Innovations driven by clinical evidence

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A B S T R A C T

The Pipeline Embolization Device (PED) has become a routine first-line interventional option for treatment of intracranial aneurysms; however, thromboembolic complications are the main adverse events with flow diversion interventional procedures. A new, third generation version of the PED, the Pipeline Flex™ Embolization Device with Shield Technology™ (PFEDST), is now available with a surface modification that includes, phosphorylcholine, a synthetic biocompatible polymer. *In vitro* investigations show reduced thrombogenicity with this device compared with earlier devices. Preliminary clinical evaluation showed deployment was technically successful with 98% of implanted PFEDST devices, and no major strokes or neurologic deaths were reported in the 30-day post-procedure period. The sizing decision on the dimensions of a device chosen to treat intracranial aneurysms is crucially important, as the dimensions and characteristics of the device can change radically during deployment. SIM&SIZE™ simulation software allows interventional neurologists to perform a simulated device sizing, to confirm whether the device dimensions initially chosen are optimal for the treatment of the aneurysm and vessels under consideration. The clinical impact of simulated device sizing is significant; it has led to the use of shorter PEDs, and has reduced the requirement for secondary device implants. Medtronic have recently initiated INSPIRE; this is an observational, prospective, multi-centre, single-arm registry established to provide continuing evaluation and periodic reporting of the safety and effectiveness of Medtronic neurovascular implant devices used in the treatment of intracranial aneurysms. The aim of this registry is to collect performance and safety data on up to 10,000 patients and will monitor existing and forthcoming implant devices over their complete life cycles.

Key words: intracranial aneurysms, Pipeline Flex Embolization Device, phosphorylcholine, simulation software, SIM&SIZE, INSPIRE.

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INTRODUCTION

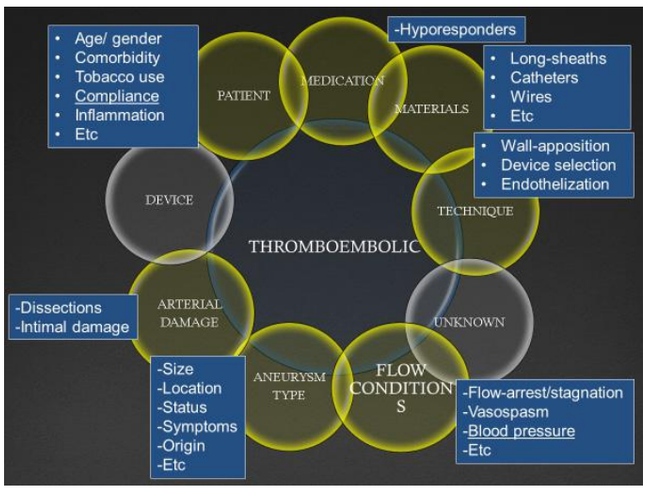
Professor Michel Mawad, as moderator, explained that this symposium was dedicated to the treatment of haemorrhagic stroke, with a specific focus on the treatment of aneurysms. The aim of the symposium was to highlight and review three interrelated areas:

- The innovation and technology associated with the Pipeline Flex™ with Shield Technology™ device. The combination of flex and shield technologies allows for more reliable deployment and ease of use, and specifically, the shield technology may have a potential role in helping to minimise the use of dual antiplatelet therapy. A key question is therefore: What promise would such a benefit hold for the treatment of aneurysms?
- The use of computer technology, image rendering, and software development with a view to optimising the positioning, fit, and utility of the pipeline stent. The principal drivers of these developments are 1: to provide more accuracy, precision, and predictability in the deployment of the Pipeline Flex™ with Shield Technology™ device, and 2: to establish a better fit between the disease itself and the optimum size/length of the pipeline embolization stent device.
- The introduction of the INSPIRE registry. This is a unique initiative undertaken by Medtronic that will capture evidence and collect anatomical data and clinical outcomes, longitudinally, within a well-designed registry.

