm occlusion 6 and 12 months after flow diverter placement using multivariate logistic regression.

Endpoint
The endpoint of this exploratory objective is the final selected multivariate logistic regression model after shrinkage including its performance measures (i.e. calibration and discrimination).

Experimental design
To explore which clinical variables have (independent) added value for predicting full aneurysm occlusion 6 and 12 months after flow diverter placement we use multivariate logistic regression methods. Candidate predictors (e.g., aneurysm location, size, medication) will be selected based on literature and expert opinion. Then, variable selection (i.e. backward selection using Akaike Information Criteria) will be used to determine the final set of predictors. Finally, internal validation and shrinkage of the model (i.e. using bootstrap methods) will be performed to correct for optimism. Information gained from this exploratory analysis can be used as valuable input for a future clinical prediction model for aneurysm occlusion.

Presentation format
The final prediction model and its performance measures (i.e. calibration and discrimination) will be presented using graphs (i.e. calibration curve and ROC curve) and tables (i.e. model including intercept and regression coefficients, c-statistic and calibration slope).

6. DATA MANAGEMENT

An e-CRF will be used to collect de-identified medical history, subjects demographics, procedure related information, protocol deviations, adverse events and device deficiencies.

The e-CRF will be used for data review, data cleaning and issuing and resolving queries. This e-CRF is a web-based e-CRF which is password protected and is 21 CFR part 11 compliant. At the end of the study the data will be stored as a frozen dataset and will be retained.

Raw image data is collected directly from the detector, and therefore is free from any subject information. All other exported data will be de-identified. This data will be collected and stored in a secure location.

6.1. Retention period

The investigator shall maintain the records related to this study during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application in the US or a notice of completion of a product development protocol. Or longer if national regulation requires this.
Philips will maintain the records for the same period as the investigator or for a period of device End of Life (EoL) plus 15 years, whichever is later.

The sponsor and principal investigator shall take measures to prevent accidental or premature destruction of these documents.

7. AMENDMENTS TO THE CLINICAL STUDY PLAN

Amendment to the Clinical investigational plan and the informed consent shall be notified to, or approved by the Medical Ethics Committee (MEC) and regulatory authority. The version number and date of amendments shall be documented. Significant changes (such as device modifications, study procedures) shall be discussed with the principal investigator prior approval. All changes will be documented with a justification and described in the latest version of the Clinical Investigation Plan.

8. DEVIATIONS FROM THE CLINICAL STUDY PLAN

The investigator is not allowed to deviate from the clinical study plan or to enroll subjects that do not comply with all inclusion and exclusion criteria. Under emergency circumstances, deviations from the clinical study plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the MEC. Such deviations shall be documented and reported to the sponsor and the MEC as soon as possible.
All deviations from the clinical study plan will be documented with date, subject, reason, actions taken and if the deviation affects subject's rights, safety and well-being or the scientific integrity of the clinical study. The deviation shall be notified to the Sponsor as soon as possible via the e-CRF. Deviations will be reviewed by the sponsor and in case of serious or repetitive deviations a corrective action plan may represent a need to initiate a corrective action plan with the principal investigator. In some cases, necessitate suspension of enrollment at the site or ultimately the principal investigator will be disqualified.

9. DEVICE ACCOUNTABILITY

The device used in this study (i.e. AneurysmFlow) is market released, CE marked and cleared in US, Canada and Argentina. AneurysmFlow is not regulated in India as a software medical device. Therefore no device accountability (e.g. documented return and disposal) will be performed.

10. STATEMENTS OF COMPLIANCE

This clinical study shall be conducted in accordance with the clinical study plan, and with the ethical principles that have their origin in the Declaration of Helsinki and all applicable regional and/or national regulations.

Furthermore, in Europe this clinical Investigation shall be conducted in accordance with the International Standards ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice and the Medical Device Directive (MDD). Studies conducted in Canada shall follow as well the ISO 14155 Clinical investigation of medical devices for human subjects — Good clinical practice.

Furthermore all investigators will complete financial disclosures, as outlined in the 21 CFR part 54 and will also comply with part 11. Investigators located in the US shall follow applicable requirements to clinical investigations and GCP: 21 CFR part 50, 56 and 812.
Clinical trials conducted in India shall follow the Ethical Guidelines issued by Indian Council of Medical Research.

This study shall not be started prior to obtaining a favorable opinion from a Medical Ethics Committee (MEC)/Institutional Review Board (IRB) and regulatory authority, if required. Any additional requirements imposed by the MEC/IRB and regulatory authority shall be followed.

