PRODUCT DEVELOPMENT OF A NEUROVASCULAR EMBOLIZATION DEVICE

A Thesis

by

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ABSTRACT

Stroke is the number one cause of adult disability in the United States and the third leading cause of death in the United States, Europe, and China. It is estimated 5% to 15% of all strokes are caused by ruptured intracranial aneurysms. In 2010, the National Stroke Association estimated the direct and indirect cost of strokes was $73.3 billion.

The most common method for treating intracranial aneurysms is with platinum coils that are deployed to pack the aneurysm and block blood flow and prevent rupture. However, coil compaction and re-bleeding are two limitations with the coils because they have limited space filling capacity. Dr. Duncan Maitland has proposed a neurovascular embolization device (NED) be made out of shape memory polymer foam (SMP). The SMP device can be compressed down into a compact size for delivery via a catheter. Once in place, the device can be stimulated to regain its primary shape and expand up to 70x for superior occlusion of aneurysms.

Design research is necessary to generate performance specifications for the NED that can assess the quality of prototypes. Customer needs are generated from interviews, activity diagrams, and market research. Functional models define the function and various sub-functions of the NED. Benchmarking highlights technology trends. A House of Quality matrix maps the customer needs to the engineering requirements. A failure modes and effects analysis emphasizes possible design deficiencies as a way of mitigating future risk. Performance specifications for the SMP foam are defined and can be used to establish a quality control program. Purification methods are suggested for the chemicals used in the synthesis of the SMP foam. Purification of the chemicals can reduce potential biocompatibility issues.

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NOMENCLATURE

CFR	Code of Federal Regulations
CoA	Certificates of Analysis
EU	Endotoxin Unit
EtO	Ethylene Oxide
FAST	Functional Analysis System Technique
FMEA	Failure Mode and Effects Analysis
GDC	Guglielmi Detachable Coils
GMP	Good Manufacturing Practice
HDE	Humanitarian Device Exemption
HFE	Human Factors Engineering
HOQ	House of Quality
MDR	Medical Device Reporting
MSDS	Material Safety Data Sheets
NCO	Isocyanate Premix Containing Nitrogen, Carbon, Oxygen
NED	Neurovascular Embolization Device
OH	Hydroxyl Monomer Premix
P&D	Delivery Pusher and Detachment Mechanism
PGPLA	Polyglycolic-Polylactic Acid
RHV	Rotating Hemostatic Valve
SAL	Sterility Assurance Level
SMA	Shape Memory Alloy
SMP	Shape Memory Polymer
T_g	Glass Transition Temperature
QSR	Quality System Regulation

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1. INTRODUCTION: THE IMPORTANCE OF RESEARCH

The need for neurovascular embolization devices (NED) stems from the fact that untreated intracranial aneurysms can result in devastating consequences. Approximately 3 out of 4 patients with ruptured aneurysms will die or become neurologically incapacitated. Ruptured aneurysms cause strokes by bleeding in between the brain and the subarachnoid space, leading to subarachnoid hemorrhage. Approximately 795,000 people each year have a stroke, killing about 137,000 people.[1] These startling statistics have led to the development of multiple products attempting to treat intracranial aneurysms.

After their approval in 1995 by the FDA, Guglielmi Detachable Coils (GDC) revolutionized the way intracranial aneurysms could be treated. A craniotomy along with surgical ligation was no longer the only option. Over the last 15 years, approximately 200,000 patients have been treated with the coiling method with positive results. However, there are limitations with the current market products that need to be addressed. Coil compaction and rebleeding are the two most prominent. These consequences result because the current market products have limited space filling capacity. The right combination of materials and design has not yet been developed and is limiting complete aneurysm occlusion.

As a solution to these problems, a device will be designed out of a urethane-based shape memory polymer (SMP). This polymeric smart material can remember a primary shape and return from a temporarily deformed shape back into the primary shape once stimulated by an external stimulus. The trigger (actuation) can be heat, light, or chemically driven.[2] The shape memory characteristic gives the device the ability to be compressed down into a compact size for delivery via a catheter. Once in place the device can be induced to regain its complex, primary shape.

2. BACKGROUND

2.1 Characteristics of Intracranial Aneurysms

In a normal artery wall there are 3 layers.[3] The innermost endothelial layer is the intima which consists of endothelial cells and is supported by an internal elastic lamina. The media is the intermediate layer and is composed of smooth muscle. Finally, the outer layer is the adventitia which is made up of connective tissue. The cause or process by which intracranial aneurysms form, grow, and rupture is not very well understood.[4] Based on examination, though, a typical aneurysm has a severely fragmented or no elastic lamina and a very thin or no media.[5] These characteristics along with hemodynamic shear stresses on the wall of intracranial arteries lead to vessel wall fatigue and the formation of an aneurysm.[4] Risk factors which contribute to an increased prevalence include family history and environmental factors like smoking and hypertension.

The prevalence of intracranial aneurysms in the adult population without specific risk factors is estimated to be approximately 2.3%.[6] It has been estimated 1 million to 12 million Americans have them.[5] The actual number of aneurysms is higher, though, considering 20% to 30% of patients have two or three in number.[5]

It is, therefore, important to understand the geometry and the risks associated with the size and location of an intracranial aneurysm.[7] The possible treatment options will depend on the shape, size, and location of the aneurysm. The shape of intracranial aneurysms can be classified as saccular, fusiform, or dissecting. Saccular aneurysms account for 90% and are rounded and berry-shaped.[8] Fusiform aneurysms take on bizarre, spindle-shaped geometries that vary both in diameter and length. Intracranial dissecting aneurysms are rare, but are caused by blood accumulating within the arterial wall because of a rip in the intima.[3]

Two important characteristics are used to describe the size of an aneurysm. One characteristic is the diameter of the fundus which is arranged into four different

categories. The diameter of the fundus for a small aneurysm is less than 5 mm, for a medium aneurysm it is 6-15 mm, for a large aneurysm it is 16-24 mm, and for a giant aneurysm it is any that are larger than 25 mm. The larger the aneurysm, the more likely it will rupture. However, most ruptured aneurysms are small to medium in size due to the fact that 90% have a fundus defined as less than 1 cm in diameter.[9] The second important characteristic is the size of the neck. Wide-necked aneurysms are considered those with a neck diameter greater than 4 mm, a dome-to-neck diameter ratio less than 2 to 1, or a neck diameter greater than one half the diameter of the parent vessel.[10]

Location is also an issue that can hinder successful occlusion. Bifurcations of major arteries are a common location for aneurysms. The exact location of the aneurysm varies but approximately 86.5% arise on the anterior circulation. Locations within the anterior circulation include the anterior communicating artery (30%), the internal carotid artery at the posterior communicating artery origin (25%), the middle cerebral artery bifurcation (20%), the internal carotid artery (7.5%), and the pericallosal/callosomarginal artery bifurcation (4%).[3] Aneurysms also arise on the posterior circulation, with the basilar artery bifurcation accounting for 7%, and an additional 3% on the posterior inferior cerebellar artery.[3]

2.2 Risks of Intracranial Aneurysm

Stroke is the number one cause of adult disability in the United States and the third leading cause of death in the United States, Europe, and China.[11,12] It is estimated 5% to 15% of all strokes are caused by ruptured intracranial aneurysms.[4] For those people fortunate enough to survive a stroke, long-term care can inflict a considerable emotional, mental, and financial burden. In 2010, the National Stroke Association estimated the direct and indirect cost of strokes was $73.3 billion.

One of the causes that accounts for 5% of strokes is subarachnoid hemorrhage which is a devastating condition.[9] Intracranial aneurysms are the cause of 85% of all subarachnoid hemorrhages.[13] The estimated incidence of subarachnoid hemorrhage

from a ruptured intracranial aneurysm is 10 per 100,000 people per year.[5] These results lead to approximately 27,000 new cases each year.[4] The glaring dangers associated with subarachnoid hemorrhage cannot be overstated. About 10% to 15% of the people who suffer a subarachnoid hemorrhage die before reaching the hospital and within 30 days the fatality rate increases to 50%.[14] An estimated 20% to 35% of the survivors will have moderate to severe brain damage, even after treatment.[15] After 6 months, untreated ruptured aneurysms have a morbidity of 48% to 78% and a mortality of 60% as a result of rerupture.[10] These statistics and associated complications reveal the importance for treatment of intracranial aneurysms ideally before they rupture.

2.2 History of Treatment

Considering the danger an intracranial aneurysm poses to a patient's survival, it is imperative to have safe and effective treatment options. Currently the two available treatment options are surgical clipping via a craniotomy or an endovascular approach. The first surgical treatment using a vascular clip was performed in 1936.[5] Morbidity was initially high from aneurysm ligation and clipping, but advances in neurosurgical techniques over the decades allowed surgery to remain the predominant treatment option.[16] Still though, surgical clipping is a highly invasive procedure. A craniotomy must be performed where a bone flap is temporarily removed from the skull. The brain is then retracted to locate the aneurysm. Once located, one small titanium clip is placed across the neck of the aneurysm to block blood flow from entering.

Due to the necessity of cutting open the skull, negative results stemming from surgery include extended hospital stays and high hospital costs.[17] As a remedy to these problems there were attempts at minimally-invasive endovascular techniques using detachable balloons, iron particles, and platinum coils. Problems arose, though, due to balloon deflation, migration of particles, and aneurysm rupture.[17] It was not until the 1995 approval of GDCs that an endovascular technique began to be widely adopted. GDCs are flexible, soft, and detachable platinum coils.

Even as coiling methods have improved there are still two main failure modes for coil embolization; the inability to completely occlude the aneurysm and coil compaction which over time leads to recanalization. Due to mounting criticism about the bare platinum coils being insufficient, development began on bioactive and coated coils. These advanced coils can be separated into two broad categories as polyglycolic-polylactic acid (PGPLA)-containing coils and hydrogel-coated coils. The PGPLA-containing coils are meant to initiate an inflammatory response when implanted in the aneurysm that generates an assemblage of thrombus and eventually fibrosis. They are supposed to elicit a faster neointimal overgrowth at the neck of the aneurysm. The hydrogel-coated coils absorb water and expand once introduced into the bloodstream. The hydrocoils expand to five times the volume of standard platinum coils.[18]

The best packing densities that have been observed in glass and silicone aneurysm models with current embolization coils range from 30% to 40%. The density drops to 20% to 30% in clinical human aneurysm treatments.[18] The random placement of coils within the aneurysm and the propensity for coils to split the aneurysm into separate partitions leaves the majority, 70% to 80%, of the aneurysm not filled with metal.[18] A limit in the packing density has ramifications which can result in recanalization of the aneurysm. Studies have shown treated aneurysms with recanalization rates of 33.6%. The recanalization rates were higher, 50.6% and 52.3%, for large and wide-necked aneurysms, respectively.[19]

Even with a robust evolution of various techniques, the endovascular approach is ultimately still falling short of complete occlusion of the aneurysm. This limitation opens up an opportunity for research into advanced materials and an improvement in the device designs to enable more space filling.

2.4 Solution for Improvement – Shape Memory Polymer

Shape Memory Polymers (SMP) are a class of polymeric materials that have the ability to change their shape upon application of an external stimulus.[20] The polymer is first processed into its permanent shape. The polymer is then deformed into a temporary shape, which is called the programming stage.[21] Programming in the Biomedical Device Laboratory consists of heating the SMP above the glass transition temperature, T_g, deforming it into a cylindrical shape, and then cooling the SMP. The permanent shape is stored into memory while the sample holds the temporary shape. Subsequent heating of the sample above the T_g induces the shape memory effect and the sample returns to its permanent shape.[21] The trigger (actuation) can be heat, light, or chemically driven.

There are many advantages that make SMP a suitable material for the treatment of intracranial aneurysms. They have a high capacity for elastic deformation, easy processing, potentially lower manufacturing cost, and versatility in designing complex geometries.[2] These materials have also been found to be biocompatible. Cytoxicity and mutagenicity tests have shown excellent results.[22] Significant potential for medical devices has recently been demonstrated.[21,23,24] The shape memory characteristic gives the material the ability to be compressed down into a compact size for delivery via a catheter. Once in place, the device can be induced to regain its complex, primary shape. The T_g can also be customized and controlled which gives versatility in the actuation method.[25]

3. RESEARCH AND DEVELOPMENT OF NED SYSTEM

3.1 Brief History of Medical Device Regulations in the U.S.

In the United States, medical device regulation was enacted in 1976 when the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act of 1938 was signed into law by Congress.[26] Good Manufacturing Practices (GMP) at that time was a quality control program for the control of manufacturing, packaging, storage, distribution, and installation of medical devices.[27] The Safe Medical Devices Act of 1990 then gave the FDA authority to add "preproduction design validation controls" to the GMP regulations, which were then incorporated into the Quality System Regulation (QSR)[28] The QSR, however, did not go into effect until 1997 and was not enforced until 1998. This mandate was put into place after an FDA study showed that over 40% of all quality problems resulting in recalls were attributable to preproduction-related problems.[29] It is now required by the FDA for medical device manufacturers to incorporate design controls while developing their products. The QSR is in Part 820 of Title 21 of the Code of Federal Regulations (CFR).[30]

In 1996, the Medical Device Reporting (MDR) regulation went into effect for the purpose of providing the FDA a way to receive information about significant adverse events with medical devices.[29] These various regulations now mean the medical device manufacturer is responsible for the entire life cycle of a medical device; from design, to manufacturing, to post-market surveillance. The regulations require that the Biomedical Device Laboratory have a quality system for the design and manufacture of the NED system intended for commercial sale in the United States.

3.2 Regulatory Guidelines for the NED System

Medical devices are organized into classes based on the associated degree of risk and intended use.[28] Class I are simple, low risk devices, while Class II are higher risk and more complex devices that are not life sustaining. Class III devices have the highest risk since they either support human life, prevent impairment of human health, or present an unreasonable risk of illness or injury.

In 1979, NEDs were initially classified into Class III due to concerns about tissue toxicity and tissue infarction. However, in 2004 they were down-classified to Class II with the stipulation that medical device manufacturers follow the FDA guidance document, "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices".

The FDA product code assigned to NEDs is 'HCG' (Table 1). With this information, predicate devices can be researched for benchmarking purposes and the indication for use can be defined. The NED being developed in the Biomedical Device Laboratory is intended for the endovascular embolization of intracranial aneurysms. This indication will set the foundation for the future direction of the development plan.

Table 1. FDA Classification for the NED System

FDA Classification for the Neurovascular Embolization Device (NED)	
Classification Regulation (21 CFR)	§ 882.5950
Regulation Medical Specialty	Neurology
Product Code	HCG
Examples	Embolization coils Polyvinyl alcohol particles Nonresorbable particles
Device Class	2
Submission Type	510(k)
GMP Exempt?	No
Identification	A neurovascular embolization device is an intravascular implant intended to permanently occlude blood flow to cerebral aneurysms and cerebral arteriovenous malformations. This does not include cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in other vascular applications are also not included in this classification, see 21 CFR 870.3300.
Guidance Document	The special control for the device is the FDA guidance document entitled "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices."

3.3 NED System Deployment and Architecture

The NED system comprises three subsystems: the NED, the delivery pusher, and the detachment mechanism (P&D). The NED is used to occlude intracranial aneurysms. The delivery pusher is used to guide the NED to the aneurysm site. The detachment mechanism is then used to release the NED into the aneurysm.

Additional components required during the endovascular procedure include: digital subtraction fluoroscope, femoral sheath, guidewire, 5-8 Fr guiding catheter, microcatheter, two rotating hemostatic valves (RHV), three-way stopcock, one-way stopcock, 20-22 gauge sterile needle (Fig. 1). Three continuous heparinized saline flush setups with pressure bags are also needed; one for the femoral sheath, one for the guiding catheter, and one for the microcatheter.

A typical endovascular procedure occurs in a catheterization laboratory under general anesthesia. A biplanar fluoroscopic system is used to visualize *in vivo* the proper positioning and placement of the radiopaque coils. To begin the procedure, a 5 to 6 French sheath is inserted into a femoral artery puncture. A guiding catheter is then introduced into the proximal parent artery, normally the left internal carotid artery. At this point the catheter is continuously flushed with saline. A preliminary angiography is performed to assess the size of the aneurysm and the tortuous vessel pathway leading to it. A microguidewire is then navigated to the base of the aneurysm. Once in place, a microcatheter is passed over the microguidewire. A coil is loaded into the microcatheter and pushed through to the distal end. The first coil implanted serves as the "framing coil" which shields the neck and follows the shape of the aneurysm wall. Subsequent smaller sized coils are then placed to slowly occlude the aneurysm. An angiography is performed to check the occlusion rate and is considered successful if no contrast material enters the aneurysm. The procedure is completed once the guide wires and catheters have been removed and pressure is applied to the puncture site.[13]

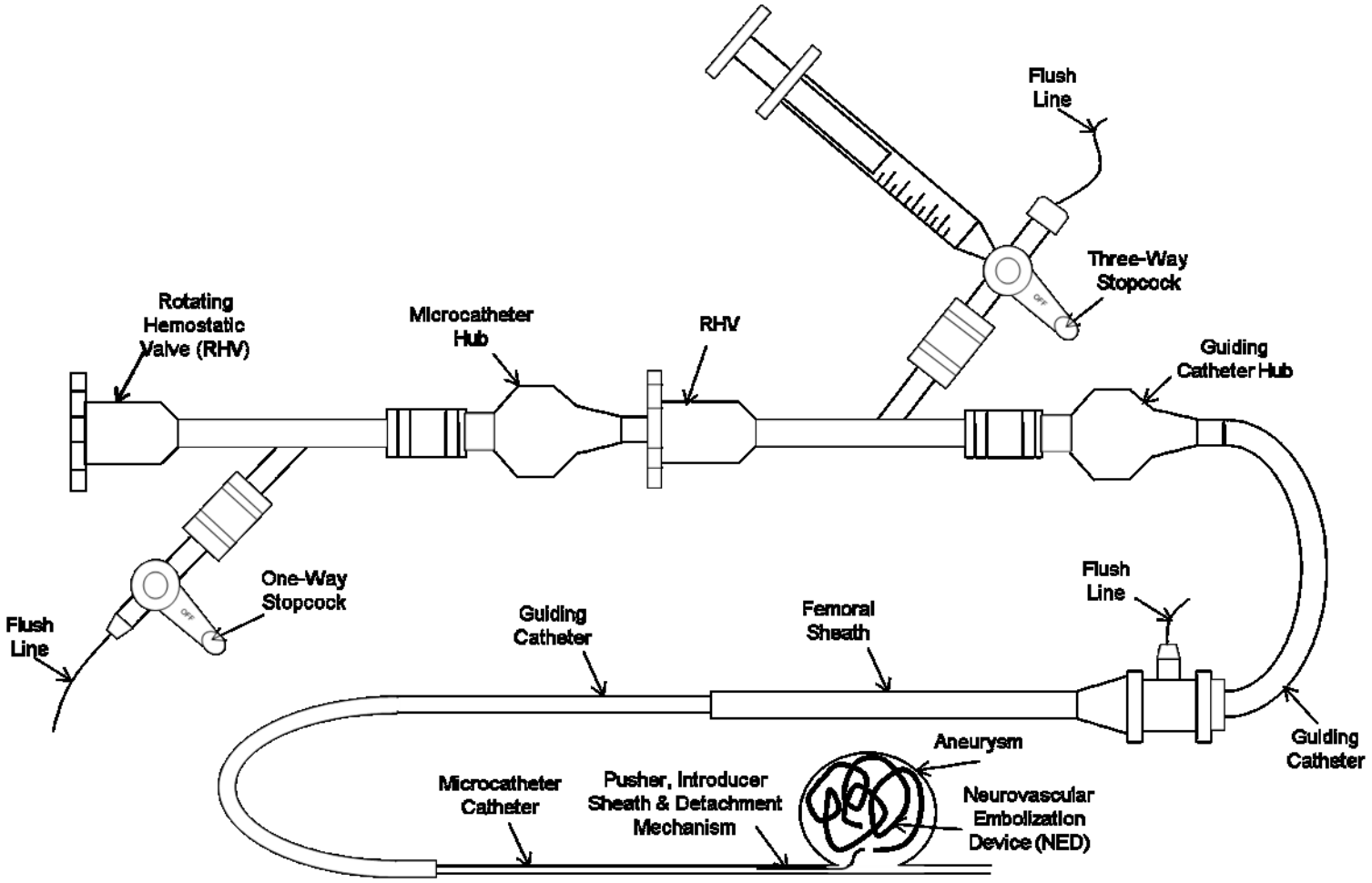


Figure 1. Required Components for the Endovascular Procedure

3.4 Current NED Prototypes

As a solution to the shortcomings of current market products, the Biomedical Device Lab is developing a NED made from SMP foam.

One design concept fabricated by Wonjun Hwang consists of a SMP foam-only device that is crimped around a resistive heating element (Fig. 2). The resistive heating element is used to deliver and actuate the foam. Once the foam is actuated, the resistive heating element is removed. A current limitation with this embodiment, is fabricating the whole system to a small enough outer diameter to facilitate easy placement into a microcatheter.