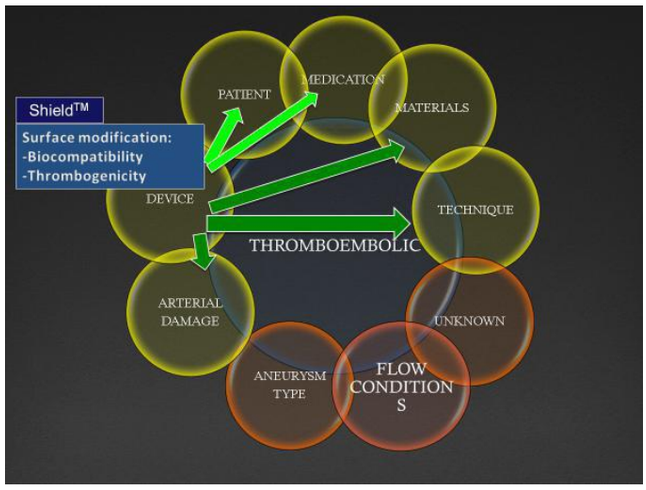
PIPELINE FLEX™ WITH SHIELD TECHNOLOGY™: MOST RECENT TECHNOLOGY AND CLINICAL DATA UPDATES. PROFESSOR MARIO MARTINEZ-GALDÁMEZ MADRID, SPAIN.

Professor Martinez-Galdámez explained that the Pipeline Embolization Device (PED), version 1.0, was introduced in 2008, and subsequently updated to version 2.0, in 2014, by including flex technology and greater precision. Thromboembolic complications were the most common procedural complications associated with initial PED versions. These complications provided the impetus for developing a device with greater haemocompatibility. The current, third generation, Pipeline Flex™ Embolization Device with Shield Technology™, now features the same version 2.0 implant, with the same porosity, but features a surface modification designed to make the device more biocompatible.

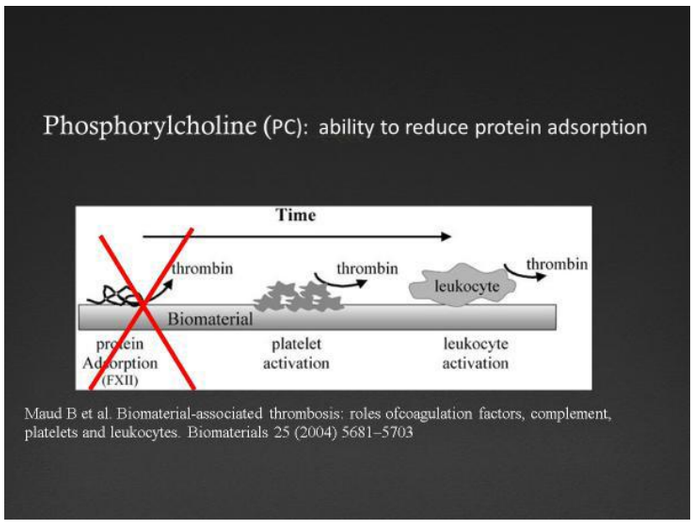
Professor Martinez-Galdámez reviewed the different, independent, pathophysiological risk factors for thromboembolic complications that can occur following a stent or flow diverter insertion. For example, significantly more complications are seen in medication hypo-responders compared with normal responders, and in patients with poor compliance, who may have stopped taking clopidogrel. The type of aneurysm, and the patient's blood pressure and blood flow status, particularly blood stagnation during the intervention have important influences, as do the specific materials and coatings used in the PED interventional components, and the techniques used to implant them. This potential array of risk factors is illustrated in the following diagram.



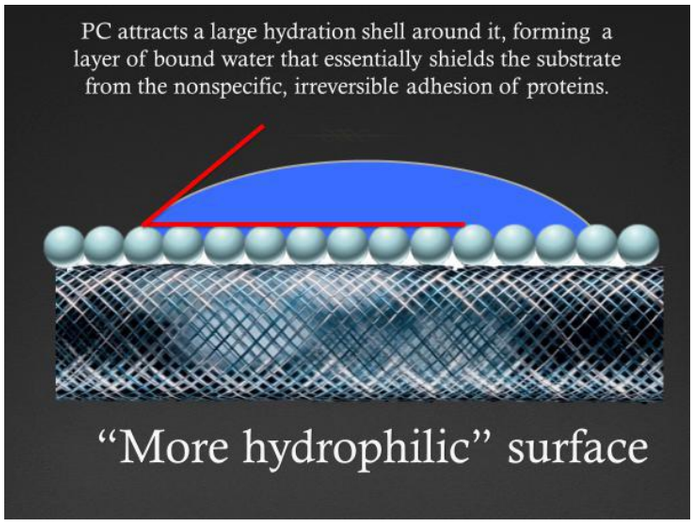
Only three of these risk factors for thromboembolic events can be linked to devices used for endovascular embolization of cerebral aneurysms, namely: arterial damage during mechanical manipulation of the device, technical issues used in the deployment of the device, and the materials used in the composition of the device. The strategic aim is to improve biocompatibility using the Pipeline™ Flex Embolization Device with Shield Technology™ and, in turn, reduce the risk of thrombogenicity. In tandem with concerted efforts to improve individual patient and medication risk factors, a reduction in the risk of thromboembolic complications associated with for endovascular embolization is anticipated. This is depicted schematically in the following diagram.