Insurance shall be provided for the subjects participating in this clinical trial according to local law.

11. INFORMED CONSENT PROCESS

Informed consent will be obtained from every subject in writing by the Investigator or his authorized designee before the clinical study is started.
The subject will be informed both orally and in writing about all aspects that are relevant to the subject's decision to participate in the clinical study, including the clinical study procedures. Ample time should be provided for the subject to read and understand the informed consent form and to consider participation. The informed consent will include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process. A copy of the signed and dated informed consent form and any other written information will be provided to the subject.

Subjects who are unwilling to provide informed consent will not be included in the clinical study.

If new information becomes available that might significantly affect the subject's future health and medical care, it shall be provided to the subjects in written form. If relevant, subject shall be asked to reconfirm their continuing informed consent in writing.

11.1. Subject unable to read or write

Informed consent shall be obtained through a supervised oral process if a subject is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

12. SAFETY REPORTING

The following event should be reported to Philips for Medical Device Reporting (MDR) according to 21 CFR part 803: Deaths and serious injuries that a device has or may have caused or contributed to. Caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of: (1) Failure; (2) Malfunction; (3) Improper or inadequate design; (4) Manufacture; (5) Labeling; or (6) User error. Medical Device Reporting shall be reported to the regular Philips Healthcare customer feedback system, i.e. contact the local Helpdesk (optional to add phonenumber e.g. +31402764777) to report these events. Also report these to the Clinical Scientist (see Appendix II *List of monitor(s)/clinical scientist)*.

13. EARLY TERMINATION OR SUSPENSION OF THE CLINICAL STUDY

There are no provisions or interim analyses planned that can result in an early termination of the trial. Serious or repetitive occurrence of deviations from study protocol or non-compliance with regulations may also be reason for early termination or suspension of a study site.

14. PUBLICATION POLICY

It is the intention of the investigator and sponsor to submit the clinical study data for publication. Prior to submission, claims on intellectual property will be assessed. This study will also be registered on clinicaltrial.gov before first enrollment.

15. ABBREVIATIONS USED

Abbreviations	Explanation of abbreviation
3D-RA	3D Rotational Angiogram
CE	Conformité Européenne (European Conformity)
CFR	Code of Federal Regulation
CRF	Case Report Form
DSA	Digital Subtraction Angiography
e-CRF	Electronic Case Report Form
FDS	Flow Diverter Stent
IA	Intracranial Aneurysm
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
MAFA	Mean Aneurysm Flow Amplitude
MEC	Medical Ethic Committee
MDD	Medical Device Directive
MDR	Medical Device Reporting

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APPENDIX I LIST OF INVESTIGATORS AND SITES

Update of this list can be provided to the study site under separate cover.

Table 1: Clinical Coordinating Investigator

Name Clinical Coordinating Investigator	Name and address investigation site
Dr. Ricardo Hanel	Baptist Medical Center Jacksonville 800 Prudential Drive Jacksonville, Fl 32207 USA

Table 2: List of principle Investigators

Name Principal Investigator(s)	Name and address investigation site(s)
Dr. Vitor Mendes Pereira	Toronto Western Hospital Department of Medical Imaging 399 Bathurst St. Toronto ON M5T 2S8 Canada
Dr. Civan Islak	İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi 34098 Cerrahpaşa-Fatih İstanbul Turkey
Dr. Ajay Wakhloo	UMass Memorial Medical Center - University Campus 55 Lake Avenue North Worcester, MA 01655 USA
Dr. Santhosh Joseph	Sri Ramachandra Medical Centre No.1 Ramachandra Nagar, Porur Chennai, Tamil Nadu, India 600 116
Dr. Pedro Lylyk	ENERI Av. del Libertador 6647 (C1428ARJ) CABA, Argentina

APPENDIX II: LIST OF MONITOR(S)/CLINICAL SCIENTIST

Update of this list can be provided to the Investigational sites under separate cover.

Table 3: List of monitor/clinical scientist

Name Monitor(s)/Clinical Scientist	Contact Information of Monitors
Joris de Groot *Clinical Trial Manager*	Best, The Netherlands Telephone: +316 116 45 166 joris.ah.degroot@philips.com
Martijn van de Giessen *Clinical Scientist*	Singapore, WA, USA Telephone: +65 963 08211 martijn.van.de.giessen@philips.com
Martine van Alfen *Clinical Scientist*	Boston, MA, USA Telephone: +1 617 7350 209 martine.van.alfen@philips.com