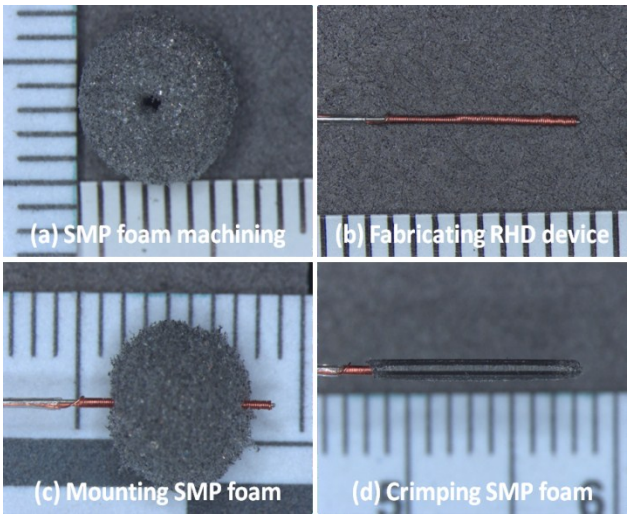


Figure 2. SMP Foam-Only Device with Resistive Heating Element

A design concept fabricated by Tony Boyle consists of a SMP foam segment crimped over a shape memory alloy (SMA) wire backbone (Fig. 3). The SMP foam-over-wire embodiment utilizes passive actuation. The foam softens during actuation which permits the SMA to resume its primary, coil shape.

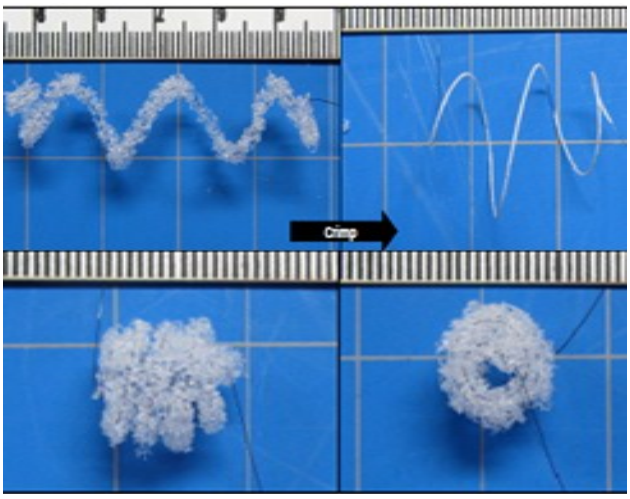


Figure 3. SMP Foam-Over-Wire Device

A concept for the detachment mechanism consists of a ball-and-socket (Fig. 4). The ball is attached to the NED and when the socket is pushed out of the microcatheter, the NED is detached.

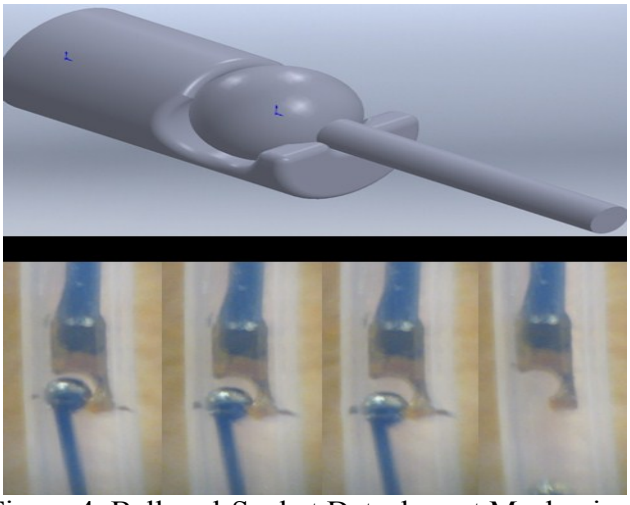


Figure 4. Ball-and-Socket Detachment Mechanism

The research for this thesis complements the current prototyping research being done in the Biomedical Device Laboratory. An attempt was made to strike a balance between remaining solution neutral versus being slightly biased towards the SMP foam-over-wire device.

4. DESIGN PLAN FOR COMPLETING AIM I AND AIM II

The design process for the NED system follows the design controls mandated by the QSR as outlined in the FDA guidance document, "Design Control Guidance for Medical Device Manufacturers". Considering the NED is listed as a Class II device, it is a QSR requirement to, "establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met."[31] The QSR provides the framework for medical devices to be designed and manufactured according to procedures that produce safe and effective devices for their intended use. The traditional design approach employs a waterfall model (Fig. 5). The design is developed in a logical sequence of stages. The output of one stage is the input for the next. The model illustrates the iterative nature of the design process as stages are reviewed, verified, and validated. As the design process evolves, improvements can be identified and incorporated into the medical device. This design approach ensures the design outputs are a result of the design inputs and that the medical device maps to the user needs.

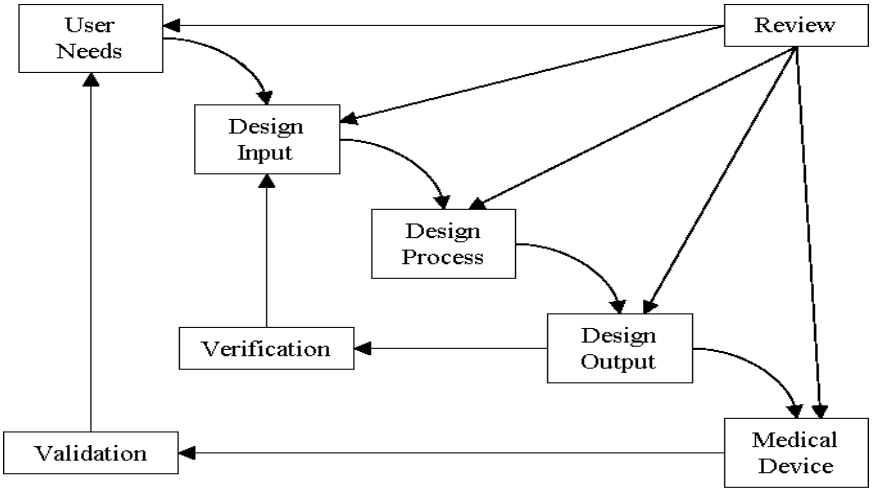


Figure 5. FDA Waterfall Design Control Process (Adapted from FDA 1997[31])

The first step in the design process is gathering the user needs and then translating them into design inputs. Benchtop tests are necessary to verify that the design requirements are met. Verification results are fed back into the design inputs to modify and improve the device design. Once all the design requirements have been met in benchtop testing, they are ultimately validated with the use of animal models and clinical studies. Again, information from the initial animal studies is fed back into the design process to validate that the device conforms to user needs and its intended use.

Due to the novelty of the NED, delivery pusher, and detachment mechanism; this design approach will be followed to comply with the QSR. However, guidewires, guiding catheters, and microcatheters that have already been cleared by the FDA will be used to reduce the regulatory burden for the rest of the NED system.

5. AIM I: PROBLEM STATEMENT

The first specific aim is to develop user requirements and performance specifications for a novel NED system. The system will comprise the NED, delivery pusher and detachment mechanism (P&D). To achieve this aim, the following list of design tools is utilized: customer interviews, activity diagrams, functional models, benchmarking, human factors engineering (HFE), House of Quality (HOQ), and failure modes and effects analysis (FMEA). The performance specifications are completed with verification tests that will ultimately need to be validated in an animal study.

To begin the product development process it is important to first understand the needs of the customer. Customer comments, though, can sometimes be subjective, biased, or vague. For this reason, they need to be translated into engineering requirements that can be verified through bench-top testing.

Activity diagrams and functional models are used to help identify latent needs that are not discussed in the interviews. Activity diagrams provide a way to visually organize how the NED is used within a catheterization laboratory. Functional models define the functions of the NED system and each subsystem.

Benchmarking can highlight where the current NED prototypes may excel or highlight design deficiencies that need improvement. HFE principles are incorporated to ensure the interface controlling the delivery pusher and detachment mechanism is intuitive and user-friendly. Once these are complete, a HOQ matrix is constructed to quantify with a measurable metric the relationship between the customer need and the corresponding engineering requirement. Due to the inherent risk associated with endovascular procedures, a risk analysis is important to identify unanticipated device-related hazards and include these risks into a risk management process. To identify and mitigate the risks, a FMEA is performed.

6. USER NEEDS

6.1 Customer Interviews

To begin implementing design controls, it is important to understand the needs of the customer. One noted study, Project SAPPHO, found that understanding the needs of the customer is the most important aspect in designing a successful product.[32] Successful products meet the customers' needs, have unique features not available on competitive products, or solve a problem the customer has with existing products.[33] The customer in this sense is defined as the end user of the product. This definition means the customer is not the patient but rather the interventional neuroradiologist who will be implanting the device.

Customer comments were gathered through an email exchange between Tony Boyle and Dr. Hartman, an interventional neuroradiologist at UCSF. Two face-to-face interviews were held at Texas A&M University; one with Dr. Miller, a professor of Cardiology and one with Ms. Grinde, a Research Associate.

To gain an understanding of the use environment, a clot extraction procedure was observed in a catheterization laboratory. The procedure was conducted at St. Joseph Mercy Oakland in Pontiac, Michigan. Witnessing the procedure provided the opportunity to see how the doctors, nurses, and technicians all interacted, how the imaging technology was utilized, and how the device was prepared prior to implantation. A lesson learned from the experience is the fact that most catheterization laboratories use bi-planar X-ray imaging. This technology necessitates that the embolization device be radiopaque so that the medical personnel can observe the device *in vivo*. An observation that could affect our specific design was at one point a new catheter, preloaded with a device, was flushed and sat in a saline bath for over forty five minutes. This observation is important because the T_g of SMP has been found to significantly decrease after immersion in water.[34] This effect will greatly influence the working time of the NED from the moment it is inserted into the first catheter and flushed with saline.

6.2 Customer Needs Assessments

Considering that customer comments are normally qualitative and subjective, they needed to be translated into needs statements. The comments and suggestions recorded during the interviews were interpreted to define what the NED system needs to do. That way the development team has concise, clear, and definitive statements to begin the design. The process of translating the raw customer data followed a five step approach.[35]

- Each customer need was expressed in solution neutral terms. Not defining how the NED system is to achieve the need allows the design team flexibility.
- Each customer need was expressed as specifically as possible to avoid confusion later when translating to performance specifications.
- Each customer need was worded with positive, not negative phrasing. Application of the need is easier when expressed positively.
- Each customer need was written as an attribute of the NED system to ensure consistency when converting into performance specifications.
- Words such as 'must' and 'should' were not used in an attempt to remain objective and avoid assigning a relative importance.

Once the customer interviews were completed, the needs were sorted according to specific categories. The categories were generated from the subsystems within the NED system and some of the functions that were defined from the Function Models described later in Section 7. The list of categories includes: ease of use, pusher, detachment, actuation, and size (Table 2).

A subjective importance rating was assigned to each device need. The rating system will help guide the development team when trade-offs and compromises need to be made while designing the NED system. The importance rating has a range of 1-5. A rating of 5 is a MUST need which is used when the customer must have that feature. A rating of 4 is a GOOD need which is a very important customer need. A rating of 3 is considered when the device SHOULD satisfy the customer requirement. A rating of 2 is

designated for a NICE need which would be nice if the device met the need but is not critical. A rating of 1 is a MAYBE need which can be interpreted as an optional requirement.[36]

Table 2. Customer Needs Assessment from Interview with Dr. Jonathan Hartman

Date: July 15, 2011	End User: Dr. Jonathan Hartman Job Title: Interventional Neuroradiologist Sacramento Medical Center Department of Neurosurgery	Neurovascular Embolization Device (NED)	
Category	Customer Statement	Interpreted Need	Importance Rating
Ease of Use	Flushed with saline solution continuously during the procedure	The NED has a working time of 10-15 minutes once placed in the microcatheter	5
	The time that each individual coil is in the microcatheter during deployment also varies with how difficult it is to put in or how difficult it is to achieve a decent configuration. Range is probably one minute on the low end and 5-10 minutes on the high end		
	Similarity to prior technology and ease of use are definitely a plus in terms of adoption	The NED behaves and actuates similarly to predicate devices	4
	Total procedure can last on the short end, 1 hr. On the long end, 5-6 hrs.	The NED can withstand 6 hrs. exposure time to saline	1
Pusher	As part of safety, ease of retrieval is a big issue	The NED can be retracted back into the microcatheter after partial deployment at least once with the NED in any configuration	5
Actuation	The main considerations for any device of this type are that it should be predictable in behavior, easily controlled/manipulated, and safe	The NED is easily pushed and pulled through the microcatheter	5
		The NED retains its crimped form until actuation	5
	Laser light actuation with need for eye protection-->not likely to be adopted unless there is a major advantage... one button to push to actuate-->highly likely to be adopted	The NED has simple to use, straight-forward actuation method	4
	Active control is a plus over passive (i.e., actuation by external heat source as opposed to by body temperature), although is not totally necessary	The NED has active user-controllable actuation	2

Basic product development resources were also studied to uncover latent customer needs that were not identified in the interviews.[32,36-38] The comprehensive list focused on identifying constant and general needs that were not necessarily discussed in the interviews (Table 3). The remaining customer need assessments and market research can be found in Appendix A in Tables 27-31.

Table 3. Customer Needs Assessment from Basic Product Development Research

Date: February 10-15, 2012	Product Development Research	Neurovascular Embolization Device (NED)
Category	Question/Prompt	Interpreted Need
Application	What is the purpose of the NED?	The NED is intended for embolization of intracranial aneurysms
	How will the NED be selected for use?	After consultation with a neurosurgeon and interventional neuroradiologist about the health of the patient and size and location of the aneurysm
	How will performance be measured?	Ease and success of delivery Occlusion percentage
Competition	What are current treatment options?	Current options include coiling, embolic agents, stenting, and clipping via surgery
	How will the NED differ from current devices on the market?	The NED will provide superior embolization of the aneurysm compared to current devices
Customer	Who will use the NED?	The NED will be implanted by a interventional neuroradiologist
	What is the user's familiarity with the device technology?	Devices have been on the market for 15 years and over 200,000 have been implanted
	How much time is the physician willing to spend implanting?	The NED will have a working time similar to predicate devices
	How much user training is required?	The NED design and delivery will be simplified to avoid complicated training
	What user characteristics affect what the NED must be like?	Predicate devices have set the precedent for familiarity and comfort
Environment	Where will the procedure for implanting the NED take place?	The NED will be implanted in a Catheterization Laboratory
Product Life Span	How often will the NED be used?	The NED will be a single use device
Life in Service	How long will the NED be in use?	The NED will be implanted for the life of the patient
Weight	Will weight or density affect delivery of device?	The NED will be compliant enough to navigate tortuous vessels
Safety	What are the safety concerns?	The NED will be safe and effective for its intended use
Maintenance	How will adjustments and monitoring of the NED be done?	The NED will be visible under fluoroscopy during implantation
Quality & Reliability	What quality is needed?	The NED will be of high quality to ensure it can be implanted correctly and stay within the aneurysm long-term
Storage	Will the NED be stored in a sterile and non-pyrogenic environment?	The NED will be packaged to maintain a sterile and non-pyrogenic environment
	Within what humidity and temperature range does the device need to be stored?	The NED will have instructions for proper storage
	Will the NED be easy to store?	The NED will be packaged similarly to predicate devices
Shipping	Does vibration affect actuation?	The NED will pass necessary vibration testing
Label	Label must define intended use	The NED will have a label that follows GMP regulations
Target Product Cost	What are the financial concerns for the NED?	TBD
Manufacturing Facility	Is certain equipment necessary?	The NED will be manufactured according to GMP regulations
Testing	Conduct applicable bench tests	The NED will undergo the same bench testing as predicate devices
Shelf Life	What is the expected shelf life of the NED?	TBD
Politics	Classification in US	The NED could be classified as Class II or Class III

6.3 Activity Diagram

Another tool used to identify user needs was an activity diagram which maps out the life cycle of the NED. Activity diagrams examine the customer and product interaction to identify customer needs. They are used as a graphical model to aid communication, organize the flow of design, and also as a way to accelerate the understanding of the design.[38] The implant procedure is a structured set of activities performed to produce a specified output. The output is defined as the successful occlusion of the aneurysm with minimal risk of re-bleeding or recanalization.

The activity diagram is broken into three stages; preparation, implantation, and follow-up (Fig. 6). From the diagram it is seen that the interventional neuroradiologist is the end user of the device and the patient is an indirect user. Some customer needs can be derived from the interaction between the device and the user. During the preparation stage, the device will be placed into a saline bath, thus necessitating the need for an established working time. The ability to push and pull on the device to obtain proper position before detachment will be an important parameter to monitor during the implantation stage. Finally during follow-up, the NED will need to be radiopaque in order to assess how well the aneurysm is occluded.

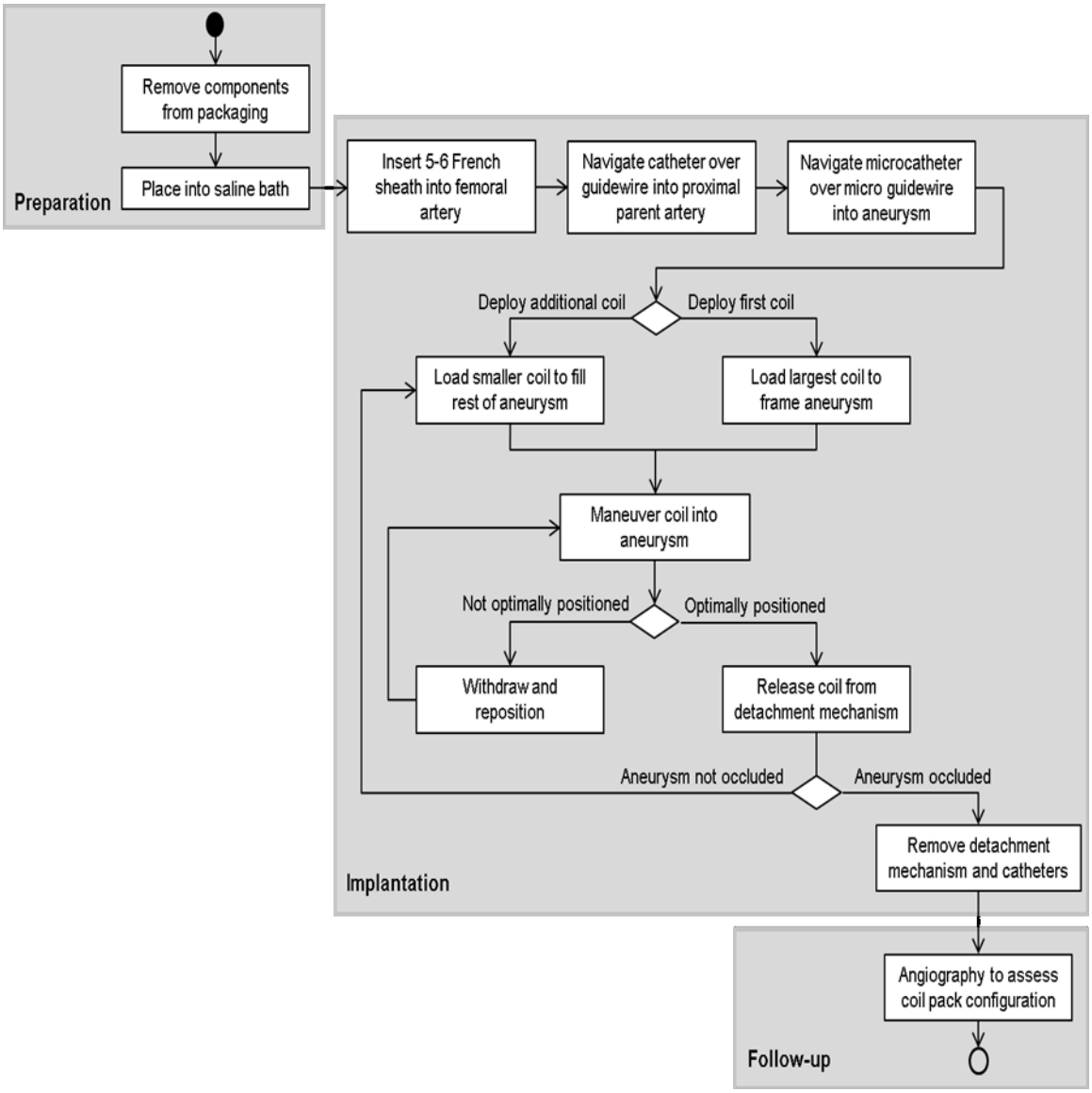


Figure 6. Activity Diagram of the NED System

7. FUNCTIONAL MODELS

7.1 Functional Models

A design technique known as functional modeling is used to ensure the design inputs of the NED system follow the user needs. Functional models simplify the medical device into the main functions it must perform to meet the user needs. A function is a declaration of a clear, repeatable relationship between an input and the desired output, while remaining independent of any particular form.[36] The product function is a simple representation of the product and is phrased as a combination of a noun and an active verb. The models decompose a problem into simpler sub-problems by focusing on *what* the device must do not *how* it will do it. This technique enables a solution neutral expression of the design task so a comprehensive search for solutions can be achieved later in the design process. The product function is then decomposed into sub-functions that correspond to subtasks which when taken together satisfy the overall function.

7.2 Functional Analysis System Technique

The first functional model that was constructed applied a top-down approach. The Functional Analysis System Technique (FAST) was used to define, examine, and understand the product sub-functions (Fig 7). The functional model can illustrate how the functions relate to each other and which functions have a higher priority for the design team. The functions were phrased with a verb and noun structure and were worded as broad and generic as possible. Phrasing the functions in broad terms can minimize any potential bias and allow the true crux of the problem to be realized.

The overall product function needed to be determined in order to assemble the functional model. The overall product function represents the main reason for the product's existence. The overall product function of the NED system is to occlude intracranial aneurysms. All other sub-functions are subordinate and support the overall

product function. The critical path was established by determining the string of sub-functions that are critical to the NED system achieving its intended use. The overall product function was listed to the far left of the diagram and the sub-functions were placed to the right. Each node to the right in the critical path answered the question of how the left node was achieved. For example, the NED can only be implanted into the aneurysm after it has been released. It can be released only after it has been properly delivered.