The Pipeline™ Flex Embolization Device with Shield Technology™ utilizes an inert phosphorylcholine (PC) surface treatment to the implant. This inert synthetic polymer is covalently bonded to the strands of the device and, in essence, mimics the outer membrane of a human red blood cell. Phosphorylcholine prevents the adsorption of protein; this is the initial stage in a series of events that ultimately results in adverse biological responses to devices that are placed within the body. By blocking this initial stage, subsequent platelet and leukocyte activation processes and the accumulation of thrombin are avoided.

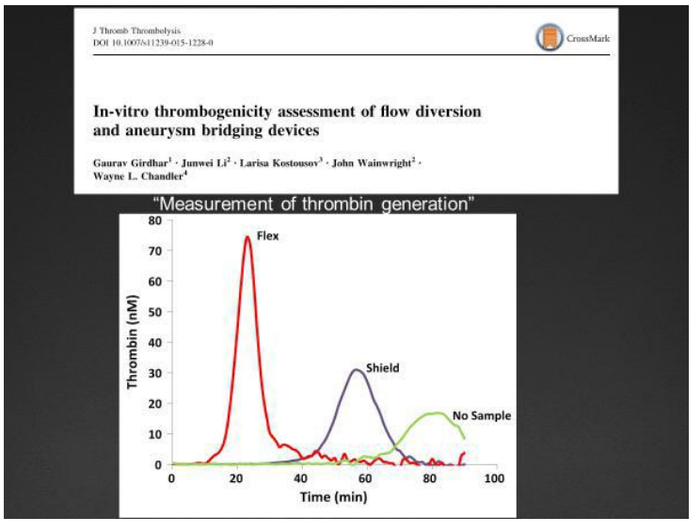


The role of PC, when the device is in situ, is to attract a large hydration shell around it, forming a layer of bound water. This hydrophilic surface essentially shields the substrate from the nonspecific, irreversible adhesion of proteins.

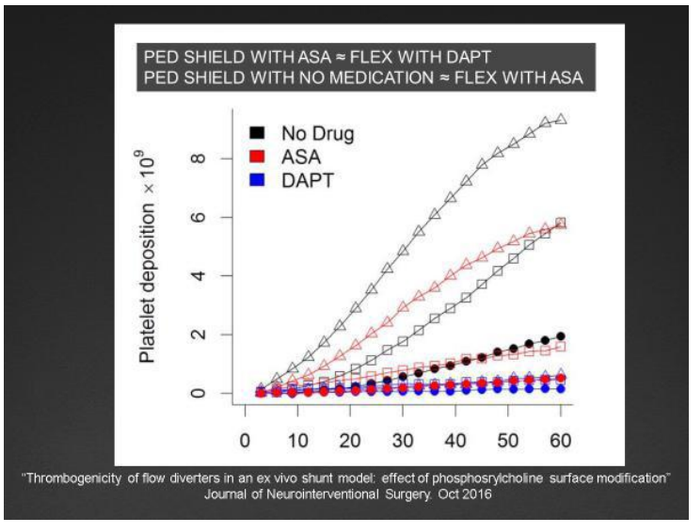


Development of these new surface characteristics has been motivated by the promise of less thromboembolic complications and a more trackable device with greater navigability.

Professor Martinez-Galdámez reviewed available evidence in support of reduced thrombogenicity with the Pipeline™ Flex Embolization Device with Shield Technology™ (PFEDST). *In vitro* thrombogenicity assessment, as measured by thrombin generation, has demonstrated significantly less (and later) thrombin generation with PFEDST than the standard Flex device without Shield Technology™ surface modification (Girdhar 2015).



Significantly reduced *in vitro* thrombogenicity attributable to phosphorylcholine surface modification has also been demonstrated in a radiolabelled platelet deposition study (Hagen 2016). The Pipeline™ embolization device (PED) plus Shield™ showed significant reductions in platelet deposition compared with unmodified PED, without antiplatelet therapy, and with dual antiplatelet therapy (DAPT). Notably, the PED plus Shield™ with acetylsalicylic acid (ASA) monotherapy was associated with comparable platelet deposition to that observed with the Flex PED and DAPT. Additionally, the PED plus Shield™ with no medication resulted in comparable platelet deposition with that seen with unmodified PED plus ASA. These observations are summarised in the graph shown below.



Clinical evaluation of the Pipeline™ Flex Embolization Device with Shield Technology™ is now underway with the PFEDST device. Professor Martinez-Galdámez presented preliminary results from a prospective clinical study conducted to assess the technical success and safety of Pipeline™ Flex Embolization Device with Shield Technology™ deployment (Martinez-Galdámez 2017). This study recruited 50 patients with predominantly small (< 10 mm) aneurysms (78%). Successful device deployment to target site was achieved with 53/54 (98.1%) of PFEDST devices used in the study's embolization interventions. Safety assessments at 30 days post-procedure revealed no evidence of major stroke in the tissue supplied by the treated artery, and no neurological death due to procedural complications related to use of the PFEDST device. Three serious adverse events were adjudicated by the Clinical Events Committee (CEC) as related to intervention with the PFEDST device. These were: one case of diplopia; a retroperitoneal haemorrhage, and a procedure-related headache. A 1-year follow-up safety and efficacy analysis is expected at the end of July 2017.

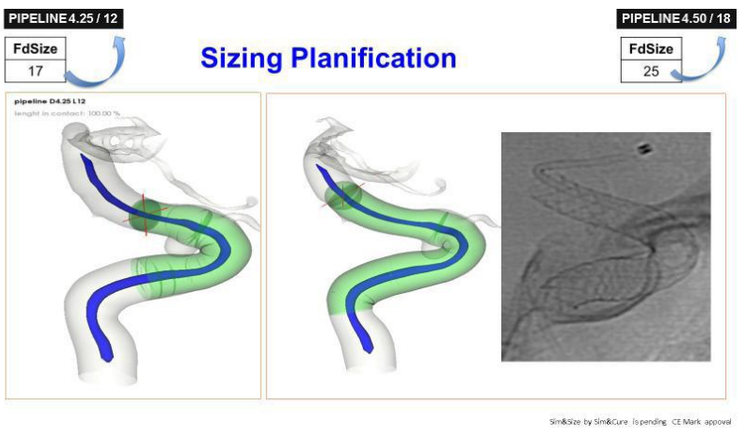
In his concluding remarks, Professor Martinez-Galdámez stressed that thromboembolic complications represent the main problem currently experienced during flow diversion interventions for the treatment of intracranial aneurysms. To date, the limited clinical trial experience with the Pipeline™ Flex Embolization Device with Shield

Technology™ is encouraging. Early indications suggest a reduced risk of thromboembolic complications may be anticipated with this device compared with earlier versions. Importantly, initial clinical trial safety assessments are promising: no thromboembolic or haemorrhagic events have arisen during and up to 30 days after deployment, and no new safety concerns have emerged. No additional technical difficulties have been encountered; the delivery technique is the same as that for the previous version of this device, and user feedback indicates greater flexibility and ease of navigation. Finally, Professor Martinez-Galdámez cautioned that because clinical data on the Pipeline™ Flex Embolization Device with Shield Technology™ are still limited, the use of dual antiplatelet therapy in conjunction with this device continues to be an obligatory requirement.

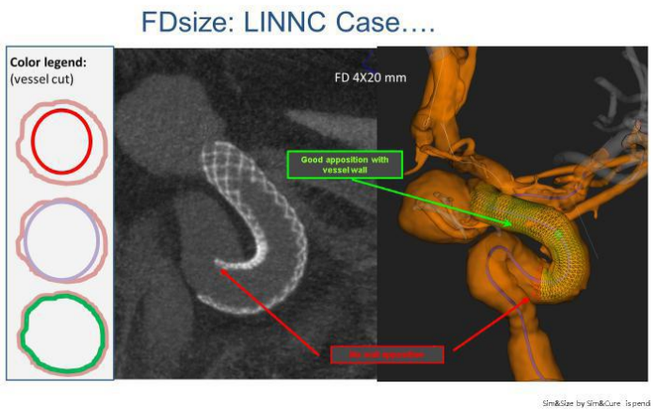
SIM&SIZE: A NEW GENERATION SOFTWARE FOR PATIENT-SPECIFIC SIZING OF FLOW-DIVERTERS AND INTRASACCULAR TREATMENT OPTIONS. PROFESSOR VINCENT COSTALAT, MONTPELLIER, FRANCE.