The rightmost extreme of the critical path is a sub-function not performed by the device and once it was reached, the system boundary was defined. The critical path functions can be decomposed into lower level sub-functions that are caused by the critical path. Sometimes unwanted side-effects are created when achieving the sub-functions. Therefore, new functions arise to mitigate the side-effects and are placed under the critical path function that caused them.

Other functions that are not part of the critical path in any way are placed above the functional model. The objective of the NED system is placed on the left, one-time functions in the center, and all-time functions on the right. The objective of the NED system is to provide superior occlusion compared to competitive coils. The one-time function is to protect the NED system during shipping and storage. The all-time functions that are always present include: behaving like similar devices, ensuring the NED system is compact, and reducing any friction for easy delivery into the aneurysm.

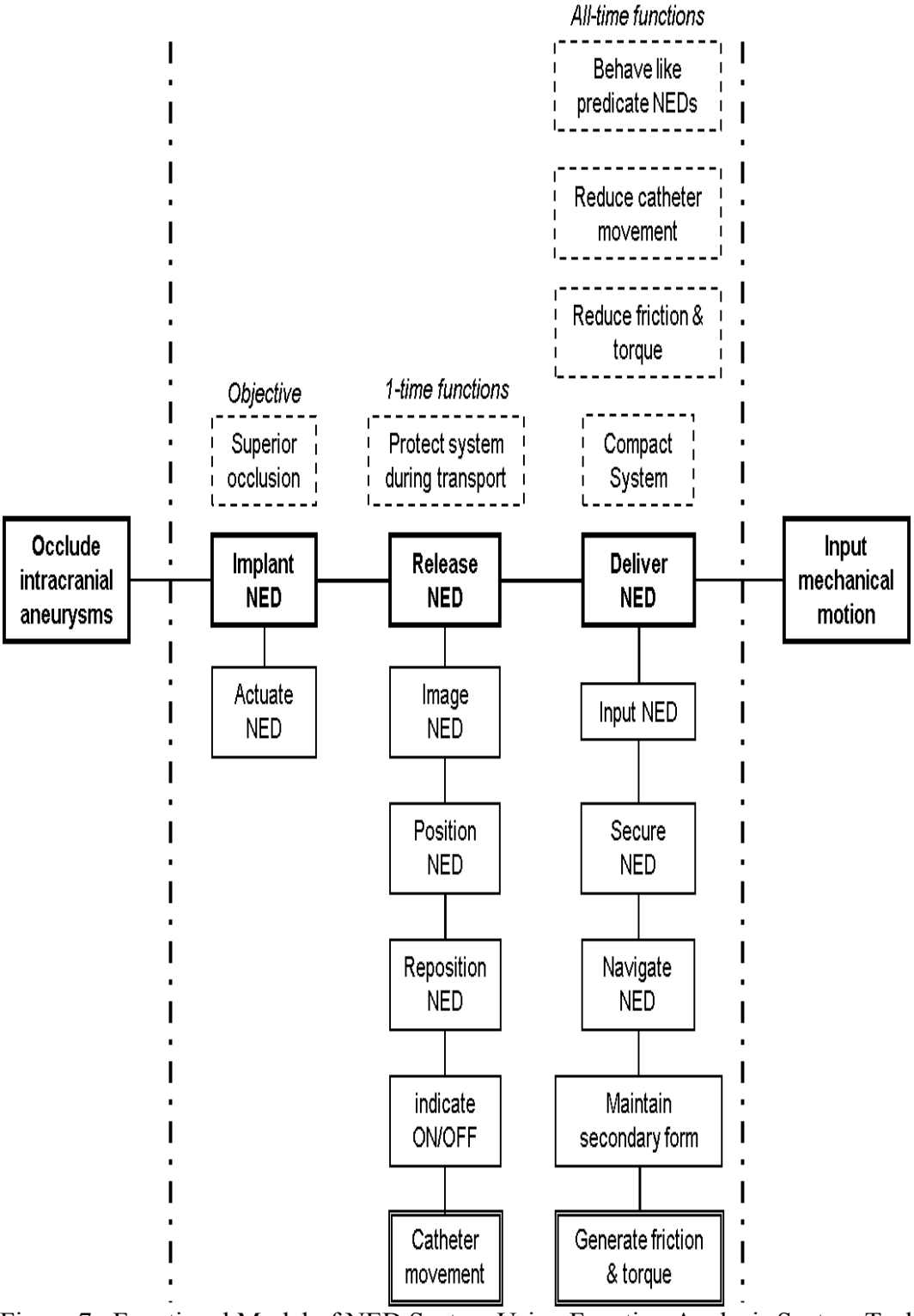


Figure 7. Functional Model of NED System Using Function Analysis System Technique

7.3 Subtract and Operate Procedure

The Subtract and Operate functional model applied a bottom-up approach. The smallest functions were first defined as those that could not be decomposed into further sub-functions. The component that supplied these smallest sub-functions were identified and then conceptually removed. By subtracting the component from the NED system, the critical contribution of that component is established. Once the component is subtracted, the NED system is tested on a conceptual basis to determine what important sub-functions were lost (Table 4). The components and features that are responsible for the primary sub-functions of the NED system are the guidewire and catheters, introducer sheath, delivery pusher, detachment mechanism, actuation method, and radiopacity. The sub-functions were then translated into a function tree (Fig. 8). The sub-functions were collected into common groups of functional description. The higher level sub-function nodes were placed above the lower level sub-functions until the function tree converged at the top into the overall product function.

Table 4. Subtract and Operate Procedure Function Structure

Guidewire & Catheters	Introducer Sheath	Pusher	Detachment	Actuation	Radiopacity
No way to implant guiding catheter, microcatheter, NED	No way to secure NED in catheter	Difficult to navigate tortuous vessels to guide NED into aneurysm	NED cannot be released	Foam cannot be expanded	Difficult to visualize NED in catheters
	No protection of foam from plasticizing agent	Difficult to properly position/reposition NED	No way to deliver NED	Cannot recover primary shape of NED	Difficult to visualize NED in aneurysm
	Difficult to minimize sliding friction	Difficult to preload NED		Cannot occlude aneurysm	
	Difficult to minimize torque				

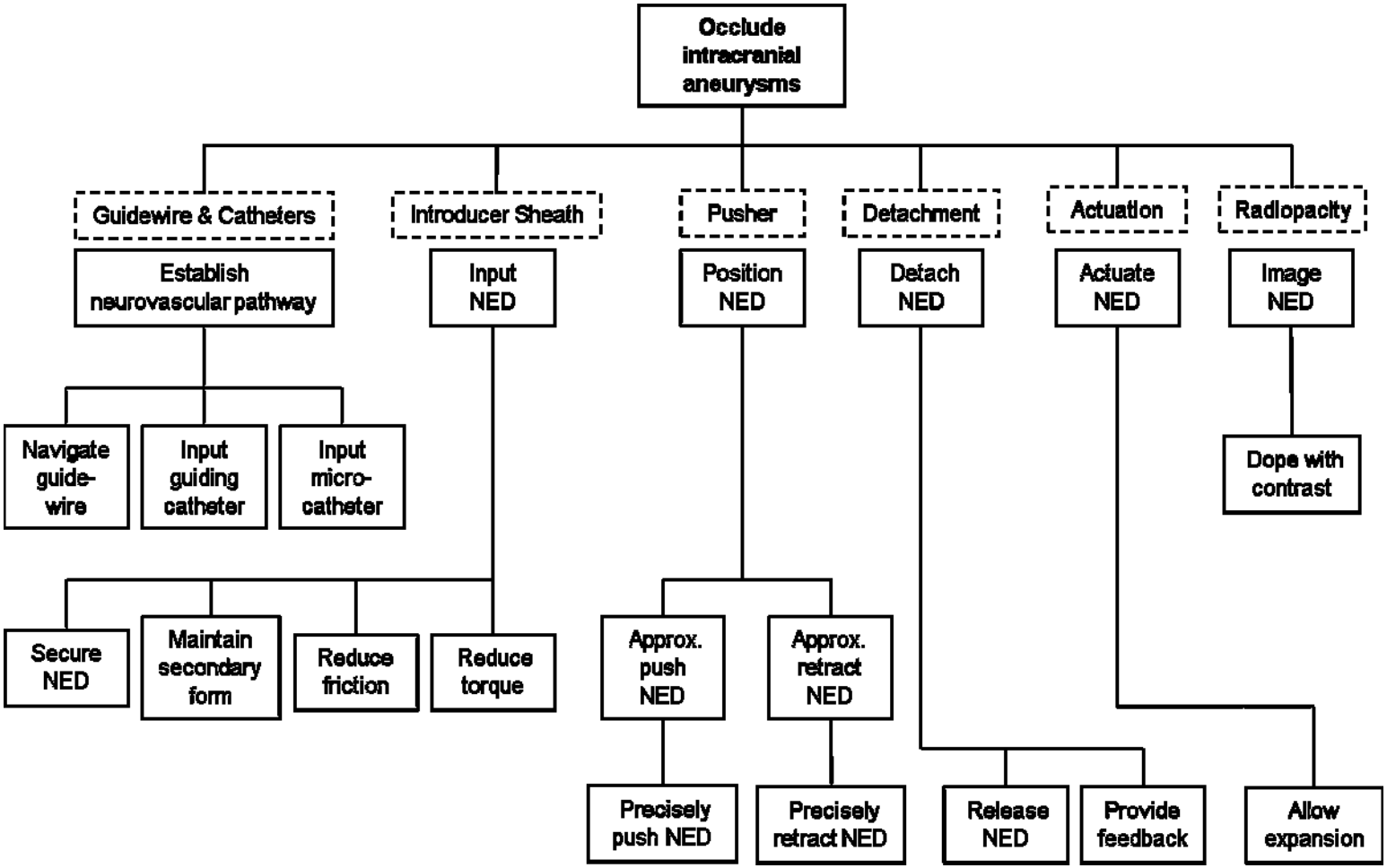


Figure 8. Functional Model of NED System Using Subtract and Operate Procedure

8. BENCHMARKING

8.1 Benchmarking Data for Current NED Systems on the Market

Benchmarking generates data to help clarify user requirements and understand current market products and technology trends. Benchmarking provides a standard for judging quality, performance, and value. The *best-in-class* product can be identified and studied to determine what attributes make it the best. These features can then be emulated and incorporated into the performance specifications. The design team must understand the market demand for a particular product and how competitors meet it. Designing similarity into the NED system aids in familiarity for the medical personnel. The benchmarking analysis for the NED system was carried out in a four-step process.

Step 1: Formed a List of Competitive Products

- The trade magazine *Endovascular Today*, 2012 BUYER'S GUIDE[39] was consulted to obtain a comprehensive listing of all the FDA-cleared NED systems available in the United States. All competitors and their different product models were listed. This list included each product launched under common platforms.

Step 2: Conducted an Information Search

- To properly benchmark the NED systems, it was important to gather as much information as possible. Information about each NED was taken from a variety of sources; marketing literature from applicable company websites, each product's Instructions for Use, published case studies, 510(k) and humanitarian device exemption (HDE) submissions, published adverse events from the MAUDE database published on www.FDA.gov, and the FDA guidance document, "*Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices"* (Table 5). The needs identified in the customer assessments were also referenced.

Step 3: Formed a List of Design Issues

- A list of design issues were developed from the information search conducted in Step 2. Particular attention was paid to what materials the devices were made from and how the devices functioned.

Step 4: Benchmark by Function

- The functional models from Section 7 were studied to help organize the benchmarking data. Three prominent sub-functions stood out as important to achieving the overall product function. From this analysis, the NED system was broken down into three sub-systems; the NED (Table 6), the delivery pusher (Table 7), and the detachment mechanism (Table 8). The acronym, ID, stands for the inner diameter of the microcatheter that is used for each coil.

Table 5. Benchmarking List of 510(k) and HDE Submissions

Company	Trade Name	510(k) Number	Clearance Date
Codman Neurovascular	MicroCoil Delivery System	K002056	1/11/2001
	TRUFILL Detachable Coil System	K014041	3/7/2002
	MicroCoil System	K031578	8/1/2003
	MicroCoil System	K033813	2/4/2004
	TRUFILL Detachable Coil System	K063254	12/7/2006
	Orbit GALAXY Detachable Coil System	K093973	5/26/2010
Covidien	Sapphire Detachable Coil System	K030392	7/21/2003
	Sapphire Detachable Fiber Coil System	K031852	8/20/2003
	Sapphire Detachable Fiber Coil System	K033372	1/9/2004
	Sapphire NXT Detachable Coil System	K041649	7/16/2004
	Nexus Detachable Coil System	K050543	4/27/2005
	Nexus Detachable Coil System	K060625	4/20/2006
MicroVention TERUMO	MicroPlex Coil System	K012145	10/29/2001
	MicroPlex Coil System and HydroCoil Embolic System with the HydroLink Syringe Kit	K022735	9/6/2002
	MicroPlex Coil System (MCS) HydroCoil Embolic System	K032590	10/22/2003
	HydroCoil Embolic System	K070656	6/15/2007
	HydroCoil Embolic System	K100454	4/22/2010
	HydroCoil Embolic System, HydroSoft Plus	K113457	12/16/2011
Penumbra	Penumbra Coil System / Penumbra Coil 400	K103305	1/26/2011
Stryker Neurovascular	Guglielmi Detachable Coils	K962503	9/20/1996
	Guglielmi Detachable Coils	K971395	7/14/1997
	Guglielmi Detachable Coils	K993418	1/21/2000
	Matrix Detachable Coils	K012985	1/31/2002
	Guglielmi Detachable Coils (GDC) Power Supply	K021494	6/6/2002
	Target Detachable Coils InZone Detachment System	K093142	2/4/2010
	Target Detachable Coils	K102672	10/15/2010
	Target Detachable Coils	K112385	9/15/2011
Company	Trade Name	HDE Number	Approval Date
NeuroVasx Inc.	cPAX Aneurysm Treatment System	H100002	4/1/2011

Table 6. Benchmarking Data for Currents NEDs on the Market

Company	Trade Name	Materials Used	Type	Shape	Working Time (min.)	Retractable	Reposition	System Size	Crimped Diameter (in.)	Coil Diameter (mm)	Overall Length (cm)
Codman Neurovascular	TRUFILL DCS ORBIT Detachable Coil System	Platinum/ Tungsten alloy (92/8) wire, Au/SN solder	Fill	Helical, complex,	Infinite	Yes	Yes	14 18	0.012	2-20	1.5-30
	Orbit GALAXY Detachable Coil System	Platinum/ Tungsten alloy wire, Au/SN solder, polypropylene stretch-resistant suture	Frame, fill, finish	Complex, helical	Infinite	Yes	Yes	14 18	0.012-0.014	2-4 2-12 6-20	1.5-10 1.5-30 20-30
	CASHMERE Microcoils	Platinum/Tungsten alloy & Au/Sn solder or Cerecyte® - stretch-resistant, absorbable PGA or non-absorbable polypropylene filaments inside of coil	Frame, fill	Straight, spherical, complex, helical	Infinite	Yes	Yes	14 All coils fit within 0.017”	0.0135 Microcatheters with ID 0.0165-0.019	2-12	2.5-30
	DELTAPAQ Microcoils		Fill, finish	Spherical , helical	Infinite	Yes	Yes	10 14 18	0.0100-0.0105 ID 0.014-0.017 ID 0.0165-0.019 0.017-0.021	1.5-10	2-25
	DELTAPLUSH Microcoils		Finish	Spherical , helical	Infinite	Yes	Yes	10	0.0100-0.0105	1.5-4	1-8
	HELIPAQ & HELIPAQ SR Microcoils		Fill	Helical	Infinite	Yes	Yes	10 18	0.010-0.014 ID 0.014-0.017 ID 0.017-0.021	2-10 2-20	1-30 4-30
	INTERPAQ Microcoils		Fill	Straight	Infinite	Yes	Yes	10	ID 0.014-0.017	4-6	10-30
	MICRUSPHERE Microcoils		Frame	Spherical	Infinite	Yes	Yes	10 18	0.010-0.015 ID 0.014-0.017 ID 0.017-0.021	2-10 2-18	2.5-20.3 2.7-30
	PRESIDIO Microcoils		Frame, fill	Spherical	Infinite	Yes	Yes	10 18	0.0105-0.0150 ID 0.017	4-8 8-20	11.5-29 30-50
	ULTIPAQ Microcoils		Fill, finish	Helical	Infinite	Yes	Yes	10	0.010 ID 0.014-0.017	2-4	1-8
Covidien	AXIUM Detachable Coils	Bare platinum, PGLA microfilament, & Nylon 6-6 microfilament	Frame, fill, finish	Helical, spherical	Infinite	Yes	Yes	10 18	0.0115-0.0145 ID 0.0165-0.17	1.5-25	1-50
	Nexus Detachable Coils	Platinum alloy enlaced with absorbable polymer microfilaments. Stretch-resistant Nitinol core	Frame, fill, finish	Helical & 3D	Infinite	Yes	Yes	10	0.010	2-18	4-30

Table 6 Continued

Company	Trade Name	Materials Used	Type	Shape	Working Time (min.)	Retractable	Reposition	System Size	Crimped Diameter (in.)	Coil Diameter (mm)	Overall Length (cm)
	NXT Detachable Coils	Platinum/iridium alloy and Nylon 6-6 fibers, coated with parylene	Frame, fill, finish	Helical	Infinite	Yes	Yes	10 18	0.010-0.018	2-15	2-30
MicroVention TERUMO	Compass Coils	Platinum/Tungsten alloy (92/8)	Frame, fill	Complex	Infinite	Yes	Yes	10 18	0.0085-0.015	2-20	
	Complex Coils		Frame, fill	Complex	Infinite	Yes	Yes	10 18	0.0095-0.015	2-20	
	Cosmos Coils		Frame	Complex	Infinite	Yes	Yes	10 18	0.010-0.015	2-24	
	Helical Coils		Fill, finish	Helical	Infinite	Yes	Yes	10 18	0.0095-0.014	2-20	
	HyperSoft Coils		Fill, finish	Helical	Infinite	Yes	Yes	10	0.010-0.011	1.5-6	
	HydroCoil Embolic System	Platinum/Tungsten alloy (92/8) with outer layer hydrophilic acrylic polymer. Cross-linked copolymer - acrylamide & acrylic acid	Frame, fill	Helical	5 Expansion 20 min.	Yes	Yes	10 14 18	0.010 Expanded 0.035	3-8	6-33
	HydroFrame HydroCoil Embolic System		Frame	Helical	30	Yes	Yes	10 18	0.012-0.015	3-20	19-50
	HydroSoft HydroCoil Embolic System		Finish	Helical	30	Yes	Yes	10	0.013	1.5-10	2-30
Penumbra Inc.	Penumbra Coil 400	Platinum/Tungsten alloy (92/8) wire with stretch-resistant nitinol wire	Frame, fill, finish	Complex	Infinite	Yes	Yes	Catheter with ID ≥ 0.025"	0.020 ID 0.025	3-32	6-60
Stryker Neurovascular	GDC 360° Detachable Coils	Platinum/Tungsten alloy wire, stainless steel & Au/Sn solder, polypropylene secured at ends	Frame, fill, finish	Helical, vortex, 3D spherical	Infinite	Yes	Yes	10 18	0.0095-0.015	2-20	2-30
	Matrix Detachable Coils	Platinum with absorbable PGLA copolymer, polypropylene secured at ends for stretch resistance	Frame, fill, finish	Helical	Infinite	Yes	Yes	10	0.011-0.012	2-24	2-40
	Target Detachable Coils	Platinum/Tungsten alloy (92/8) wire	Frame, fill, finish	Complex, spherical, helical	Infinite	Yes	Yes	10	0.010-0.012	2-15	
NeuroVasx Inc.	cPAX Aneurysm Treatment System	Hydrophilic coated, polyethylene with tungsten	Frame, fill	Straight	Infinite	Yes	Yes	18	0.016	N/A	Up to 80

Table 7. Benchmarking Data for Current Delivery Pushers on the Market

Manufacturer	Trade Name	Method of Coil Attachment	Introducer Materials	Delivery Materials	Pusher Stiffness (lbs.)	Working Length (cm)
Codman Neurovascular	EnPOWER Device Positioning Unit	High tensile strength, highly oriented polyethylene fiber. Mechanical Elastomeric Press Fit with articulating detachment junction	Variable stiffness polyethylene introducer tip, translucent introducer body	Stainless steel hypotube (proximal), stainless steel braid (mid), nitinol and platinum, polymer (distal) sheathing for 2 copper conduction wires and distal RH coil	0.0058	155-210
	TRUFILL DCS Hydraulic Release System	Soft polymer gripper, slide coil into polymer delivery tube	Tube designed to protect coil	Tube comprised of hub, strain relief, stiff proximal section, floppy distal section		175
Covidien	AXIUM Delivery Pusher	Floating eyelet	Introducer sheath	Hypotube composite with radiopaque positioning marker		
	NXT Guiding System	Laser welded	Teflon outer jacket	Stainless steel wire with radiopaque positioning coil partially covered in Teflon		
MicroVention TERUMO	V-TRAK Delivery Pusher	Proximal end of coil incorporates platinum/iridium (90/10%) coupler and a polyolefin elastomer. Filament runs through inner lumen of coil coupler and is attached to distal end of Pusher	Introducer sheath on outside of delivery pusher	Variable stiffness, stainless steel pusher and tapered mandrel, 2 layers of PET tubing cover distal end, layer of polyimide tubing covers proximal end	0.0045	185
	HydroLink	PET tubing is heat shrunk over coupler/pusher junction to act as retention sleeve	2 outer layers of PET tubing (distal), layer of polyimide tubing (proximal), introducer needle	Variable stiffness, stainless steel tube with several outer layers of PET tubing, luer hub at proximal end of pusher		185
Penumbra	Penumbra Delivery Pusher	Ball and socket	N/A	Flexible Nitinol coil reinforced PTFE-lined pusher. Stainless steel/polymer detachment pusher		145-175
Stryker Neurovascular	InZone Detachment Pusher	Welded or soldered to delivery pusher, laser ablated/etched	High density polyethylene introducer	Ground 316LVM stainless steel delivery wire, Teflon outer jacket at distal section, flushing dispenser coil assembly	0.0090	50-200
	GDC Pusher	Soldered to delivery pusher	N/A	Ground stainless steel core wire, Teflon outer jacket proximal to detachment zone		130-180