Sizing aneurysms and arteries to decide on the best size of implant to fit and to avoid elongation or foreshortening errors, and the need for more than one implant, constitutes a major challenge for interventional neurologists. SIM&SIZE is a simulation software that helps to optimize the choice of endovascular devices for the treatment of intracranial aneurysms. Professor Costalat explained that the development of SIM&SIZE has followed a paradigm shift in simulation as an assessment tool in neuroradiology, based initially on purely haemodynamic considerations, to a more recent biomechanical approach. Biomechanical simulation now offers practical assistance to questions raised in the angiography suite regarding most appropriate size of flow diverters and where to start deployment from.

An important consideration in the sizing decision is that the flow diverter may change radically during deployment depending on the choice of diameter selected. The extent of elongation and foreshortening that will occur during deployment in the patient is difficult to predict. Professor Costalat provided the following example, where pipeline embolization devices (PEDs) with dimensions of 4.25 mm x12 mm and 4.50 x18 mm, when deployed in patients, would take on lengths of 17 and 25 mm, respectively.

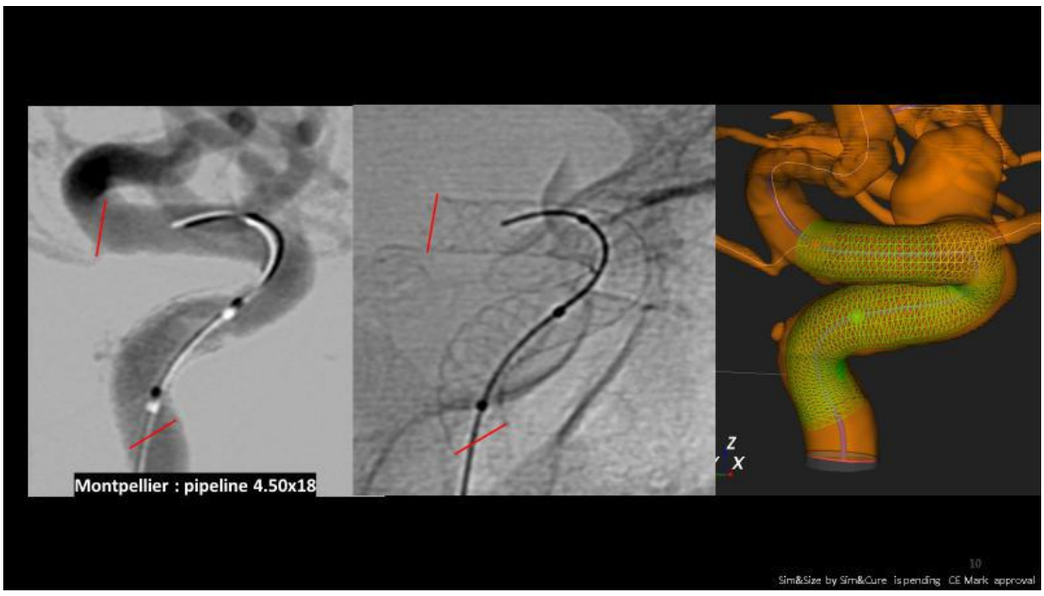


PEDs vary in the extent of elongation; this can be between 0 and 80%. Conversely, foreshortening or less than expected elongation may be experienced during deployment. Other problems that may occur during the deployment procure include incomplete or loss of vessel wall apposition, as illustrated in the following image.

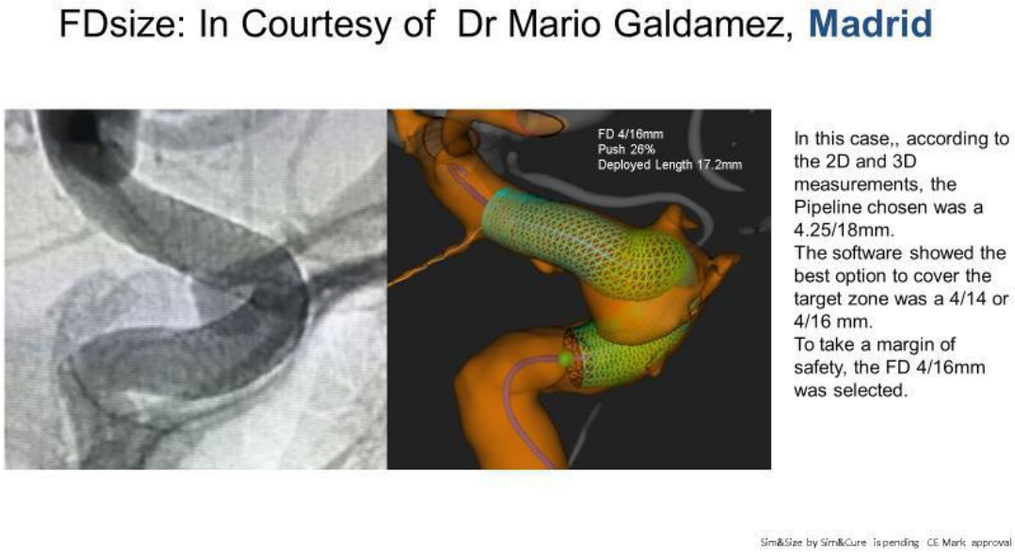


Given the inherent difficulties that can arise following a PED size decision, that may lead to a less than ideal fit, there is a clear unmet need for better information for interventional neurologists to base their PED size decisions on. The SIM&SIZE simulation process, based on retrospective validation of over 300 cases is now available to aid PED size decisions. This software allows neurologists to validate their choice of PED and its dimensions. SIM&SIZE simulation software represents a next generation tool that can estimate the endovascular device deployment and apposition. In effect, these sizing tools offer a "second opinion" regarding the selection of the most appropriate size of PED best suited for the characteristics of the specific aneurysm under assessment for intervention.

The following image shows a successful validation in a case where the PED positioning was initially too short at the neck of the aneurysm. This simulation shows the arrival of the stent in correct alignment with the proximal end of the artery.



Professor Costalat explained the timing involved to perform a simulated device sizing is approximately 10 minutes. This allows for loading data from a USB stick and processing the simulation based on the area of interest. The following example images illustrate how simulated device sizing can be used to select pipeline device dimensions with an appropriate margin of safety.



Professor Costalat stressed the measurable clinical impact of simulated device sizing using SIM&SIZE software, in his hospital department, has been the use of shorter devices and less implants per procedure. The most frequently used length of pipeline device used at Montpellier is now 12 mm and illustrates a significant shift in the deployment of shorter implants in Professor Costalat's department.

The use of a bridge between the non-perfectly opposed proximal part of the stent and the straight section of the vessel, using a second stent implant, was relatively common in Professor Costalat's department. The secondary implant rate for this was, until recently, around 12%. However, the routine use of SIM&SIZE simulation has reduced this secondary implant rate considerably, to around 3.7%.

Less Implant per procedure

Year	Implanted PED	Not Implanted	Procedures	PED number per Procedure	Second Implant Rate
2015	77	9	59	1.305	**12%**
2016	90	5	80	1.125	**5.5%**
Last 6 months of 2016*	53	2	49	1.08	**3.7%**
2017 Based on first 6 months*	110	4	100	1.1	**3.7%**

** With Fdsize Being used in clinical routine*

Sim&Size by Sim&Cure is pending CE Mark approval

Hence, the use of simulation device sizing provides a useful "goodness of fit" validation of device dimensions, chosen by neurologists, prior to committing to intervention and implantation. The SIM&SIZE software provides simulations for sizing stent, intrasaccular, and flow diverter implants. Use of this simulation software can prevent the possibility of having to repeat an implant procedure, should the initial implanted device prove to be less than optimal in its dimensions.

THE INSPIRE REGISTRY: A UNIQUE CLINICAL INITIATIVE TO COMBINE INNOVATION AND CLINICAL EVIDENCE. PROFESSOR ISTVAN SZIKORA, BUDAPEST, HUNGARY.

The INSPIRE registry, supported by Medtronic, is a growing depository of longitudinal data involving a large number of patients with intracranial aneurysms treated with various device implants. Professor Szikora provided a historical perspective of events that have led to the formation of INSPIRE. He noted the Guliemi Detachable Coil (GDC) technology was first presented at the American Society of Neuroradiology (ASNR) in 1991, and gained limited US approval, under FDA surveillance, in 10 sites for five years. In Europe, the International Subarachnoid Aneurysm Trial (ISAT) was conducted over the period 1995-2001 and, on completion, was followed by widespread application of GDC interventions from 2002 onwards. By comparison, flow diverter (FD) technology was first presented in France in 2007, followed by European commercial approval in 2008. Widespread application of FD usage was evident in Europe by 2011 and FDA approval was also obtained in 2011.