Table 7 Continued

Manufacturer	Trade Name	Method of Coil Attachment	Introducer Materials	Delivery Materials	Pusher Stiffness (lbs.)	Working Length (cm)
NeuroVasx Inc.	Pusher	Polyethylene bridge	N/A	Hydrophilic coated polyethylene shaft with polyurethane strain relief, polycarbonate hub, hemostasis valve		160

Table 8. Benchmarking Data for Current Detachment Mechanisms on the Market

Manufacturer	Coil Compatibility	Trade Name	Method of Coil Detachment	Mechanism of Release	Power Source	Detachment Time (s)	Portability	# of Coils per Controller	Detachment Feedback	Comments
Codman Neurovascular	TruFill DCS ORBIT Detachable Coil System Orbit GALAXY Detachable Coil System	TRUFILL DCS Syringe II	Hydraulic-fluid pressure expands gripper material	Rotate knob clockwise, 3 pressure levels	N/A	3	Hand held	5	Rapidly decreasing pressure indicates coil detached	14-cc syringe barrel with pressure gauge, threaded plunger assembly with latch mechanism, flexible high-pressure extension tube
	Micrus Endovascular MicroCoil System	Blue ENPOWER Detachment Control System	Electrolytic-heat shearing of PE fiber	1 detach button	Battery Lithium Ion	2	Mounted onto IV pole	>5000	"Detach Cycle" light turns off. Beep sounds for 5s while detaching	Self-grounded, closed circuit. Lithium Ion eliminates battery changes. Electrical energy heats platinum resistive heating coil
		Black ENPOWER Detachment Control System		1 detach button	Battery 6 AA	5				
Covidien	AXIUM Detachable Coils	Linear Release System	Mechanical actuator-freely rotating ball and socket	Thumb slide	N/A	Instant	Hand-held	25	Thumb-slide stops and clicks	No cables, boxes, or batteries
	Nexus Detachable Coils, NXT Detachable Coils	NXT Detachable System	Electrolytic - dissolves small detachment element	Switch	Battery 9V	Instant	N/A	N/A	Acoustic sound and indicator flashes	Patient return electrode
MicroVention TERUMO	MicroPlex Coil System, HydroCoil Embolic System, HyperSoft Finishing Coil	V-GRIP Detachment Controller	Electrolytic - melts polyolefin elastomer filament at coupler/pusher junction	1 detach button	Battery	0.75	Hand-held	20	3 beeps and light flashes	No accessories, patient grounding, connecting cables, or additional batteries. 2 silver electrical leads run along outside of mandrel. Platinum and stainless steel wires wound around mandrel to form electrical heater

Table 8 Continued

Manufacturer	Coil Compatibility	Trade Name	Method of Coil Detachment	Mechanism of Release	Power Source	Detachment Time (s)	Portability	# of Coils per Controller	Detachment Feedback	Comments
		HydroLink Detachment System	Hydraulic-creates pressure at proximal end of Pusher	Syringe	N/A	instant	Hand-held	N/A	N/A8	Consists of purge syringe, 0.25-cc syringe detachment syringe, filling cannula
Penumbra	Penumbra Coil 400	Penumbra Coil Detachment Handle	Mechanical actuator-ball & socket	Thumb slide	N/A	instant	Hand-held	multiple	Thumb-slide stops and clicks	No cables, boxes, or batteries
Stryker Neurovascular (manufactured by Boston Scientific)	GDC 360°, Matrix, Target Detachable Coils	InZone Detachment	Electrolytic-dissolves positioning wire near coil junction	1 detach button	Battery	<5	Hand-held	1	Visual and audible signals	No cables, needles, or battery changes needed
	GDC Detachable Coils	GDC SynerG Power Supply		1 detach button	Battery 9V	5	Hand-held	1	5 beeps and light flashes	Patient return electrode
NeuroVasx Inc.	cPAX	cPAX Delivery Detacher Device	Electrolytic - melting of cPAX	1 detach button	Battery 2 AA	4	Mounted onto IV pole	1	Change in audible tone	Core wire with electric lead wire attached to heater coil at distal end

9. PERFORMANCE SPECIFICATIONS

9.1 Human Factors Engineering

Implementing Human Factors Engineering (HFE) principles into the design of medical devices reduces the risk of injury or death to the patient. This focus is accomplished with the careful and systematic design of an effective user interface that is compatible with the abilities of the user population.

To eliminate user error it helps to design the product to be similar in form and function to what is currently being used in clinical practice. People tend to respond to new situations based on established habits. An intuitive design that is comparable to existing technology helps to reduce potential problems. The following general rules of thumb will be considered for the hardware and possible software performance specifications of the delivery pusher and detachment mechanism (Table 9).[40]

Table 9. Human Factors Considerations

Category	Human Factor
User	The interface is consistent with user expectations, keeping in mind the user's prior experience and well-established conventions
	The basic capabilities of the user such as strength, memory, reach, vision, hearing, and dexterity
Controls	Any control switches and knobs correspond to normal conventions and are arranged and spaced to avoid accidental activation
	Any controls provide tactile feedback
Sound	The pitch and intensity of any auditory signal can be heard easily above ambient noise
Visual Display	The brightness of displays can be perceived by users under different ambient illumination.
	The displays can be viewed from multiple distances and angles, keeping in mind contrast, color, and symbol size
	The controls and display arrangements are well-organized and the association between the controls and displays is obvious
	Any symbols, text, and abbreviations follow conventional standards and are defined in the user manual
Data Input	Use conventional symbols, colors, abbreviations, and formats
	Keeps users aware of the device status at all times
	Provide clear and immediate feedback
	Use prompts and menus to guide the user
	Provide a way to correct input errors
Data Output	Convey information quickly and reliably, using conventional symbols, colors, abbreviations, and formats
	Use dedicated displays for critical information
Alarm	Alerts should be attention-getting and in view

Benchmarking results from Section 8 were reviewed to accommodate the user needs. Anthropometric data was analyzed to supply necessary information for the sake of assessing portability of a potential external controller for the detachment mechanism. The anthropometric data guided the process of selecting sizes and can help determine the proper placement of any control switches or knobs. Considering interventional neuroradiologists come from ethnically diverse populations, it will be important to understand the variation in sizes. At a minimum, the design should accommodate adults who range from the 5th-percentile female to a 95th-percentile male in size.[41]

Potential specifications for the sound and visual display of an alarm system or feedback signals was generated (Table 10).[41]

Table 10. Auditory and Visual Display Specifications for Feedback Signals

#	Functional Requirement	Unit	Upper Limit	Lower Limit	Ideal Direction
1	Auditory frequency range for fundamental	Hz	1000	150	+
2	Auditory frequency range for harmonics	Hz	4000	300	+
3	Auditory pulse ON time	S	0.2	0.075	+
4	Auditory pulse OFF time	S	0.125	0.05	+
5	Auditory rise time	%	20	10	+
6	Auditory loudness	dB	25	15	+
7	Visible brightness distance	m	10	4	+
8	Visible color	Color	red	yellow	+
9	Visible flashing frequency	Hz	2.8	1.4	+
10	Visible ON duty cycle	%	60	20	+

9.2 House of Quality

The next step in the design process was to create the design inputs known as the performance specifications. This was no trivial task as the establishment of performance specifications for a product is the most important aspect of the design process.[35,4231] The specifications were developed by tying together the needs from the customer interviews and the data from benchmarking activities using a House of Quality (HOQ) matrix for the NED (Table 11), and for the delivery pusher and detachment mechanism (Table 12). A HOQ is a conceptual map that aids in functional planning and communication.[43] It is a methodology that is used to define what the customer wants, prioritizing these

requests, converting them into engineering requirements, establishing target specifications, and then showing how everything is related together.

The HOQ was built by first listing and organizing the customer needs with their subjective importance ratings according to their specific categories. The customer needs, though, only mentioned *what* the device should do. They needed to be translated into engineering requirements to describe *how* the device would satisfy the needs. Along the top of the HOQ, engineering requirements were placed that affect one or more of the customer needs. The engineering requirements describe the NED system in measurable terms and are meant to directly affect customer perceptions.[43] Sometimes a customer need was quite general and broad, so it required more than one engineering requirement to fully satisfy the need. There are also certain engineering requirements the FDA has identified which were incorporated into the HOQ.

- coil strength (i.e., the force required to deform the coil shape – primary and secondary diameters, as well as coil tensile strength, torsional resistance and fatigue)
- ease of delivery, as measured by friction when advancing and/or retracting the coil through a recommended catheter positioned in a simulated tortuosity
- for coils with fibers, a description of the fiber attachment mechanism and pull-out force
- a description of the detachment mechanism and data on the detachment time
- reliability of the detachment mechanism.[44]

The next step was to fill in the body of the house by evaluating the strength of the relationship between the customer needs and the engineering requirements. A rating of 9 was used for strong relationships, 3 for moderate, and 1 for weak. At the bottom of the house, the technical importance ratings were calculated by taking the sum of the products between the strength of a particular engineering requirement and the subjective importance rating of each customer need. The technical importance rating can highlight significant engineering requirements that require attention. Results from benchmarking data, relevant scientific literature, and 510(k) and HDE submissions were reviewed to establish the initial units and target values of each engineering requirement. A lower and

upper limit for the target values along with an ideal direction was defined and placed below the technical importance rating. The ideal direction provides guidance about whether the design should strive to achieve the upper or lower limit.

Finally, the roof of the house was filled in by determining the correlations between the engineering requirements. Each engineering requirement was evaluated against all the other engineering requirements to determine how various aspects of the NED system are all related. This data highlights the interrelationships between requirements and illustrates how changing one requirement could have a ripple effect on the rest of the design. A rating of 2 was used for a strong positive correlation, 1 for moderate positive, a blank space for no correlation, and '-', for a negative correlation. For example, if the design team wants to increase the filling percentage in order to achieve greater occlusion of the aneurysm, at first thought it seems like a good idea since the technical importance rating is 168. However, achieving a higher filling percentage will most likely require more foam volume, which would have a negative impact on the crimped diameter. When taking into consideration the fact that the crimped diameter has a higher technical importance rating of 268, the design team may reevaluate their decision about increasing the filling percentage. The HOQ can be used as a guide for the design team to help prioritize the engineering requirements. The HOQ can highlight the engineering requirements that require the most attention.

Table 11. House of Quality for the NED

1	Filling percentage																														
2	Coils used		2																												
3	Radiopacity		1	1																											
4	Crimped diameter		-		-																										
5	Sharp edges or corners																														
6	MRI - Static magnetic field				-																										
7	MRI - Spatial gradient field				-			1																							
8	MRI - Max averaged specific absorption rate (SAR)				-			1	1																						
9	Advancement force					1	1																								
10	Retraction force					1	1				1																				
11	Prep time																														
12	Axial shear					1	1				2	2																			
13	Circumferential shear					1	1				2	2		1																	
14	Minimum radius of curvature					1	1				2	2		1																	
15	Working time					-					1	1	1	1	1	1															
16	Particulate generation													1			1														
17	Complete retractions into sheath after 90% deployed					1	1					2		2	1	1	2	2													
18	Complete retractions into microcatheter after 90% deployed					1	1					2		2	1	1	2	2	2												
19	Tip deflection force				-	1	1				2	2				2	1														
20	Shape memory recovery of foam		1	1																-	-										
21	Shape recovery forces of foam		1	1																-	-		2								
22	Force required to deform primary coil shape		1	1																-	-		1	1							
23	Time to learn actuation method												1																		
24	Actuation time		1	1													-			-	-		1	1	1	1					
25	Physiologically compatible temperature		2	1										1	1	1						1	1		1		2				
26	Range of device lengths		2	1							1	1				2						1									
27	Range of coiled diameters		2	1							1	1				2						1									2
			Engineering Requirements																												
Category	Customer Needs	Importance	Filling percentage	# of coils used	Radiopacity	Crimped diameter	Sharp edges or corners	MRI - Static magnetic field	MRI - Spatial gradient field	MRI – Max averaged specific absorption rate (SAR)	Advancement force	Retraction force	Prep time	Axial shear	Circumferential shear	Minimum radius of curvature	Working time	Particulate generation	# of complete retractions into sheath after 90% deployed	# of complete retractions into microcatheter after 90% deployed	Tip deflection force	Shape memory recovery of foam	Shape recovery of foam	Pressure required to deform primary coil shape	Time to learn actuation method	Actuation time	Physiological temperature	Range of device lengths	Range of coiled diameters		
Ease of Use	Visible under fluoroscopy during/after implantation	5	3		9			1	1	1													3	3	3						
	Easily pushed and pulled through the microcatheter	5				9	3				9	9		3	3	9	9					3									
	Withstand being twisted and bent	5				3	1				3	3		9	9	9	3	3				1							1		
	Working time of 10-15 minutes once placed in the microcatheter	5				3					1	1	9				9	3	9	9	3						1	3			
	Use fewer coils to provide superior embolization of the aneurysm over time compared to current devices	4	9	9	3	3																3	3	3		1	3	9	9		
	Similarity to prior technology and ease of use are definitely a plus in terms of adoption	4	3	1	9		9	9	9	9	9	9	3	9	9	9	9		9	9	9				3	3	9	9	9		
	MR conditional	3			3			9	9	9																					
	Ready to use right out of the package	3				3	1						9													3		1			
	Withstand 6 hrs. exposure time to saline	1				1							9				9	3										1			

Table 11 Continued

Pusher	Retracted back into the sheath and repositioned after partial deployment at least once	5				9	3				3	9		9	3		9	9	9		3	3	3	3		9	3		3
	Retracted back into the microcatheter after partial deployment at least once with the NED in any configuration	5				9	3				3	9		9	3		9	9		9	3	3	3	3		9	3		3
	Foam pieces do not break off when retracted	5				1	1					3		9			3	9	9	9		1	3						1
	Retracted and repositioned 2-3 times is preferred	3				9	3				3	9		3	1		9	9	9		3	3	3	1		9	1		3
Detach	Does not alter the position of the microcatheter during positioning, detachment, and actuation	5				3	3				9	9		3	1	9	3				9	3	1			3	3		
	Remain in the aneurysm once detached	5	9	3		3							3					9					9	9	3		9	3	1	1
Actuate	Retains its crimped form until actuation	5				3							3				9		3	3							9	3		
	Actuates into stable, known configuration and diameter	5	3	1													1					9	9	9		3	3	1	1
	Actuates to cover the neck of the aneurysm	4	9	3		1											1					3	3	9		3	3	1	1
	Simple to use, straight-forward actuation method	4											9				3								9	3	3		
	Conform to range of shapes	3	3	1		1																9	9	3		3		9	9
	Active user-controllable actuation	2															3								3	9	3		
Size	Manufactured with multiple sizing options	5				3	1				1	1		1	1	1	1		1	1	1	1	1	1				9	9
	Technical Importance		168	75	102	286	123	68	68	68	190	283	144	260	139	176	374	240	218	191	160	220	220	170	63	309	190	163	202
	Units		%	#	%	in.	#	Tesla	G/cm	W/kg	g_f	g_f	s	g_f	g_f*m	degree	min.	#	#	#	g_f	%	kPa	kPa	min.	min.	°C	cm	mm
	Upper Quantitative Limit		100	20	100	0.020	0	3	720	2	50	50	120	inf.	inf.	180	15	0	3	3	7	95	700	700	5	20	50	40	20
	Lower Quantitative Limit		30	1	8	0.010	0	1.5	1	1	1	1	1	150	150	180	5	0	0	1	1	80	0.05	0.05	0.5	0.1	37	4	3
	Ideal Direction		+	-	+	-	=	+	+	+	-	-	-	+	+	=	+	=	+	=	-	+	+	+	-	-	-	+	+

Table 12. House of Quality for the P&D

1	Radiopacity																			
2	Outer diameter		-																	
3	Working length		1																	
4	Sharp edges or corners																			
5	Advancement force			2		1														
6	Retraction force			2		1	1													
7	Prep time																			
8	Tensile strength of NED and Detachment zone							2												
9	Tensile strength of Detachment zone and Pusher							2		1										
10	Tip deflection force			1		1	2	2												
11	Buckling force			1		1	1													
12	Detachment time																			
13	Reliability after fatigue									1	1	1		1						
14	Time to learn how to detach NED								1						1					
15	Exchanges through guiding catheter													1	1					
16	Length of controller																			
17	Diameter of controller																			
18	Weight of controller																	-	2	
			Engineering Requirements																	
Category	Customer Needs	Importance	Radiopacity	Outer diameter	Working Length	Sharp edges or corners	Advancement force	Retraction force	Prep time	Tensile strength of NED and Detachment zone	Tensile strength of Detachment zone and Delivery Pusher	Tip deflection force	Buckling force	Detachment time	Reliability after fatigue	Time to learn how to detach NED	Exchanges through catheter	Length of external controller	Diameter of external controller	Weight of external controller
Ease of Use	Visible under fluoroscopy during implantation	5	9	3	1															
	Withstand being twisted and bent	5		3		1	3	3		1	1	1	1							
	Ready to use right out of the package	3		3	3	1			9							3		1	1	1
Pusher	NED retracted back into the micro-catheter and repositioned after partial deployment at least once.	5				3	3	9												
	Removed from the body with the NED in any configuration Retracted back into the microcatheter after partial deployment at least once	5				3	3	9												
	Delivery Pusher does not alter the position of the microcatheter during positioning, detachment, and actuation	5		1		3	9	9	3	1	3	9			1					
	Delivery Pusher is easily pushed and pulled through the microcatheter	5					9	9												
Detach	Detachment mechanism does not alter the position of the microcatheter during positioning, detachment, and actuation	5		3	1	3	9	9		3	3	9	3	3	1					
	Detachment is easily pushed and pulled through the microcatheter	5		3	3	3	9	9		9	9	3	9							
	Immediate and reliable	5												9	9					
	Simple, user-controllable detachment	4												3	3	9				

Table 12 Continued

Actuate	Less number of exchanges through guiding catheter the better	3																9				
Size	Portable	3																	9	9	9	
Technical Importance			45	74	34	83	225	285	42	70	80	110	65	72	67	45	27	30	30	30		
Units			%	in.	mm	#	g_f	g_f	min.	g_f	g_f	g_f	g_f	s	cycles	min.	cycles	mm	mm	lbs.		
Upper Quantitative Limit			100	0.020	200	0	100	100	5	inf.	inf.	7	infinite	5	30	5	2	120	75	2		
Lower Quantitative Limit			8	0.010	150	0	1	1	0.5	150	150	1	150	0.5	6	0.5	1	75	38	0.25		
Ideal Direction			+	-	+	=	-	-	-	+	+	-	+	-	+	-	-	+	-	-		

10. RISK ANALYSIS

10.1 Failure Modes and Effects Analysis

Endovascular treatment is a complicated and delicate procedure incorporating a team of medical personnel and highly sophisticated technology. The technical failure rate for procedures has been reported to range between 4.8% to >10%.[13] Therefore, there are certain risks the FDA has identified that require mitigation measures to be taken (Table 13). Risk management begins once the performance specifications are defined. A risk analysis is necessary to evaluate the proposed specifications against any risks imposed by the NED system.

Table 13. FDA Identified Risks for NEDs[44]

Identified Risk	Recommended Mitigation Measures
Blood vessel perforation or rupture	Preclinical testing Animal testing Clinical testing Labeling
Unintended thrombosis	Preclinical testing Animal testing Clinical testing Labeling
Adverse tissue reaction	Preclinical testing Animal testing Clinical testing
Infection	Sterility
Hematoma formation	Preclinical testing Animal testing Clinical testing Labeling

A Failure Modes and Effects Analysis (FMEA) was performed to identify any other risks specific to the NED system. The results of the FMEA were based on previous prototype testing done by Wonjun Hwang in the Biomedical Device Laboratory and reviewing adverse events listed on the MAUDE database published on www.FDA.gov. The results of the MAUDE research can be found in Appendix B in Tables 32-34.

Only one FMEA was constructed because the process inherently focuses on the entire product layout, not just individual components or subsystems. There are three basic elements of FMEA: f*ailure modes* which involve identification, *failure effects* which involve ramifications, and *failure criticality* which measures the relative importance of a failure.

Each component of the NED system is listed in the FMEA along with the basic functions taken from the functional models described in Section 7. Three categories are used to examine each failure mode. The first category is the potential effects of the failure modes. The idea is that the failure could occur before, during, or after being implanted into the aneurysm. The severity of the failure mode is estimated and given a number based on a defined scale (Table 14). The second category is a potential root cause of the failure. The likelihood of occurrence of the potential root cause is rated and given a number based on a defined scale (Table 15). The third category is the design controls and testing that are in place to detect the failure from occurring. The likelihood of detection is intended to estimate how well the control will detect a failure mode before the customer is affected and it is given a number based on a defined scale (Table 16).