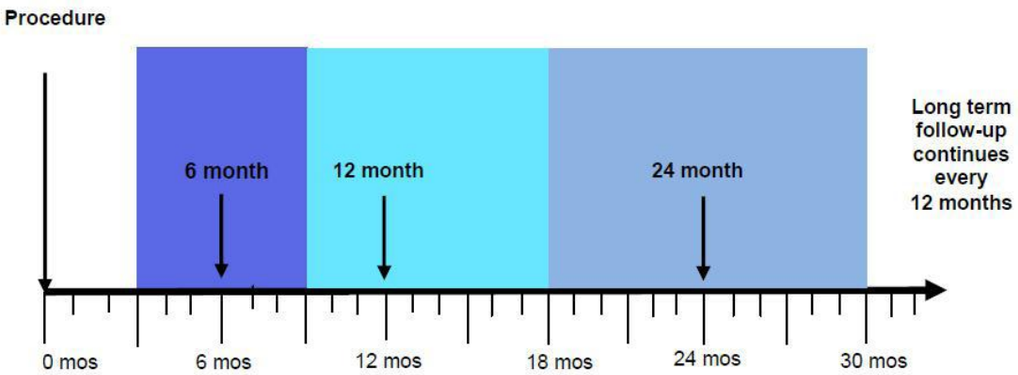
Since the introduction of these technologies, Professor Szikora highlighted a growing number of reports of complications with FDs. For example, intra-aneurysmal thrombosis was reported as a possible cause of delayed aneurysm rupture after flow diversion (Kulcsár 2011). This caused a loss of enthusiasm and trust in FD technology within the neuro-interventional community and led to the formation of a retrospective registry, by the European Society for Minimal Invasive Neurological Therapy (ESMINT), and published as the RADAR study in 2012. Subsequently, the International Retrospective Study of Pipeline Embolization Device (IntrePED) registry was jointly initiated, for retrospective data collection, by physicians and industry in 2015. With coiling, the time from first presentation of initial results to ISAT publication, and clarification of the benefits and short-falls of coiling, was 11 years (1991-2002). With FD technology, the first

presentation was in 2008, the Pipeline for Uncoilable or Failed Aneurysms (PUFS) study was published in 2013, and IntrePED was published in 2015. Professor Szikora noted that during these periods, potentially, a substantial number of patients may have been treated inappropriately, and he stressed the important need for ongoing data collection from the patient's initial implant.

The INSPIRE product surveillance registry has been recently initiated by Medtronic. This prospective, non-randomized, single-arm, multicentre, observational study is being conducted to monitor product performance, safety, and clinical outcomes associated with Medtronic devices, particularly those deployed for the treatment of complex intracranial aneurysms. The recruitment indication for this study is endovascular embolization of any intracranial aneurysms, that are not amenable for treatment by coils alone, with patients selected at the physician's discretion. The devices monitored in INSPIRE include: the Medina™ Embolization Device, the Pipeline™ Flex Embolization Device, the Pipeline™ Flex Embolization Device with Shield Technology™, the Artisse™ intrasaccular device and the Barrel™ vascular reconstruction device. Any new devices subsequently introduced by Medtronic will also be monitored by, and contribute to, the INSPIRE registry.

The primary endpoint for INSPIRE is complete aneurysm occlusion, as measure by the Raymond–Roy occlusion classification, at one year. Secondary endpoints include: target aneurysm recanalization, rupture and retreatment; device and procedure related adverse events; intracranial haemorrhage; adequate aneurysm occlusion; mortality; device deployment success, and safety, as assessed by a composite of neurological death, major stroke in target vascular territory and any intracranial haemorrhage.

Patient eligibility is assessed at the treating institution. The inclusion criteria are the patients' written authorization and consent, and a stated intention to treat with the eligible device. Patients inaccessible for follow-up, and patients currently enrolled in or who plan to enroll in any concurrent drug and/or device study will be excluded. The follow-up reporting time-line for INSPIRE is shown below.



A tabular summary of the data to be collected in the INSPIRE study is illustrated in the following figure.