Table 14. Ratings for Potential Severity (S)[36]

Ratings for Potential Severity (S)	
1	No effect
2	Very minor (only noticed by discriminating customer)
3	Minor (affects very little of the system; noticed by average customer)
4/5/6	Moderate (most customers are annoyed)
7/8	High (causes a loss of a primary function; customers are dissatisfied)
9/10	Very high and hazardous (product becomes inoperative; customers are angered; the failure may result unsafe operation and possible injury)

Table 15. Ratings for Likelihood of Occurrence (O)[36]

Ratings for Likelihood of Occurrence (O)	
1	No effect
2/3	Low (relatively few failures)
4/5/6	Moderate (occasional failures)
7/8	High (repeated failures)
9/10	Very high (failure is almost inevitable)

Table 16. Ratings for Likelihood of Detection (D)[36]

Ratings for Likelihood of Detection (D)	
1	Almost certain
2	High
3	Moderate
4/5/6	Moderate – most customers are annoyed
7/8	Low
9/10	Very remote to absolute uncertainty

The Risk Priority Number (RPN) was then calculated based on:

$$RPN = (S) \times (O) \times (D)$$

The RPN prioritizes the relative importance of the failure modes and ranges from 1-1000. The higher the number: the more hazardous the failure. An important thing to note is the scale is nonlinear. Ratings above 100 will occur, while ratings below 30 usually are reasonable and typical.[36] The FMEA is completed with recommended actions to reduce the risk (Table 17). The RPN can be referenced to determine the failure modes that require immediate action. Some corrective actions that can be implemented include revised sub-system design, revised verification tests, updated material specifications, or new prototypes. Once the corrective actions have been completed, the RPN should be recalculated to reevaluate the performance of the design. As an example, to reduce the risk of overexpansion of the foam, there are a couple recommended actions that are identified. The shape memory recovery and the shape recovery of the foam will need to be selected to ensure the device does not expand to such an extent that it bursts the aneurysm.

Table 17. FMEA for the NED System

Component	Function	Potential Failure Mode	Potential Effect(s) of Failure	S	Potential Cause(s) of Failure	O	Current Design Controls/Tests	D	Recommended Actions	RPN
Guide Catheter	Position and secure microcatheter	Fatigue	Weakening of catheter	6	Too many exchanges through catheter	1	Reliability after fatigue testing	2	Bench top testing of full assembly	12
		Cracking	Blood vessel perforation or rupture	7	Overstress, improper implantation	1	Select catheter with established reputation	2	Bench top testing of full assembly	14
		Misalignment	Improper implantation	3	Kink in line	2	Determine necessary radiopacity	2	Bench top testing of full assembly	12
Sheath	Secure NED within microcatheter	Stiffness	Prevent delivery	8	Inadequate material selected	1	Use material with strong mechanical properties	1	Bench top testing of full assembly	8
		Sticking	Prevent delivery	6	Inadequate material selected	2	Use material with strong mechanical properties, establish working time	3	Bench top testing of full assembly	36
		Loose fittings	Improper implantation	6	Improper size	1	Selection of sheath with proper size	4	Bench top testing of full assembly	24
Microcatheter	Position and secure NED	Fatigue	Weakening of catheter	6	Too many exchanges through catheter	1	Reliability after fatigue testing	2	Bench top testing of full assembly	12
		Cracking	Blood vessel perforation or rupture	7	Overstress, improper implantation	1	Select catheter with established reputation	2	Bench top testing of full assembly	14
		Misalignment	Improper implantation	3	Kink in line	2	Select catheter with established reputation	2	Bench top testing of full assembly	12
Delivery Pusher and Detachment	Deliver and detach NED into aneurysm	Sticking	Prevent delivery, remove microcatheter, blood vessel perforation or rupture	9	Inadequate material selected, oversized	3	Measure advancement and retraction forces	3	Bench top testing of full assembly	81

Table 17 Continued

Component	Function	Potential Failure Mode	Potential Effect(s) of Failure	S	Potential Cause(s) of Failure	O	Current Design Controls/Tests	D	Recommended Actions	RPN
		Stiffness	Prevent delivery, remove microcatheter	9	Inadequate material selected	3	Determine maximum angle of curvature, tip deflection force	2	Bench top testing of full assembly	54
		Surge	Blood vessel perforation or rupture	10	Axial compression or tension forces	2	Verify distal shaft of microcatheter is not under stress before detaching NED	3	Bench top testing of full assembly	60
		Buckling	Prevent delivery, remove microcatheter	9	Sticking, inadequate material selected	3	Determine distal tip buckling, advancement and retraction forces	3	Bench top testing of full assembly	81
		Scratching	Damage microcatheter	7	Abrasive ends or surface	2	Select manufacturing process capable of smooth surfaces	2	Bench top testing of full assembly	28
		Fracture	Prevent delivery, coil migration into parent artery	10	Inadequate material selected	2	Determine tensile strength of coil and release zone	3	Prototype testing of assembly	60
		Bonding Failure	Prevent delivery, coil migration into parent artery	10	Inadequate material selected	2	Determine tensile strength of pusher and detachment	3	Prototype testing of assembly	60
		Misalignment	Coil migration into parent artery	10	Not viewable under fluoroscopy	3	Determine radiopacity, tip deflection force	4	Bench top testing of full assembly	120
		Material Yield	Prevent delivery	10	Need high retraction forces	2	Use material with strong mechanical properties	3	Bench top testing of full assembly	60
		Oxidation	Prevent delivery	7	Inadequate material selected	1	Use material with strong mechanical properties	2	Bench top testing of full assembly	14
		Non-biocompatible	Infection	10	Inadequate material selected	2	Biocompatibility testing	3	Animal testing	60
NED	Occlude aneurysms	Degradation	Coil migration into parent artery, unintended thrombosis	10	Biological environment	2	Biocompatibility testing	3	Animal testing	60

Table 17 Continued

Component	Function	Potential Failure Mode	Potential Effect(s) of Failure	S	Potential Cause(s) of Failure	O	Current Design Controls/Tests	D	Recommended Actions	RPN
		Binding	Prevent delivery, coil migration into parent artery	10	Device oversized or undersized for Detachment	2	Determine tensile strength of coil and release zone, detachment time	4	Bench top testing of full assembly	80
		Tear	Unintended thrombosis	10	Foam breaking off during retraction	5	Retraction tests with visual inspection	5	Bench top testing of full assembly	250
		Sticking	Coil migration into parent artery, unintended thrombosis	5	Crimped foam diameter too large, exceed working time	10	Establish working time, select appropriate size	2	Bench top testing of full assembly	100
		Stripping	Prevent delivery, coil migration into parent artery, unintended thrombosis	9	Foam not adhered to coil	3	Axial and circumferential shear tests	3	Prototype testing of assembly	81
		Misalignment	Coil migration into parent artery, blood vessel perforation or rupture	10	Not viewable under fluoroscopy	2	Determine radiopacity, tip deflection force	4	Bench top testing of full assembly	80
		Non-biocompatible	Infection	10	Inadequate material selected	2	Biocompatibility testing	3	Animal testing	60
		Air emboli	Ischemia	10	Improper saline flush	3	Continuous flush of catheter with heparinized saline	5	Animal testing	150
		Under-expansion	Compaction, recanalization	3	Long actuation time, low foam recovery force	2	Determine actuation time, shape memory recovery and shape recovery of foam	8	Animal testing	48
		Over-expansion	Coil migration into parent artery, blood vessel perforation or rupture	10	Too high shape memory recovery and recovery force of foam	2	Determine shape memory recovery and shape recovery of foam	9	Animal testing	180

11. TESTING

11.1 Verification

Adhering to the waterfall design process, the performance specifications need to be verified. Tests needed to be written to provide an objective method of analysis to prove each specification falls within the established limits. The result of each verification test is the design output for this stage of development. As required in the QSR, verification needs to confirm that design outputs meet design inputs and the results are used as a key quality control technique.[31] The verification tests for the NED have the method for the test as well as the acceptance criteria determined in the HOQ (Table 18). The same is true for the verification tests for the P&D (Table 19).

The methods of verification involve tests, analyses, and inspections. Benchmarking data, 510(k) and HDE submissions, patents, relevant scientific literature, and materials' standards were referenced to construct the verification tests. Recognized standards are mentioned in the verification tests as a guidance tool but complying with them exactly is not necessary.[44] The verification tests are written so that all engineering requirements are verified in as few tests as possible. This approach will eliminate unnecessary paperwork when documenting the results.

Table 18. Performance Specifications and Verification Tests for the NED

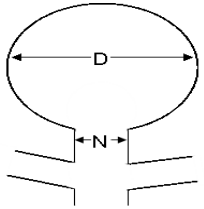
NED #	Engineering Requirement	Unit	Upper Limit	Lower Limit	Ideal Direction	Method of Verification
1	Filling percentage	%	100	30	+	 Verify by calculating the volume of an aneurysm model made out of PDMS using the equations below as guidelines depending on the shape of the aneurysm. Calculate the volume of the NED with expanded foam using the cylinder equation below. Compare the results to the volume of the aneurysm and calculate filling percentage Cylinder $v = \pi r^2 * h$ Sphere $v = 4/3\pi * r^3$ Ellipsoid $v = 4/3\pi * r_1 r_2 r_3$
2	# of coils used	#	20	1	-	
3	Radiopacity	%	100	8	+	Verify radiopacity by using appropriate medical imaging equipment and image the NED within a catheter and then compare to a metal guidewire. Use image capturing software to compare the contrast in pixel intensities between the background and the NED, once complete compare the results between the background and a metal guidewire
4	Crimped diameter	in.	0.020	0.010	-	Verify with calibrated caliper gauge to measure diameter
5	Sharp edges or corners	#	0	0	=	Verify with visual inspection of the NED
6	MRI - Static magnetic field	Tesla	3	1.5	+	Verify temperature rise does not exceed 0.3°C at stated upper limit for MR system-reported whole-body-averaged specific absorption rate (SAR) for 20 minutes of scanning in stated limit of static magnetic field system and stated spatial gradient field
7	MRI - Spatial gradient field	Gauss/cm	720	1	+	
8	MRI - Maximum averaged specific absorption rate (SAR)	W/kg	2	1	+	
9	Advancement force	g_f	50	1	-	Verify advancement force of the NED does not exceed stated upper limit when tested in a simulated anatomical location at 37°C through various microcatheters and a hemostasis valve
10	Retraction force	g_f	50	1	-	Verify with tests 17 & 18
11	Prep time	s	120	1	-	Verify the time it takes to prepare the NED for placement into the catheter once it has been removed from its packaging

Table 18 Continued

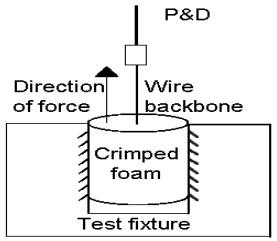
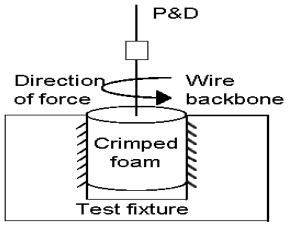
NED #	Engineering Requirement	Unit	Upper Limit	Lower Limit	Ideal Direction	Method of Verification
12	Axial shear	g_f	infinite	150	+	 Verify the adhesion strength of the wire backbone does not break free under axial shear load. Secure the distal end of the crimped foam in a fixture within a calibrated load cell and pull on the delivery pusher and detachment mechanism to ensure the force to failure is more than the stated lower limit. Follow ASTM D3574 Test E for guidance
13	Circumferential shear	g_f	infinite	150	+	 Verify the adhesion strength of the wire backbone does not break free under circumferential shear load. Secure the distal end of the crimped foam in a fixture within a calibrated load cell and twist the delivery pusher and detachment mechanism to ensure the force to failure is more than the stated lower limit. Follow ASTM D3574 Test E for guidance
14	Maximum angle of curvature	degrees	180	180	=	Verify the maximum advancement force and retraction force are not exceeded when the NED is deployed in a microcatheter and advanced/retracted through the maximum angle of curvature
15	Working time	min.	15	5	+	Verify the NED can be fully retracted back into the sheath/microcatheter after 90% of the NED has been pushed out of the microcatheter when tested in a simulated anatomical location at 37°C within the defined working time of the foam. (Working time begins when the foam is first exposed to liquid and ends when the NED can no longer be retracted back into the microcatheter). Successful retraction is when 100% of the device is retracted without any foam tearing free
16	Particulate generation	#	0	0	=	
17	# of complete retractions into sheath after 90% deployed	#	3	0	+	
18	# of complete retractions into microcatheter after 90% deployed	#	3	1	=	

Table 18 Continued

NED #	Engineering Requirement	Unit	Upper Limit	Lower Limit	Ideal Direction	Method of Verification
19	Tip deflection force	g_f	7	1	-	Verify by measuring the force required to achieve 20° deflection of the distal edge of the NED when deployed in a microcatheter. Measure the bending moment as: $M_w = WL\sin\Theta$ M_w = actual bending moment at angle Θ W = total applied load (g_f) L = Length of pendulum arm (in.) Θ = Angle through which pendulum rotates Follow ASTM D747 Apparent Bending Modulus Test for guidance
20	Shape memory recovery of foam	%	95	80	+	Verify by securing foam between two parallel plates in a calibrated rheometer and heat the temperature to T_g + 30°C and deform to 80% compressive strain at rate of 2.5 mm/min. Then cool foam to T_g - 20°C maintaining 80% strain. Release strain at rate of 2.5mm/min. and measure distance between plates at 10g axial force
21	Shape recovery of foam	kPa	700	0.05	+	Verify by using a calibrated rheometer and run a dynamic temperature ramp test using a frequency of 1 Hz and heating rate of 1°C/min. from 25 to 50°C. Use shear strain of 0.2%. Maintain torque of 0.5-5 g*cm
22	Pressure required to deform primary coil shape	kPa	700	0.05	+	Verify by securing an actuated coil in its primary shape between parallel plate fixtures and ensure the force required to achieve 90% compression is above the stated lower limit
23	Time to learn actuation method	min.	5	0.5	-	Verify the time it takes for an inexperienced interventional neuroradiologist to learn how to actuate the foam
24	Actuation time	min.	20	0.1	-	Verify the time and temperature it takes for the foam to go from the crimped diameter to full expansion when tested in a simulated anatomical location at 37°C
25	Physiologically compatible temperature	°C	50	37	-	
26	Range of device lengths	cm	40	4	+	Choose appropriate coil length and diameter based on angiographic results evaluating diameter, width, and height of aneurysm and width of aneurysm ostium
27	Range of coiled diameters	mm	20	3	+	

Table 19. Performance Specifications and Verification Tests for the P&D

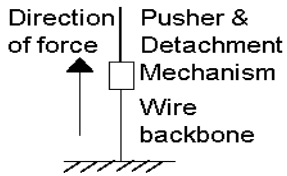
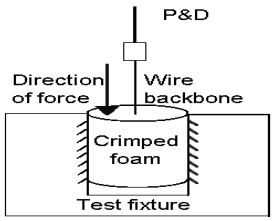
P&D #	Engineering Requirement	Unit	Upper Limit	Lower Limit	Ideal Direction	Method of Verification Delivery Pusher & Detachment Mechanism (P&D)
1	Radiopacity	%	100	8	+	Verify radiopacity by using appropriate medical imaging equipment and image the Pusher & Detachment (P&D) mechanism within a catheter and then compare to a metal guidewire. Use image capturing software to compare the contrast in pixel intensities between the background and the P&D, once complete compare the results between the background and a metal guidewire
2	Outer diameter	in.	0.020	0.010	-	Verify with calibrated calipers to measure diameter
3	Working length	mm	200	150	+	Verify with a tape measure to measure length
4	Sharp edges or corners	#	0	0	=	Verify with visual inspection of P&D mechanism
5	Advancement force	g_f	100	1	-	Verify advancement force of the detachment mechanism does not exceed upper limit when tested in a simulated anatomical location at 37°C through a standard microcatheter and a hemostasis valve
6	Retraction force	g_f	100	1	-	Verify retraction force of the detachment mechanism does not exceed upper limit when tested in a simulated anatomical location at 37°C through a standard microcatheter and a hemostasis valve
7	Prep time	min.	5	0.5	-	Verify the time it takes to prepare the detachment mechanism for placement into the catheter once it has been removed from its packaging
8	Tensile strength of NED and Detachment zone	g_f	inf.	150	+	 Verify by securing the NED wire backbone and the Pusher (attached to Detachment Mechanism) in a tensile testing machine and apply a tensile force, testing until failure to ensure the tensile strength is greater than the stated lower limit
9	Tensile strength of Detachment zone and Delivery usher	g_f	inf.	150	+	
10	Tip deflection force	g_f	7	1	-	Verify by measuring the force required to achieve 20° deflection of the distal edge of the P&D when deployed in a microcatheter. Measure the bending moment as: $M_w = WL\sin\Theta$ M_w = actual bending moment at angle Θ W = total applied load (lbf) L = Length of pendulum arm (in.) Θ = Angle through which pendulum rotates Follow ASTM D747 Apparent Bending Modulus Test for guidance

Table 19 Continued

11	Buckling force	g_f	inf.	150	+	 Verify by securing the distal end of the crimped foam in a fixture within a calibrated load cell and advance the P&D mechanism down a channel. Test until failure to ensure the buckling force is greater than the stated lower limit
12	Detachment time	s	5	0.5	-	Verify the time it takes to completely detach the NED when tested in a simulated anatomical location at 37°C
13	Reliability after fatigue	cycles	30	6	+	Verify the first fire detachment reliability is greater than 95% and second fire detachment reliability is 100% within the allotted detachment time following the stated number of deployment cycles. Also verify there is no premature detachment caused by exposure to blood, body fluids, body temperatures, or repeated manipulation
14	Time to learn how to detach NED	Min.	5	0.5	-	Verify the time it takes for an inexperienced interventional neuroradiologist to learn how to detach the NED from the detachment mechanism
15	Exchanges through guiding catheter	cycles	2	1	-	Verify the NED can be delivered and detached in a simulated anatomical location at 37°C through a standard microcatheter without exceeding the upper limit of exchanges
16	Length of external controller	mm	120	75	+	Verify with calibrated calipers to measure length
17	Diameter of external controller	mm	75	38	-	Verify with calibrated calipers to measure diameter
18	Weight of external controller	lbs.	2	0.25	-	Verify with calibrated scale to measure weight

11.2 Biocompatibility

Biocompatibility testing will need to be performed on the NED system per, "ISO 10993-1 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing". The NED is categorized per ISO 10993-1 as a permanent implant device that comes in contact with circulating blood (Table 20). The delivery pusher and detachment mechanism are both categorized per ISO 10993-1 as external communicating devices in contact with circulating blood with limited contact duration (Table 21).

The SMP foam is a complex material that utilizes additives to control polymerization, processing, and stabilization. Therefore, there will need to be material testing performed to determine the level of leachable substances and degradation byproducts.[45] The biocompatibility evaluation is organized into eight categories of tests: "single dose toxicity, repeated dose toxicity, chronic toxicity, genotoxicity, carcinogenicity, reproductive toxicity, pharmacokinetics, and special toxicity".[45]

Single dose studies are only administered to the test system within a 24-hour period so they would not apply to the NED system. Repeated dose studies are used for multiple days of dosing and are appropriate for the NED system because of the long term contact with tissues. A subacute or subchronic assay normally lasts less than 90 days, while chronic assays are normally exposures lasting beyond 10% of the lifespan of the test animal. Genotoxicity assays focus on the effects of the SMP foam on the nucleic acids of the genes or chromosomes. The FDA recommends a carcinogenicity study be conducted if a genotoxicity test result is positive. The toxicity of the chemical components used in the synthesis of the SMP foam need to be considered when evaluating potential carcinogenicity.[44] Reproductive toxicity assays determine the effects on the reproductive system. Toxicokinetic assays consider the absorption, distribution, metabolism, and elimination of foreign chemicals like those identified in extraction studies. Special toxicity assays commonly used on medical devices include immunotoxicity, hemocompatibility, and irritation.[45]

The NED system will need to meet strict pyrogenicity and sterility limits. Since ethylene oxide (EtO) sterilization may cause neurotoxicity, the EtO residue levels will need to be measured along with obtaining biocompatibility information on the sterilized NED. This information can be obtained by studying the tissue response after intracranial implantation.[44] The NED system needs a sterility assurance level (SAL) of 1×10^{-6}. The pyrogenicity needs to be evaluated and the amount of endotoxin allowed in the final, sterilized NED system should be less than 0.06 Endotoxin Units (EU)/ml.[44]

Table 20. Biocompatibility Tests for the NED

Test	Description	ISO Standard
Cytotoxicity	MEM Elution Test Evaluation	10993-5
Sensitization	Guinea pig maximization sensitization test with device extracts (saline and cottonseed oil extracts)	10993-10
Intracutaneous Reactivity	Intracutaneous reactivity test with device extracts (saline and cottonseed oil extracts)	10993-10
Acute Systemic Toxicity	Acute systemic toxicity test with device extracts (saline and cottonseed oil extracts)	10993-11
Subacute and Subchronic Toxicity	*In vivo* Subacute Toxicity	
Material-Mediated Pyrogenicity	Rabbit pyrogen test with saline extract of the device	10993-11
Genotoxicity	Bacterial Reverse Mutation Assay conducted with Device Extracts (Saline and PEG extracts)	10993-3
	In Vitro Chromosomal Aberration Assay conducted with Device Extract (cell culture medium extract)	10993-3
	Mouse Bone Marrow Micronucleus Assay conducted with saline extract of the device	10993-3
Implantation	Evaluate in an animal bifurcate aneurysm model at 14 and 90 days	
Hemocompatibility	In vitro hemocompatibility test with human blood and with saline extract of the device	10993-4
	Direct contact hemolysis test using rabbit blood	10993-4
	Indirect contact (extract) hemolysis test with saline extract of the device and rabbit blood	10993-4

Table 21. Biocompatibility Tests for the P&D

Test	Description	ISO Standard
Cytotoxicity	MEM Elution Test Evaluation	10993-5
Sensitization	Guinea pig maximization sensitization test with device extracts (saline and cottonseed oil extracts)	10993-10
Intracutaneous Reactivity	Intracutaneous reactivity test with device extracts (saline and cottonseed oil extracts)	10993-10
Acute Systemic Toxicity	Acute systemic toxicity test with device extracts (saline and cottonseed oil extracts)	10993-11
Hemolysis	Indirect contact (extract) hemolysis test with saline extract of the device and rabbit blood	10993-4
Unactivated Partial Thromboplastin Time (UPTT)	UPTT test using human plasma and saline extract of the device	10993-4

11.3 Validation

Once the verification tests are complete the NED system needs to be validated to prove by objective evidence that the user needs and intended use are consistently fulfilled. Validation is a pivotal step in completing the waterfall design process. Verification activities are completed to demonstrate the NED system performs according to the performance specifications. Engineering methods are used to properly construct the performance specifications; however, the process is based largely on intuition and experience. Thus, validation confirms that the specifications are correct and that the NED system properly occludes intracranial aneurysms.[3]

FDA recommends conducting pre-clinical animal studies to evaluate the NED system. Initial validation efforts in the Biomedical Device Laboratory have used porcine models to assess biocompatibility and performance of the SMP foam-only plug. The non-GLP study protocol, written by Julie Grinde at the Texas A&M Institute for Preclinical Studies, can be found in Appendix C. Per the FDA "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices", study objectives in future animal trials will evaluate and validate the NED system based on the specified parameters (Table 22).