DATA COLLECTION

DATA COLLECTION ITEMS	ENROLLMENT /BASELINE	PROCEDURE	FOLLOW-UP
Demographics and Medical History	✓		
Antiplatelet Medications	✓	✓	✓
Modified Rankin Scale Score		✓	✓
Imaging	✓	✓	✓
Study Device Placement		✓	
Device- and Procedure related Adverse Events and Neurological Events of Interest	Reported upon awareness		

INSPIRE | LINNC 2017 | Confidential

The international scope of the INSPIRE registry is significant; it is anticipated to receive data from over 40 sites in over 20 countries. INSPIRE's goal is treat up to 10,000 patients. Site selection is subject to criteria intended to minimize site selection bias. Professor Szikora listed these criteria as:

- The presence of a research team at the site;
- A consideration of the number of endovascular procedures conducted in the last 12 months;
- Previous clinical research at the site that is judged to be sufficient, with experienced clinical teams.

Additionally, all sites will have to comply with local regulatory requirements, and Ethics Committee approval will be required. Currently, 17 sites have obtained this approval, with remaining sites either under ethics review, or their submissions are in progress.

Professor Szikora reviewed the advantages and benefits that are expected to emerge from the INSPIRE registry. These are summarized in the table below.

INSPIRE: the expected benefits

Widespread benefits and stakeholder engagement	INSPIRE will support the interest of patients, hospitals, clinicians, regulatory authorities, payers, and industry interests.
Extendable design	INSPIRE allows for easy integration of multiple registries. The flexible foundation supports multiple product evaluation.
Monitored data	INSPIRE will provide a reliable source of meaningful clinical data that is continually monitored and updated.
Outcomes	INSPIRE promises greater understanding of the relationship between device performance vs. clinical outcomes, thereby providing a basis for the selection of optimal treatment for different aneurysms.
Networking	INSPIRE can be expected to generate an important and cohesive international network amongst participating sites and the wider neuro-interventional community.
Reimbursement	INSPIRE will provide the necessary clinical evidence for obtaining reimbursement and improving product access.
New technology access	INSPIRE will facilitate easy and rapid access to newly introduced technologies following marketing approval of new devices.
Performance assessment over a product's life cycle.	INSPIRE will allow the early detection of potential product safety issues and will generate long-term outcome data. INSPIRE will provide regular reporting on individual device performance.
Clinical Evidence	INSPIRE will provide an extensive repository of "real world" data and evidence. INSPIRE will help to address unmet clinical needs and support therapy acceptance.

As at mid-June 2017, Professor Szikora advised that seven sites are now authorized to enroll, and over 20 sites are involved in the INSPIRE study initiation process. Two sites have already enrolled over 11 patients.

CONCLUSIONS

The use of endovascular techniques developed for the treatment of intracranial aneurysms has expanded in recent years, and the number of implantable devices available for these procedures continues to grow; however, thromboembolic complications, collectively, constitute the biggest adverse event risk with device implantation. This symposium reviewed important initiatives currently underway that seek to minimize the risk of thromboembolic complications, and identify any associated risk as early as possible, and throughout the lifecycle of individual implant devices.

Shield Technology™ is a device surface modification where a synthetic phosphorylcholine (PC) polymer is covalently bonded to the strands that make up the Pipeline

Embolization Device braid. In preclinical models, PC modification, as applied to the Pipeline™Flex Embolization Device with Shield™ Technology, is associated with reduced thrombogenicity compared with earlier devices. Furthermore, initial clinical safety data based on 50 intracranial aneurysms, are encouraging, with no thromboembolic or any intracranial haemorrhagic events reported over 30 days post-procedure.

Deciding on the specific dimensions of an implant that will fit the intracranial pathophysiological vascular anatomy associated with aneurysms is crucially important, and represents a major challenge for interventional neurologists, because the characteristics and dimensions of devices can change during deployment. The development of SIM&SIZE™ software now allows device deployment simulation to be undertaken, to help verify device sizing decisions and ensure greater implant precision. Use of SIM&SIZE™ is allowing shorter devices to be deployed and reduces the requirement for secondary implants.

INSPIRE is an observational, prospective, multi-centre, single-arm registry established to provide continuing evaluation and periodic reporting of the safety and effectiveness of Medtronic neurovascular implant devices used in the treatment of intracranial aneurysms. The introduction and growth of the INSPIRE registry is set to collect an extensive longitudinal clinical data set that will monitor individual Medtronic devices for identification of any emergent safety or technical deployment issues arising throughout the life-cycle of each Medtronic device. Accordingly, the "real life" clinical performance data provided by INSPIRE will accumulate evidence to help interventional neurologists in their choice of the most appropriate device and intervention for treating patients with intracranial aneurysms.

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