Table 22. NED System Validation

FDA Guidance Document Recommendations	Swine Bifurcate Aneurysm Study Objective	Method of Validation
Ease of delivery (friction and tortuosity)	Demonstrate that the delivery and trackability of the NED is acceptable based upon subjective assessment of co-investigator	Evaluate fluoroscopic visualization, trackability, ease of advancing through the catheter, ease of aneurysm filling, ease of retrievability
Acute complications (e.g. rupture or puncture of the blood vessels)	Demonstrate that the acute (local and systemic) effects of the NED deployment are acceptable with regard to vessel perforation, life threatening alterations in vital signs, and any other notable events	Ensure there is a 0% incidence rate of acute complications
Recanalization of the vessels/durability of occlusion	Demonstrate that the SMP foam can achieve aneurysm filling and occlusion results statistically comparable to literature reviewed results of Guglielmi detachable coils (GDC) using a similar model. Occlusion results are measured by: • Volumetric filling of > 30% for each treated aneurysm based on angiographic calculation of aneurysm volume and calculation of SMP foam volume based on length used and volume expansion of SMP foam • Occlusion of 100% in > 30% of treated aneurysms on treatment day and on sacrifice (follow-up) day	MRA or CTA may be performed in addition to standard digital subtraction and 3-D angiography to characterize chronic changes in aneurysm filling, including aneurysm exclusion, intraluminal thrombus formation, or distal emboli
Local and systemic foreign body reactions	Determine whether the acute (local and systemic) effects of SMP are acceptable via assessment based on angiographic evaluation for vessel perforation, life threatening alterations in vital signs and any other notable effects Determine the carotid tissue's response to treatment with SMP based on evaluation of histopathology by the Study Pathologist Determine organ response to the SMP treatment based on evaluation of histopathology by the Study Pathologist Determine tungsten levels in the blood prior to and after implantation of the SMP foam at follow-up	At necropsy, skin at body surfaces will be examined. Analysis will be performed from histological examination of the aneurysm sac, carotid arteries adjacent to aneurysm, and targeted vessels. Tissue from each group will be compared using the following factors: Degree of inflammation, fibrosis, tissue damage Extent and severity of damage will be compared within the group Histopathological evaluation will be conducted on lung, mediastinal lymph node, cervical lymph node, liver, spleen, adrenals, kidney, and brain to assess systemic toxicity of SMP foam

Table 22 Continued

FDA Guidance Document Recommendations	Swine Bifurcate Aneurysm Study Objective	Method of Validation
Device migration	The positional stability and aneurysm occlusion maintained through at least 6 months of implant	Digital subtraction and 3-D Angiography will be performed post SMP foam placement to document parent vessel integrity and check for any possible migration of the SMP foam. MRA may be performed
Embolization effectiveness	Evaluate as % occlusion at follow-up	Digital subtraction and 3-D Angiography will be performed post SMP foam placement to assess aneurysm filling. MRA may be performed

12. AIM II: PROBLEM STATEMENT

The second specific aim is to develop performance specifications for SMP foam used in the development of a novel NED. To achieve this aim, the chemicals used in the synthesis of the SMP foam are identified, activity diagrams are created, and performance specifications with verification tests are defined.

Part of the QSR is to have manufacturing controls in place to ensure a quality product can be produced consistently and reliably. When establishing the quality control program, the first major hurdle was defining the performance specifications for the NED system. The system was broken down into three distinct subsystems. The NED subsystem was further broken down into the individual components that will be used. Of those components, SMP foam is the one that is developed in the Biomedical Device Laboratory, so it becomes the focus of attention. It is, therefore, important to establish performance specifications that will be used to assess the quality of the SMP foam.

The performance specifications are completed with verification tests that will ultimately need to be validated in an animal study. Once the specifications are defined, raw materials can be selected that best meet the specifications. Before any process validation can occur it is important to understand what makes up the composition of the SMP foam. The chemicals and associated toxicity data are identified. Purification methods are suggested to help mitigate any biocompatibility issues and reduce the amount of impurities.

Activity diagrams are generated to provide a means of process mapping. The activity diagrams help illustrate the various steps and components involved in the synthesis of the SMP foam.

13. PERFORMANCE SPECIFICATIONS

13.1 Performance Specifications and Verification

Now that the performance specifications for the NED system are defined, it is important to focus on the development of the SMP foam and how it will affect the design. Essential material properties of the SMP foam were identified by taking pertinent functional requirements from the NED HOQ. These material properties will need to be monitored as to how well they meet the NED performance specifications. The vital requirements at the subsystem level were used as inputs to determine the vital material properties at the component level. Target values were then assigned to the appropriate material property. A lower and upper limit for the target values along with an ideal direction was defined. The ideal direction provides guidance about whether the design should strive to achieve the upper or lower limit.

Once the target values are chosen, the performance specifications need to be verified. Tests needed to be written to provide an objective method of analysis to prove each specification falls within the established limits. The design output for this stage of development is the result of each verification test. The performance specifications and verification tests have the method for the test as well as the acceptance criteria (Table 23).

Table 23. Performance Specifications and Verification Tests for the SMP Foam

Foam #	Engineering Requirement	Material Property	Unit	Upper Limit	Lower Limit	Ideal Direction	Method of Verification
1	Filling percentage	Shape memory recovery	%	98	80	+	Verify by securing foam between two parallel plates in a rheometer and heat the temperature to T_g + 30°C and deform to 80% compressive strain at rate of 2.5 mm/min. Then cool sample to T_g - 20°C maintaining 80% strain. Release strain at rate of 2.5mm/min. and measure distance between plates at 10g axial force.[46]
2		Volume expansion	%	7000	5000	+	Verify by first measuring the crimped diameter with calibrated caliper gauge then actuate the foam and measure the expanded foam with same calibrated caliper gauge. Calculate net volume expansion (ignoring change in length) as follows: Volume expansion = (recovered diameter / compressed diameter)^2
3	Crimped diameter	Density	g/cm^3	0.025	0.015	-	Verify by following Test A – Density Test as defined in ASTM D3574. Calculate density based on equation: Density = M/V x 10^6 M = mass of specimen in grams V = volume of specimen in mm^3
4		Cell morphology	%	Open	Closed	+	Verify by visual inspection under a microscope
5		Cell size	µm	500	100	+	Verify by measuring the polar diameter (parallel to direction of foam rise) and equatorial diameter (perpendicular to direction of foam rise) with microscope and image processing software.[46]
6	Physiologically compatible temperature	Glass transition temperature (T_g)	°C	70	45	-	Verify by using Differential Scanning Calorimetry. Cool sample to -40°C and then run through a heat-cool-heat cycle from -40 to 120°C. The half-height of transition during second heat can be taken to estimate T_g.[46]
7		ΔT_g of foam	°C	20	1	-	Verify by using a rheometer and run a dynamic temperature ramp test at a frequency of 1 Hz and constant heating rate of 1°C/min. from 25 to 50°C. Use an initial shear strain of 0.2%. As temperature increases maintain torque range of 0.5-5 g/cm ΔT_g (breadth of transition = $2(T_{\delta s} - T_{onset})$.[46]
8	Shape recovery	Rubbery storage modulus ($G'_{rubbery}$)	kPa	15	5	+	
9		Glassy storage modulus (G'_{glassy})	kPa	300	200	+	

14. ACCEPTANCE ACTIVITIES

14.1 Identification of Chemicals

A component, as defined in 820.3(c) of the QSR, is any material or substance that will be included in the finished NED.[30] Since the SMP foam is not a FDA approved material it will be the component that is the primary point of concern for getting the NED cleared or approved.

A way to mitigate uncertainty the FDA may have with the NED, is to list the chemicals used in the synthesis of the SMP foam. Per the FDA's, "Class II Special Controls Guidance Document: Vascular and Neurovascular Embolization Devices", the raw materials and reagents used to synthesize the SMP foam were identified (Table 24).

Table 24. SMP Foam Chemicals Used

Chemicals	CAS	Vendor	Part #	Chemical Contents
Hexamethylene Diisocyanate 1,6 diisocyanatohexane (HDI)	822-06-0	TCI America	H0324	$C_8H_{12}N_2O_2$
N,N,N',N'-Tetrakis(2-hydroxypropyl ethylenediamine) (HPED)	102-60-3	TCI America	T0781	$[CH_2N(C_3H_6OH)_2]_2$
Triethanolamine 2,2',2"-Nitrilotriethanol (TEA)	102-71-6	Sigma Aldrich	90278	$C_6H_{15}NO_3$
RO water	N/A	Texas A&M	N/A	H_2O
Dabco BL-22 Catalyst	112-18-5	Air Products	BL-22	$C_{14}H_{31}N$
Dabco T-131 Catalyst	N/A	Air Products	T-131	C-Sn (Organotin)
Dabco DC1990 Surfactant	6430-39-3	Air Products	Dabco DC1990	Trade secret – siloxanes and silicones
Dabco DC5179 Surfactant	N/A	Air Products	Dabco DC5179	Trade secret
Tungsten Powder	7440-33-7	VWR	AA44210-36	W
Enovate 3000	460-73-1	Honeywell	HFC-245fa	1,1,1,3,3-Pentafluoropropane
Hydrochloric acid solution, 1.0	7647-01-0	VWR	BDH3202-1	HCl
Contrad 70	1310-58-3	Decon Laboratories	42000-000	KOH

The FDA also recommends identifying any reagent that is potentially toxic. Thus, material safety data sheets (MSDS) were consulted to obtain toxicological information about each chemical (Table 25).

The LD_{50} value stands for lethal dose and represents the quantity of material that will cause 50% of the animal subjects to perish. A large LD_{50} value means it takes a large amount of that material to be a health hazard. The toxicity units are expressed in the amount of material per kilogram of subject-body-weight.

Table 25. SMP Foam Chemicals' Toxicological Information

Chemicals	Toxicological Information	
Hexamethylene Diisocyanate 1,6 diisocyanatohexane (HDI)	Rat LD_{50} (oral)	710 µL/kg
	Rat LC_{50} (inhalation)	124 mg/m^3/4H
	Rabbit LD_{50} (skin)	570 µL/kg
	Skin irritation	Severe
	Eye irritation	Severe
	Carcinogenic effects	No data available
	Mutagenic effects	No data available
	Teratogenic effects	No data available
	Developmental toxicity	No data available
N,N,N',N'-Tetrakis(2-hydroxypropyl ethylenediamine) (HPED)	Rat LD_{50} (oral)	500 mg/kg
	Man LD_{50} (unknown)	3900 mg/kg
	Skin irritation	No data available
	Eye irritation	No data available
	Carcinogenic effects	No data available
	Mutagenic effects	No data available
	Teratogenic effects	No data available
	Developmental toxicity	No data available
Triethanolamine 2,2',2"-Nitrilotriethanol (TEA)	Rat LD50 (oral)	5,530 mg/kg
	LC50 (inhalation)	No data available
	Rabbit LD50 (dermal)	>22.5 g/kg
	Skin irritation	May be harmful
	Eye irritation	May cause irritation
	Respiratory sensitization	No data available
	Germ cell mutagenicity	No data available
	Carcinogenic effects	No data available
	Reproductive effects	No data available
	Teratogenic effects	No data available
RO water	N/A	
Dabco BL-22 Catalyst	Rat LD_{50} (ingestion)	>1,630 mg/kg
	Rat LC_{50} (inhalation)	>580 mg/l
	Rabbit LD_{50} (skin)	280 mg/kg
	Eye irritation	Severe
	Acute dermal irritation	Severe

Table 25 Continued

Chemicals	Toxicological Information	
Dabco T-131 Catalyst	Rat LD_{50} (ingestion)	510 mg/kg
	LC_{50} (inhalation)	No data available
	Rabbit LD_{50} (skin)	>2,000 mg/kg
	Eye irritation	severe
	Skin irritation	Severe
Dabco DC1990	Rat LD_{50} (ingestion)	2,550 mg/kg
	Inhalation	No data available
	Eye irritation	Severe
	Acute dermal irritation	Moderate
Dabco DC5179 Surfactant	Ingestion	No data available
	Inhalation	No data available
	Skin	No data available
	Eye irritation	No data available
Tungsten Powder	Skin irritation	Irritant to skin and mucous membranes
	Eye irritation	Irritating effect
	Chronic exposure	May result in permanent lung damage
	Carcinogenic effects	No data available
Enovate 3000	Rat LC_{50} (inhalation)	>200,000 ppm
	Rat LD_{50} (skin)	>2,000 mg/kg
	Teratogenic effects	Not a teratogen
Hydrochloric acid solution, 1.0 N	Rabbit LD_{50} (oral)	900 mg/kg
	Mouse LC_{50} (inhalation)	1108 ppm
	Ingestion irritation	May cause burns to mouth, throat, and stomach
	Inhalation irritation	Irritating to respiratory system
	Skin irritation	Corrosive
	Eye irritation	Corrosive
	Carcinogenic effects	No known significant effects
	Mutagenic effects	No known significant effects
	Teratogenic effects	No known significant effects
Contrad 70	Inhalation	May cause respiratory irritation
	Skin irritation	May cause reddening and irritation
	Eye irritation	May cause irritation and damage
	Chronic health effect	None known

14.2 Purification Methods for Chemicals

When synthesizing the SMP foam it is desirable to start with chemicals that have the highest purity level commercially available. However, even when selecting the highest grade chemical, there still may be unspecified impurities present. A 'manufacturing material', as defined in 820.3(p) of the QSR, is any material or substance used in or produced during manufacturing which is on or in the processed NED as a residue or impurity.[30] Therefore, it becomes important to establish methods to further purify the chemicals. Considering purity has different levels, the objective is to reduce the impurities as much as necessary. There are various ways to assess the degree of purity. Physical properties can be examined such as density, optical rotation, and refractive index at a specified wavelength and temperature. Physical tests can be performed such as emission and atomic absorption spectroscopy, chromatography, X-ray or mass spectroscopy and electron spin resonance. Spectroscopic properties can also be examined such as infrared spectroscopy, nuclear magnetic resonance, and ultraviolet spectroscopy.[47]

Ultimately, the right amount of purification will need to be verified in the biocompatibility tests and validated when the NED is implanted during an animal study. An initial draft of purity information and suggested methods for further purification was written (Table 26). Certificates of Analysis (CoA) for each chemical were studied to understand the incoming purity level of the chemicals.

Table 26. SMP Foam Chemicals' Purification Methods

Chemicals	Purity (%)	Chemical Analysis	Method of Purification
Hexamethylene Diisocyanate 1,6 diisocyanatohexane (HDI)	99.7	Gas chromatography Specific gravity Refractive index	Fractional distillation under vacuum.[47]
N,N,N',N'-Tetrakis(2-hydroxypropyl ethylenediamine) (HPED)	99.8	Gas chromatography Neutralization titration Refractive index	Fractional distillation under nitrogen to prevent reaction with CO_2 and water.[47]
Triethanolamine 2,2',2"-Nitrilotriethanol (TEA)	98	Visual Gas chromatography Refractive index Karl Fischer titration Residue on ignition Proton NMR spectrum Metal trace analysis	React aqueous ammonia with ethylene oxide in the liquid phase at elevated temperature and under pressure. Remove excess ammonia, water and monoethanolamine from the reaction product. React the resulting crude product with ethylene oxide at temperatures of 110 to 180 C., and then rectify the mixture in the presence of phosphorous or hypophosphorous acid.[48]
RO water	N/A	N/A	Distillation
Dabco BL-22 Catalyst	N/A	Gas chromatography Karl Fischer titration	Distillation
Dabco T-131 Catalyst	N/A	N/A	
Dabco DC1990 Surfactant	N/A	Appearance Viscosity	Mix surfactant with 1/1 ratio of water and oil in a flask and place in waterbath. Stir solution until equilibration then remove oil-phase containing most of the oleophilic impurities. Add back as much pure oil as was removed. Adjust waterbath to new temperature and stir solution again. After equilibration and phase separation, remove the waterphase containing most of the hydrophilic impurities. Add back as much pure water as was removed and repeat the process 4-6 times. Concentrate surfactant by distilling remaining oil and water under vacuum at 50°C.[49]
Dabco DC5179 Surfactant	N/A	Appearance Viscosity	
Tungsten Powder	100	Not listed	Clean with concentrated NaOH solution. Wash with boiled and cooled conductivity water and dry on filter paper.[47]
Enovate 3000	99.9	Assay Water	Distillation[50]
Hydrochloric acid solution, 1.0 N	0.1004 Normality	Appearance	Fractional distillation as constant boiling point acid, and then dilute with H_2O.[47]
Contrad 70	N/A	N/A	Add slight excess of saturated $BaCl_2$ or $Ba(OH)_2$ to the solution and shake well. The $BaCO_3$ will separate out.[47]

14.3 Activity Diagrams

Activity diagrams were used to illustrate the procedures of synthesis and post synthesis processing of the SMP foam. The synthesis of the SMP foam was broken down into the preparation of two separate premixes used in the foam, as well as the post synthesis activities of annealing, etching, and cleaning (Fig. 9).

The first premix, isocyanate pre-polymer containing nitrogen, carbon, and oxygen (NCO), is used to optimize the rheology of the system of monomers during the foaming reaction to facilitate the creation of low density foams. The preparation of NCO can be found in Appendix D in Figure 10. The second premix, a hydroxyl monomer (OH), is prepared to create a uniform liquid mixture of as many of the remaining foam components as possible. The OH premix is then added to the NCO premix during the foaming reaction. Preparing the premixes beforehand ensures both better mixing of each premix and also a more consistent composition from one batch of foam to the next. The preparation of OH can be found in Appendix D in Figure 11.

Post synthesis activities begin with annealing the foam under vacuum. Annealing removes residual volatile components and completes the reaction of residual isocyanate. The annealing process can be found in Appendix D in Figure 12. Mechanical processing by compression and expansion of the SMP foam, fractures residual cell membranes to facilitate better etching and cell membrane removal. The mechanical processing can be found in Appendix D in Figure 13. Etching the foam removes residual mobile species and also removes cell membranes to open cells. Cleaning the foam further removes debris and any possible biological material that the foams were exposed to during synthesis. The etching and cleaning process can be found in Appendix D in Figure 14.

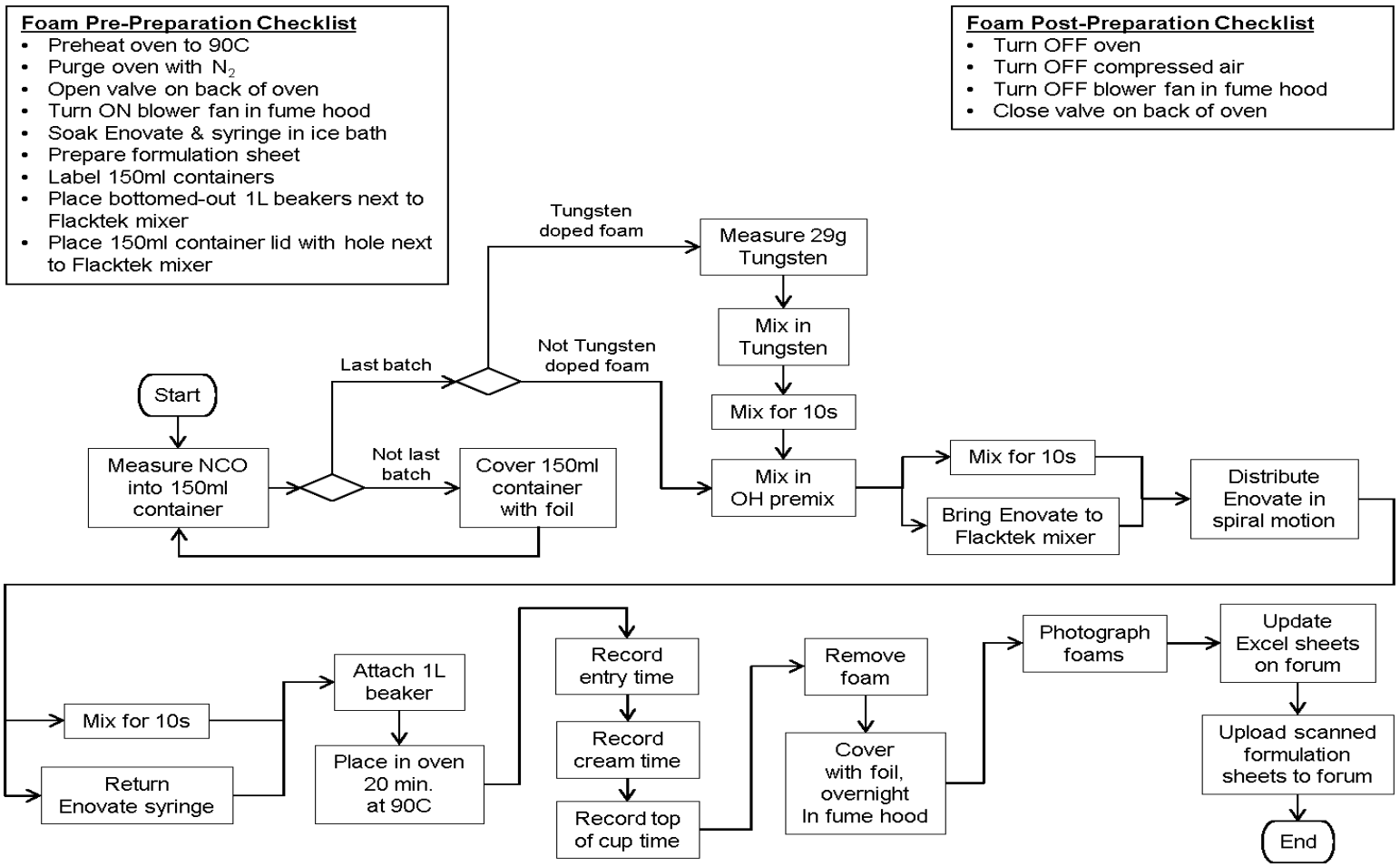


Figure 9. Activity Diagram for SMP Foam Preparation

15. SUMMARY

The design research performed has the objective of aiding in the development of a NED system for occluding intracranial aneurysms. If left untreated, ruptured intracranial aneurysms can lead to devastating consequences. Current treatment options, offered through a minimally invasive endovascular approach, only occlude approximately 30% of the aneurysm which can lead to recanalization and re-bleeding. Therefore, it is imperative to develop devices that can achieve higher occlusion rates. The Biomedical Device Laboratory, led by Dr. Maitland, is developing an NED system made out of SMP foam. The shape memory characteristic of the SMP will give the NED an ability to be compressed down into a compact size for delivery via a catheter. Once in place the device can be induced to regain its complex, primary shape and expand up to 70x for superior occlusion of aneurysms.

The first specific aim focused on the front-end of the product development process. Customer needs were generated from interviews, activity diagrams, and market research. Functional models were used to define the function and various sub-functions of the NED system and to ensure the design inputs follow the user needs. Benchmarking was conducted to help clarify user requirements and understand current market products and technology trends. The customer needs were then translated into quantifiable engineering requirements. A HOQ matrix was used to map the customer needs to the engineering requirements and help elucidate the relationships between the needs and the requirements and between the requirements themselves. Acceptance criteria were established with an ideal direction for the design to achieve. An FMEA was performed to highlight possible design deficiencies as a way of mitigating future risk. The performance specifications for the NED system were defined with verification tests for each requirement. Verification of the NED system must consist of determination through documented testing that each subsystem will reliably perform its function under the most adverse environmental conditions in which they will be used.

The second specific aim focused on the initial concerns of establishing manufacturing controls for the synthesis of the SMP foam. The performance specifications for the NED system were used to identify vital material properties of the SMP foam that will have an impact on the device design. Each chemical that goes into synthesizing the SMP foam was listed along with the toxicological information. When synthesizing the SMP foam it is important for the chemicals to have the highest purity level commercially available. Therefore, an initial draft of purity information and methods for further purification was suggested. Activity diagrams were then used to illustrate the procedures of synthesis and post synthesis processing of the SMP foam.

Further work into the design of the NED system will inevitably result in new performance specifications. All the design documentation will need to be reviewed and updated as new information about the NED system becomes available. The waterfall design process, though, is structured for changes and improvements to be incorporated back into the design effort. It is an iterative process that can be adapted and tweaked as necessary. Any changes will need to go through verification and ultimately validation to ensure the redesigned NED system meets the needs of the user and is safe and effective at treating intracranial aneurysms.

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APPENDIX A

CUSTOMER NEEDS ASSESSMENTS

Table 27. Customer Needs Assessment from Market Research of Doctors' Opinions on Current FDA Cleared Devices

Date: February 15-17, 2012	Market Research		Neurovascular Embolization Device (NED)	
Category	End User	Customer Statement	Interpreted Need	Importance Rating
Ease of Use	Dr. David Kallmes - Mayo Clinic, Rochester MN	Device is easily guided, positioned and repositioned, and released through standard microcatheters	The NED will be visible under fluoroscopy during implantation	5
			The NED can be retracted back into the micro-catheter and repositioned after partial deployment at least once.	5
	Dr. Michael Horowitz - University of Pittsburgh Medical Center	Coils deliver with minimal resistance or snaking through 0.021" microcatheters	The NED is easily pushed and pulled through the microcatheter	5
	Dr. Michael Horowitz - University of Pittsburgh Medical Center	Ability to fill interstices is exceptional	The NED will use fewer coils to provide superior embolization of the aneurysm over time compared to current devices	4
Detachment	Dr. W.J. van Rooij - The Netherlands	Coils went in smoothly and detached immediately	The NED has Detachment that is immediate and reliable	5
	Dr. Demetrius Lopes - Neurosurgical Orthopedic Hospital, Chicago IL	Complexity of case required fast and reliable detachment of coils, may decrease length of case and complications from poor detachment		
	Dr. Michael Horowitz - University of Pittsburgh Medical Center	New release system makes procedures simpler and quicker by providing instantaneous coil deployment, obviating need for cables, boxes, and batteries		
Actuation	Dr. Behrat Mehta - Henry Ford Hospital, Detroit MI	Angiographic occlusion of the aneurysm was achieved without neck remnant	The NED actuates into known configuration and diameter	5

Table 28. Customer Needs Assessment from Interview with Ms. Grinde

Date: April 5, 2012	Interviewee: Julie Grinde Job Title: Research Associate Texas A&M University	Neurovascular Embolization Device (NED)	
Category	Customer Statement	Interpreted Need	Importance Rating
Ease of Use	Will want some kind of radiopaque marker so physician will know when the device is no longer retractable	The NED is visible under fluoroscopy during/after implantation	5
	Important to minimize friction, want 1:1 movement to ensure predictability of where coil is positioned within microcatheter	The NED is easily pushed and pulled through the microcatheter	5
	Might consider deep positioning of catheter to enable sideways coiling of device for better neck coverage	The NED can withstand being twisted and bent	5
	Matrix coating broke down too quickly, led to loss in volume and compaction	The NED uses fewer coils to provide superior embolization of the aneurysm over time compared to current devices	4
	Between 8-20 coils are used to occlude larger aneurysms		
	Matrix compared performance to GDCs	Similarity to prior technology and ease of use are definitely a plus in terms of adoption	4
Pusher	When retracting device could run into problems with multiple foam pieces on wire. Want to eliminate stutter when retracting. Foam pieces might catch on catheter during retraction	The NED can be retracted back into the sheath and repositioned after partial deployment at least once	5
	GDC and Matrix coils could be 100% out of the catheter and still be retracted. Sometimes it does happen in clinical setting that device is retracted after being fully deployed		
	Device should be able to be retracted 2-3 times	The NED can be retracted and repositioned 2-3 times is preferred	3
Detachment	Matrix Detachment System took too long, 30-60s. Micrus had immediate detachment	The NED has Detachment that is immediate and reliable	5
	Want to limit catheter movement, painting. Some doctors don't mind catheter movement, helps them locate the device	The NED has Detachment that does not alter the position of the microcatheter during positioning, detachment, and actuation	5
Actuation	Want uniform shape	The NED actuates into stable, known configuration and diameter	5
	Matrix had stiff detachment zone which created a tail that stuck out into the parent vessel		
	Matrix had no expansion so you know exactly where coil will be positioned		
	Main point to coiling is covering the neck of the aneurysm. Coverage across the neck is an important parameter	The NED actuates to cover the neck of the aneurysm	4
	Dome is the thinnest part of the aneurysm, want to make sure foam expansion doesn't rupture the aneurysm	The NED conforms to range of shapes	3
Size	Hospitals have limited storage for quantities of coils. Need to determine right sizes and shapes to treat majority of aneurysms	The NED is manufactured with multiple sizing options	5

Table 29. Customer Needs Assessment from Market Research of Marketing Literature on Current FDA Cleared Devices

Date: February 15-17, 2012	Market Research	Neurovascular Embolization Device (NED)	
Category	Customer Statement	Interpreted Need	Importance Rating
Ease of Use	Enhanced trackability through microcatheter	The NED will be visible under fluoroscopy during implantation	5
	Smooth movement through microcatheter	The NED is easily pushed and pulled through the microcatheter	5
	Smoother coil positioning		
	Remove coil if unusual friction or "scratching" is noted		
	Safety and handling characteristics equivalent to existing products	The NED behaves and actuates similarly to predicate devices	4
	Balance of softness, stability, and volume through entire coil line		
	Softest coil ever - unites finishing-coil softness with Gold Standard in shape		
	Three grades of softness for progressive coil compliance		
	Minimized set-up time with simple sheath system	The NED is ready to use right out of the package	3
	No prep, no steaming		
Pusher	Responsive placement and repositioning	The NED Delivery Pusher does not alter the position of the microcatheter during positioning, detachment, and actuation	5
	New, more flexible delivery pusher minimizes catheter movement		
	Pushability and flexibility, new level of tactile sensation		
	Soft gripper tube results in minimal catheter tip deflection while coiling. Stable coil delivery		
	Balanced stiffness zones provide flexibility and pushability yield one-to-one feel	The NED Delivery Pusher is easily pushed and pulled through the microcatheter	5
Detachment	No movement of coil after coil placement or prior to detachment	The NED had Detachment that does not alter the position of the microcatheter during positioning, detachment, and actuation	5
	Soft floating detachment link minimizes catheter kick out		
	Softer, shorter junction to minimize kickback for increased control and stability		
	Softer, shorter detachment zone reduces microcatheter deflection, increases coil placement ability		
	Minimal migration	The NED will remain in the aneurysm once detached	5
	Fast detachments and real-time feedback with a single click	The NED has detachment that is immediate and reliable	5
	Velocity you appreciate, simplicity required		
	Fast detachments with no compromise to tensile strength		
Actuation	Designed to resist deformation from hemodynamic forces with aim to retain original shape	The NED retains its crimped form until actuation	5

Table 29 Continued

	Stability with coil frame, microcatheter position & improved neck coverage	The NED actuates into stable, known configuration and diameter	5
	Loop to length ratio enhances biomechanical stability		
	Improved stability upon marker alignment		
	Coil coverage across neck	The NED actuates to cover the neck of the aneurysm	4
	Conformability and neck-to-dome stability		
	First or second coils should NEVER be less than width of neck (ostium)		
	Variable diameter loops provide optimum framing		
	First two loops smaller allow for more controlled deployment		
	Two initial helical loops help anchor the coil within the aneurysm		
	First 1.5 loops 25% smaller than stated secondary coil diameter to reduce coil herniation		
	Tight loops form a mechanically interconnected structure to resist compaction		
	Initial loop sizes to aneurysm, mitigating risk prolapse into parent vessel		
	Frames from outside in, utilizes inner coil loops to provide optimal bracing for frame support		
	Open loops for conformance to shapes while minimizing compartmentalization		
	Without assuming pre-determined 3D shape can frame many morphologies	The NED can conform to range of shapes	3
	Treats range of shapes - spherical to multi-lobed		

Table 30. Customer Needs Assessments from Interview with Dr. Miller

Date: September 20, 2011	End User: Dr. Matthew Miller Job Title: Professor of Cardiology Department of Small Animal Medicine and Surgery College of Veterinary Medicine, Texas A&M University	Neurovascular Embolization Device (NED)	
Category	Customer Statement	Interpreted Need	Importance Rating
Ease of Use	Want maneuverability and flexibility Want it to feel secure enough	The NED can withstand being twisted and bent	5
	If the working time is only 5-10 minutes per coil, there is added pressure of implanting within a short time window 15 minutes may be better, but 20 minutes is a long time especially if there are multiple coils to place	The NED has a working time of 10-15 minutes once placed in the microcatheter	5
Pusher	There are severe issues and limitations if not retractable	The NED can be retracted back into the sheath and repositioned after partial deployment at least once	5
	Problems arise with too much reworking and repositioning including damage to the endothelium and possibly bursting the aneurysm	The NED has a Detachment that is immediate and reliable	5
		The NED has a simple, user-controllable Detachment	4
	Pieces of foam do not break off	The NED does not have foam pieces break off when retracted	5
	Provide a failsafe that the device can always be pulled back into guiding catheter. Possible to remove entire system from body and try new implant if necessary	The NED can be retracted back into the microcatheter after partial deployment at least once with the NED in any configuration	5
	Would be ideal if it was always retractable, practical need is that it is retractable at least once	The NED can be retracted and repositioned 2-3 times is preferred	3
Detachment	Deploying will not alter shape or stiffness of catheter	The NED does not alter the position of the microcatheter during positioning, detachment, and actuation	5
Actuation	Do not want the coil to protrude out of the aneurysm Do not compromise the parent vessel	The NED actuates into known configuration and diameter	5
	Size to maximal diameter If undersized relative to aneurysm could have a ball of foam bouncing around	The NED will remain in the aneurysm once detached	5
	Without actuation, how will the coil stay in place?		
	Too many exchanges through the catheter could cause problems	The NED has few number of exchanges through the guiding catheter	3
	Infinite working time may not be optimal, it can lead to complications	The NED has active user-controllable actuation	2
	Light actuation is the most interesting Chemical actuation is normally biocompatible but not as controllable		
Size	Want a wide variety of different lengths, diameters, and number of revolutions available	The NED is manufactured with multiple sizing options	5

Table 31. Customer Needs Assessment from Observation of Clot Extraction Procedure

Date: August 5, 2011 Procedure: Clot extraction using the Penumbra System	End User: Dr. Andrew Xavier Job Title: Interventional Neuroradiologist St. Joseph Mercy Oakland Stroke Center	Neurovascular Embolization Device (NED)	
Category	Observations	Interpreted Need	Importance Rating
Ease of Use	Each stent was in the microcatheter from 2-10 minutes	The NED has a working time of 10-15 minutes once placed in the microcatheter	5
	The neurovasculature was tortuous, with multiple bends and odd angles	The NED can withstand being twisted and bent	5
	Once the catheter was opened from the package, it was placed in a saline bath and left there until needed	The NED can withstand 6 hrs. exposure time to saline	1
Pusher	The stent was retracted once before being properly placed	The NED can be retracted back into the sheath and repositioned after partial deployment at least once	5
	There were two separate attempts at implanting the stent. The stent was completely removed from the body before another attempt was made	The NED can be retracted back into the microcatheter after partial deployment at least once with the NED in any configuration	5
	The reperfusion catheter and stent were repositioned multiple times before the doctors were satisfied with the placement	The NED has a Delivery Pusher that does not alter the position of the microcatheter during positioning, detachment, and actuation	5
		The NED can be retracted and repositioned 2-3 times is preferred	3
Detachment	The doctors instructed the nurses to turn the Penumbra pump on while keeping their eyes on the imaging screens and controlling the reperfusion catheter	The NED has a simple, user-controllable Detachment	4
	Multiple nurses were switching the Penumbra system on and off, depending on who was near the pump		
Actuation	The doctors had the Penumbra turned on and off multiple times while they were positioning the reperfusion catheter	The NED has active user-controllable actuation	2
Size	The doctors used a wide variety of different sized catheters	The NED is manufactured with multiple sizing options	5

APPENDIX B

ADVERSE EVENTS FROM MAUDE

Table 32. Adverse Events Reported for the NED

#	Company	Trade Name	Event Type	Adverse Event Description	Manufacturer Narrative	Date
1	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	Difficult to advance due to resistance/friction During repositioning, coil stretched	Additional information will be submitted w/in 30 days	3/30/2012
2	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Injury	Coil stretched during placement, broke during withdrawal. Coil and part of microcatheter containing coil remained in patient's body	Additional information will be submitted w/in 30 days	3/27/2012
3	Micrus Endovascular	PRESIDIO Microcoils	Injury	Physician experienced "unraveled feeling", coil came off at detachment zone	Additional information will be submitted w/in 30 days	3/26/2012
4	Stryker Neurovascular	GDC 360° Detachable Coils	Malfunction	Radiopaque markers were not visible	N/A	3/26/2012
5	Micrus Endovascular	DELTAPLUSH Microcoils	Malfunction	Coil got entangled while pulling back into microcatheter during preparation	Additional information will be submitted w/in 30 days	3/26/2012
6	Micrus Endovascular	MICRUSPHERE Microcoil	Malfunction	Quality inspection noticed device was unpacked and lost its sterility	Additional information will be submitted w/in 30 days	3/26/2012
7	Stryker Neurovascular	GDC 360° Detachable Coils	Injury	During withdrawal resistance was encountered, coil stretched and broke from delivery wire and protruded from aneurysm	N/A	3/26/2012
8	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Injury	Coil got stuck in microcatheter Delivery pusher kinked/bent Thrombus in microcatheter may have caused adherence	Additional information will be submitted w/in 30 days	3/23/2012
9	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	During repositioning, coil stretched	Additional information will be submitted w/in 30 days	3/23/2012
10	Covidien	AXIUM Detachable Coils	Injury	Aneurysm ruptured	Device not returned for evaluation	3/22/2012
11	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Injury	Patient complained of abducens paralysis	No known device problem	3/22/2012

Table 32 Continued

#	Company	Trade Name	Event Type	Adverse Event Description	Manufacturer Narrative	Date
12	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	During withdrawal, coil detached from gripper at coil detachment point	Additional information will be submitted w/in 30 days	3/22/2012
13	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	Coil stretch and could not be used	Lot inspection did not reveal any discrepancies	3/21/2012
14	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	During repositioning, coil stretched	Additional information will be submitted w/in 30 days	3/21/2012
15	Micrus Endovascular	PRESIDIO Microcoils	Malfunction	During repositioning, coil stretched	Additional information will be submitted w/in 30 days	3/20/2012
16	Micrus Endovascular	CASHMERE Microcoils	Malfunction	During withdrawal, coil unraveled in microcatheter	Additional information will be submitted w/in 30 days	3/20/2012
17	Micrus Endovascular	CASHMERE Microcoils	Malfunction	During repositioning, coil stretched	Additional information will be submitted w/in 30 days	3/20/2012
18	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	Coil stretch and could not be used	Additional information will be submitted w/in 30 days	3/19/2012
19	Stryker Neurovascular	Target Detachable Coils	Malfunction	After implanting, small part of coil was protruding into parent vessel	Operational context is most likely cause of event	3/16/2012
20	Stryker Neurovascular	Target Detachable Coils	Malfunction	During withdrawal, coil detached within the microcatheter	N/A	3/15/2012
21	Stryker Neurovascular	Target Detachable Coils	Malfunction	During unpacking, proximal end of delivery wire broke	N/A	3/14/2012
22	Stryker Neurovascular	Target Detachable Coils	Injury	During delivery, some resistance was encountered. Aneurysm ruptured	Operational context is most likely cause of event	3/13/2012
23	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	Coil delivery system was difficult to move out of coil introducer During prep, coil stretched	Additional information will be submitted w/in 30 days	3/12/2012
24	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Death	During delivery, coil prematurely detached 1/3 of the way through mc, also stretched. Coil protruded from aneurysm	Based on the available information no conclusion can be made regarding the reported stretching & premature detachment of the orbit coil prior to exiting the microcatheter	3/6/2012
25	Penumbra Inc.	Penumbra Coil 400	Injury	During withdrawal, coil broke and protruded from aneurysm	Without the return of the device, the root cause of the issue cannot be determined	3/6/2012
26	Stryker Neurovascular	Target Detachable Coils	Injury	During implanting, coil dislodged from aneurysm and migrated into artery	Operational context is most likely cause of event	3/1/2012

Table 32 Continued

#	Company	Trade Name	Event Type	Adverse Event Description	Manufacturer Narrative	Date
27	Micrus Endovascular	Micrus Microcoil System	Injury	After implanting, coil broke free and protruded from aneurysm ,causing stroke	Without the return of the device, the exact root cause of the problem reported could not be determined	2/29/2012
28	Penumbra Inc.	Penumbra Coil 400	Injury	Intracranial hemorrhage with definite relationship to the penumbra coil system	Determined that the reported event was an anticipated procedural complication.	2/28/2012
29	Codman Neurovascular	TRUFILL DCS Orbit Detachable Coil System	Malfunction	Coil auto-released in microcatheter	Additional information will be submitted within 30 days of receipt	2/24/2012
30	Codman Neurovascular	Orbit GALAXY Detachable Coil System	Malfunction	After implanting, coil did not seek perimeter of aneurysm instead compartmentalized	Additional information will be submitted within 30 days of receipt	2/23/2012

Table 33. Adverse Events Reported for the Delivery Pusher

#	Company	Trade Name	Event Type	Adverse Event Description	Manufacturer Narrative	Date
1	Codman Neurovascular	Orbit GALAXY Detachable Coil System	Malfunction	Physician made kink in pusher wire, bent it straight, then wire broke immediately	Additional information will be submitted w/in 30 days	3/27/2012
2	Micrus Endovascular	PRESIDIO Microcoils	Injury	Detached prematurely inside microcatheter	Additional information will be submitted w/in 30 days	3/27/2012
3	Stryker Neurovascular	GDC 360° Detachable Coils	Malfunction	Coil detached from pusher wire	Coil was detached from pusher wire	3/27/2012
4	Codman Neurovascular	Orbit GALAXY Detachable Coil System	Malfunction	During withdrawal, blue stopper/introducer became dislodged/separated	Additional information will be submitted w/in 30 days	3/20/2012
5	Penumbra Inc.	Penumbra Coil 400	Injury	During repositioning, lost control of coil which was no longer attached to the pusher	If the tip of the microcatheter was pressed tight against the wall of the aneurysm, a sharp angle between the coil and the tip of the catheter would be created. The angle may have caused the distal detachment tip of the pusher assembly to catch on the tip of the catheter when the catheter was advanced over the pusher assembly and coil during repositioning as described in the complaint. This may have resulted in stretching the flexible tip of the pusher assembly just enough to relax the pre-compression in the pull wire and disengage the coil	3/15/2012
6	Stryker Neurovascular	GDC 360° Detachable Coils	Malfunction	Coil was not attached to delivery wire	Not soaking the coil in saline resulted in difficulties, coil was broken off at the junction, at first uncovered primary wind of coil	3/14/2012
7	Codman Neurovascular	Orbit GALAXY Detachable Coil System	Malfunction	During withdrawal, coil could not be re-sheathed and was kinked	Cause of the reported event and damages found on the unit cannot be conclusively determined	3/5/2012
8	Penumbra Inc.	Penumbra Coil 400	Injury	During repositioning, coil protruded out of aneurysm and became stuck and broke from pusher	Without the return of the device, the root cause of the problem cannot be determined	3/2/2012
9	Penumbra Inc.	Penumbra Coil 400	Injury	During repositioning, coil detached and protruded from aneurysm	Returned condition of the device is not consistent with the event description therefore an exact root cause cannot be determined	3/2/2012

Table 34. Adverse Events Reported for the Detachment Mechanism

#	Company	Trade Name	Event Type	Adverse Event Description	Manufacturer Narrative	Date
1	Micrus Endovascular	ENPOWER Detachment Control System	Injury	Ready light did not illuminate Could not detach 1st coil, problem with 1st cable	Additional information will be submitted w/in 30 days	3/28/2012
2	Micrus Endovascular	ENPOWER Detachment Control System	Malfunction	Could not detach coil	Product not returned. Lot inspection did not reveal any discrepancies	3/27/2012
3	Micrus Endovascular	PRESIDIO Microcoils	Malfunction	Ready light did not illuminate Could not detach 1st coil, other coils detached with same cable	Additional information will be submitted w/in 30 days	3/27/2012
4	Codman Neurovascular	TRUFILL DCS Syringe II	Malfunction	2 syringes used but could not detach coils	Additional information will be submitted w/in 30 days	3/26/2012
5	Micrus Endovascular	ENPOWER Detachment Control System	Injury	Coil would not detach While repositioning the coil accidently detached	Additional information will be submitted w/in 30 days	3/26/2012
6	Stryker Neurovascular	Target Detachable Coils	Injury	After detachment 1 cm of coil remained in microcatheter	N/A	3/26/2012
7	Micrus Endovascular	ENPOWER Detachment Control System	Malfunction	Coil failed to detach	Additional information will be submitted w/in 30 days	3/26/2012
8	Codman Neurovascular	TRUFILL DCS Syringe II	Malfunction	2 syringes used but could not detach coils During withdrawal, coil delivery system kinked	Lot inspection did not reveal any discrepancies	3/21/2012
9	Codman Neurovascular	TRUFILL DCS Syringe II	Malfunction	During prep, air was trapped in the hub	Additional information will be submitted w/in 30 days	3/19/2012
10	MicroVention TERUMO	V-GRIP Detachment Controller	Death	During implant the coil did not detach, during withdrawal coil stretched and detached	Root cause cannot be determined	3/9/2012
11	Codman Neurovascular	TRUFILL DCS Syringe II	Malfunction	Delivery system severed several centimeters from proximal hub connection, coil could not detach	Additional information will be submitted within 30 days of receipt	2/23/2012

APPENDIX C

NON-GLP STUDY PROTOCOL WRITTEN BY JULIE GRINDE

STUDY TITLE			
Shape Memory Polymers for Treating Stroke			
STUDY TYPE:	Non-GLP	STUDY PROTOCOL #	TIPS-00612
AUP #	2011-254		

TESTING FACILITY	Texas A&M Institute for Preclinical Studies (TIPS) 800 Raymond Stotzer Pkwy College Station, Texas 77843 Phone 979-847-8477 Fax 979-845-6522	SPONSOR	NIH National Institute of Health Building 1 1 Center Drive Bethesda, Maryland 20892

APPROVALS			
ROLE	PRINTED NAME	SIGNATURE	DATE
STUDY DIRECTOR/ PRINCIPAL INVESTIGATOR	Matthew W. Miller, DVM, DACVIM		
DIRECTOR – TIPS MANAGEMENT	Theresa W. Fossum, DVM, PhD, DACVS		
SPONSOR'S REPRESENTATIVE	Duncan Maitland		

Table 35. Key Personnel - Roles and Responsibilities

Contact Information	Responsibilities
Study Director, Veterinarian, VSAM Professor, Board Certified Cardiologist Texas A&M University Texas A&M Institute for Preclinical Studies 979-845-2351 mmiller@cvm.tamu.edu	Matthew W. Miller, DVM, DACVIM Overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results and represents the single point of study control.
Director, Texas A&M Institute for Preclinical Studies, Professor of Surgery, College Station, TX 77843 979-847-8477 tfossum@tamu.edu	Theresa Fossum, DVM, PhD, DACVS TIPS Management
Scientific Director Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5754 egemen.tuzun@tamu.edu	Egemen Tuzun, MD Provide technical support to the Study Director as needed.
Veterinarian Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5468 cruoff@vprmail.tamu.edu	Cathy Ruoff, DVM Provide veterinary care to study animals, provide contributing scientist report for animal health. Work with CMP Veterinarian and study director to monitor animal health and address all animal health issues.
Veterinarian Texas A&M University Texas A&M Institute for Preclinical Studies vetjjg@gmail.com	Lee Jae Guo, DVM Provide surgical and technical support to the Study Director. Work with the TIPS Veterinarian to monitor animal health.
Comparative Medicine Veterinarian/ Attending Veterinarian Texas A&M University College of Veterinary Medicine Comparative Medicine Program 979-845-7433 elliottjj@tamu.edu	Jim Elliott, DVM Collaborate with TIPS veterinary staff to provide animal care and husbandry. Oversees the Comparative Medicine Program (CMP).

Table 35 Continued

Contact Information	Responsibilities
Laboratory Manager Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5469 hmaass@tamu.edu	Heather Maass Manage anesthesia services, post-surgical care, and routine observations of study animals. Manage archives, and provide record quality control oversight, provide technical support, and assist with data collection as needed.
Assistant Research Specialist Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5733 aarrington@tamu.edu	Aimee Arrington Provide anesthesia, post-op, animal health care, daily observations, surgical support, supervise veterinary technicians, assist with data collection.
Senior Research Associate Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5481 bspanhel@tamu.edu	Brian Spanhel, BS, MLS (ASCP)^{CM} Provide clinical pathology, laboratory testing, compile data, and provide data to the study director.
Research Associate Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5742 jgrinde@tamu.edu	Julie Grinde, BS Serve as lead study coordinator. Provide assistance to the Study Director and coordination of study activities, monitor animals, collect study data, compile study data, and assist in preparation of reports.
Research Associate Texas A&M University Texas A&M Institute for Preclinical Studies 979-458-5747 kbonugli@tamu.edu	Katy Bonugli BS, RVT, RDMS Provide assistance to the Study Director and coordination of study activities, monitor animals, collect study data, compile study data, and assist in preparation of reports.
Associate Research Specialist Texas A&M University Texas A&M Institute for Preclinical Studies sbrownlee@tamu.edu	Sheila Brownlee, CST/CFA Oversee operating room personnel, provide surgical assistance, assist in data collection and preparation of surgical reports.

Table 35 Continued

Contact Information	Responsibilities
Pathologist, Texas A&M University College of Veterinary Medicine Cardiovascular Pathology Laboratory (TAMU-CVP) 979-458-1074 fclubb@cvm.tamu.edu	Fred Clubb, DVM, PhD, DACLAM Lead pathologist, provide pathology services, perform gross necropsies, perform histological evaluations, and prepare a contributing scientist report.
Pathologist, Texas A&M University College of Veterinary Medicine Cardiovascular Pathology Laboratory (TAMU-CVP) 979-458-1074 ktrainor@cvm.tamu.edu	Karen Trainor, DVM, MS, DACVP Provide pathology services, perform gross necropsies, perform histological evaluations, and assist in the preparation of a contributing scientist report.
Pathologist Texas A&M University College of Veterinary Medicine Cardiovascular Pathology Laboratory (TAMU-CVP) 979-845-0789 bweeks@cvm.tamu.edu	Brad Weeks, DVM, PhD Provide pathology services, perform gross necropsies.
Histology – Manager Cardiovascular Pathology Laboratory Texas Heart Institute 832-355-2825 ppotts@heart.thi.tmc.edu	Pamela Potts, BS Provide management oversight for THI Pathology Lab services.
Associate Lab Manager Texas A&M University College of Veterinary Medicine Cardiovascular Pathology Laboratory (TAMU-CVP) 979-458-1074 bcarpenter@cvm.tamu.edu	Brian Carpenter, BS Provide management oversight for A&M Pathology Lab services.

Table 36. Testing Facility and Other Sites - Responsibilities

Location	Responsibilities
Texas A&M Institute for Preclinical Studies (TIPS) 800 Raymond Stotzer Parkway College Station, Texas 77845	Testing Facility Responsible for overall technical conduct of the study including, administration of test articles, animal acquisition, animal care and husbandry, veterinary care, clinical assessments and observations, clinical diagnostic testing, and preparing a comprehensive final report.
Texas A&M University College of Veterinary Medicine Cardiovascular Pathology Laboratory (TAMU-CVP) 4467 TAMU College Station, Texas 77843	Pathology Responsible for gross necropsy, tissue harvest, microscopic analysis of target organs, and providing a contributing scientist's report.
Texas Heart Institute (THI-CVP) Cardiovascular Pathology Research Laboratory 6770 Bertner Avenue Houston, Texas 77030	Histology Responsible for preparing tissue for light microscopy including tissue processing, preparing slides, and staining tissue.

1. BACKGROUND OF THE DISEASE AND TREATMENT OPTIONS

This protocol covers the animal studies under a National Institute of Health (NIH) grant titled "Shape Memory Polymers for Treating Stroke (R01EB000462)". The grant supports the research and development of technologies that may be able to improve the treatment and prevention of stroke. Stroke is a major cause of mortality and the primary cause of long-term disability in the United States. According to the National Stroke Association, approximately 732,000 Americans suffer a stroke each year of which 160,000 do not survive. The American Heart Association estimates the total cost of stroke to the U.S. to be about $56 billion. Of all strokes, approximately 20% are hemorrhagic, 60% are large vessel occlusions, and 20% are due to small vessel disease, resulting in "lacunar" infarcts.

2. OBJECTIVES

The objectives of the study are:

1) Test the applicability of a unique catheter-delivered device for management of experimentally induced vascular abnormalities with the intention of applying these devices to disease in human beings.

2) Implement a mechanical thrombectomy device that will greatly improve the efficacy of removing clots, extend the window that the treatment can be implemented (from 5 to as long as 12 hours), and provide a treatment that does not have the bleeding risks of t-PA.

3. REGULATORY COMPLIANCE

A. GOOD LABORATORY PRACTICE

Data from this study is not intended for submission to the United States Food and Drug Administration (FDA) to support safety. This study is not subject to and will not be conducted in accordance with the FDA, Good Laboratory Practices for Non-clinical Laboratory Studies, 21 CFR, Part 58.

B. AMENDMENTS AND DEVIATIONS

Changes to the study protocol will be issued in the form of amendments and will be approved by the Study Director, Sponsor Representative, and TIPS Testing Facility Management. Deviations from the study protocol will be documented as "Notes to Study" and will be authorized by the Study Director. Study amendments impacting approved procedures involving animals as described in the Animal Care and Use Protocol will be submitted to the Texas A&M Institutional Animal Care and Use Committee for review and approval prior to initiating a study protocol amendment.

C. ANIMAL WELFARE

Animals will receive humane care in compliance with the "Principles of Laboratory Animal Care," formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals" (NIH Publication). The Testing Facility and Testing site will conduct the study in accordance with the Animal and Plant Health Inspection Service, United States Department of Agriculture, Animal Welfare Act, 9 CFR, Parts 1, 2, and 3 as applicable; according to an Animal Use Protocol (AUP) approved by the University's Institutional Animal Care and Use Committee (IACUC); and this Sponsor-approved "study" protocol. TIPS is part of the TAMU USDA registered AAALAC accredited program and Public Health Service (PHS) assurance. As stated in section 3.B. study amendments impacting approved procedures involving animals as described in the Animal Care and Use Protocol will be submitted to the Texas A&M Institutional Animal Care and Use Committee for review and approval prior to initiating a change to the approved procedures.

4. DATES

Study Initiation Date – The date the protocol is signed by the Study Director.
Study Completion Date – The date the final report is signed by the Study Director.

5. STUDY DESIGN

Animals will undergo anesthesia for aneurysm creation surgery. Vascular abnormalities (saccular aneurysms) will be created in major blood vessels (carotid arteries) in pigs followed by treatment of the aneurysms with the test and control devices that will help support the diseased vessel, prevent vessel rupture and promote healing. The devices will be deployed by either a catheter based technology through the femoral artery or by surgically placed devices directly into the created aneurysm using direct visualization. The animals will undergo imaging studies (fluoroscopy, CT angiography (CTA), and/or MR angiography (MRA)). The animals will be recovered and survived for their assigned time point. At the end of the study the animals will again be anesthetized and will undergo imaging studies (fluoroscopy, CTA, and/or MRA). The animal will then undergo testing of the thrombectomy device on clots placed in the branches of the external carotid artery, subclavian artery, and/or renal/mesenteric arteries. The animals will be euthanized and carotid arteries/aneurysms and tissues that underwent clot removal will be harvested.

Table 37. Description of Each Test Group Used in Animal Study

Test Group	Number of Animals	Duration of Experiment
I	14 pigs	30 days
II	14 pigs	90 days

6. STUDY DURATION

The in-life phases of each animal in the study will be 30 days (± 2 days) or 90 days (± 3 days) depending on the assigned group.

7. TEST SYSTEM

Table 38. Description of Animals Used in Animal Study

Total Number:	28
Species:	Swine
Strain:	Domestic cross (Yorkshire, Yorkshire-cross)
Weight:	30 to 45 kg
Age:	Mature
Sex:	Either
Source/Supplier:	TAMU or CMP approved vendor

A. ANIMAL IDENTIFICATION

The animals will be identified by an ear tag or tattoo (Standard Operating Procedure (SOP) CMP-02-002, Identification of Swine, Ovine, Caprine, Canine, Bovine). All animal records and data sheets will contain the unique animal identification number. TIPS personnel will verify the animal's number by checking the ear tag or tattoo prior to performing any procedures. A cage card containing a minimum of the animal's number, name of Study Director, the Animal Use Protocol (AUP) number, and the Study Protocol number will be maintained on the cage and moved with the animal at all times. If animals have more than one identification number in their records, documentation will be retained in the animal's file clearly referencing all assigned numbers and names (if any).

B. ANIMAL HOUSING

The animals will be individually housed indoors in aluminum pens (24 sq. ft. minimum) on raised slated flooring. Optimal environmental conditions will target a range of 30-70% humidity and a target temperature range of 61^0-81^0 Fahrenheit. The humidity and temperature may be observed outside of the target range during periods of cleaning. A twelve (12) hour on / twelve (12) hour off light cycle will be maintained. Cages will be cleaned in the morning and, if they are soiled, in the afternoon. Cages will be disinfected at least weekly.

C. FOOD AND WATER

Animals will be fed a commercially available laboratory swine diet twice daily and will have free access to water filtered through reverse osmosis (SOP CMP-02-006, Feeding and Watering GLP Research Animals). The animals may be given treats as part of enrichment. All treats will be recorded in the animal's record. There are no known contaminants in the food that will impact the study. Water analysis has been performed and there are no known contaminants in the water that will impact the study.

D. ANIMAL HEALTH

i) ACQUISITION – QUARANTINE

(1) The animals will be received and quarantined at TIPS for a minimum of fourteen (14) days prior to study.
(2) If animals require vaccination or deworming upon arrival to TIPS, quarantine may be extended an additional fourteen (14) to thirty (30) days from treatment at the discretion of a CMP Veterinarian.
(3) Animals will be weighed upon arrival and a visual exam performed by a veterinarian. Animals will be evaluated daily during quarantine for signs of illness by a veterinarian or a qualified animal health technician.
(4) Daily observations, vaccinations, examinations, weights, treatments, and any diagnostic tests (hematology, serology, parasitology) will be documented in the animal's records.
(5) Animals may be conditioned to handling during the quarantine period and may be given small quantities of food treats approved by the Study Director and CMP Veterinarian. All food treats will be recorded in the animal record.
(6) At least three (3) days after arrival at TIPS and prior to release from quarantine, the animals will undergo a complete physical examination and blood collection. Jugular blood samples will be collected using an appropriately sized needle. Approximately 1-12cc of blood will be

withdrawn and submitted for a complete blood count (CBC), coagulation analysis, and blood chemistry analysis (basic health screen) (see Section 7). The animals will be sedated with Telazol (5-10 mg/kg IM) for the blood collection.

ii) RELEASE FROM QUARANTINE & STUDY ENROLLMENT

Prior to study assignment and release from quarantine the animals will be in good health as determined by physical examination from a CMP veterinarian, assessment of hematology and blood chemistry parameters (see Section 11).

iii) ANIMAL OBSERVATIONS AND VETERINARY CARE

(1) After animal assignment to the study, daily health care will be provided by TIPS veterinary staff (veterinarians and trained veterinary technicians) in cooperation with a CMP Veterinarian. Animals observed to have any abnormal condition will be evaluated by veterinary staff and the findings will be documented. Any medications and treatment instructions will be documented in the animal's record.

(2) CMP animal care staff will record daily food intake, general condition as observed during routine husbandry, and presence/absence and consistency of stool. Any abnormalities observed by animal care staff will be recorded in the animal's record and promptly reported to a CMP Veterinarian who will assess the animal and notify the TIPS Veterinarian. The TIPS Veterinarian will notify the Study Director. The CMP Veterinarian will make a reasonable attempt to reach the TIPS Veterinarian and/or Study Director when health problems arise. In the event the TIPS Veterinarian or Study Director cannot be reached the CMP Veterinarian will decide the best method to resolve the health problem to prevent unnecessary pain and discomfort to the animal.

NOTE: If necessitated by the animal's health, more frequent or extended observations may occur at the discretion of the Study Director, TIPS Veterinarian, or CMP veterinarian in collaboration with the Study Director.

E. MORIBUND ANIMALS

Severe health problems (reasons for euthanasia) include moribund status, inability to get food and water, intractable pain, and major organ system dysfunction (as indicated by blood work). If any of the preceding occurs and is not correctable by conventional veterinary therapy, and are deleterious to the animal and/or is intractable to treatment, the animal will be euthanized. The animal may be sedated with Telazol (5-10 mg/kg IM) prior to euthanasia.

The Study Director, TIPS Veterinarian, and CMP Veterinarian will cooperatively make decisions related to early sacrifice. If possible, a final data collection will be performed prior to sacrifice.

If an animal requires early euthanasia, every effort will be made to collect final data. The animals will be Heparinized and euthanized as described in Section 16. Animals that are euthanized early or expire unexpectedly will undergo a necropsy as described in Section 17 and the tissues listed in Section 18 will be harvested and archived. Heparin (30,000 units) will be administered IV at least 5 minutes prior to euthanasia. If the necropsy cannot be performed immediately the carcass will be stored in the necropsy cold room until the necropsy can be performed.

8. EQUIPMENT AND COMPUTERIZED SYSTEMS

The following is a list of equipment that may be used in this study and either generates, measures, or assesses data or has been deemed critical study equipment.

TIPS Equipment and Computerized Systems

Landmark Vetland EX3000 or VSA 2100 Veterinary Anesthetic Machine
Hallowell EMC or SurgiVet VetPAC Ventilator
Capnograph – Novametrix Tidal Wave Model # 615
Pulse Oximeter – Nellcor Model # N65 or Model # NPB40
Welch Allyn SureTempPlus Veterinary Thermometer
Cardell MAX-12/MAX-12 DUO
Floor Scale – GSE Model Digital Weigh Indicator/Rough Deck Floor Scale
Abbott Cell-Dyn 3700 Hematology Analyzer
Beckman Coulter Olympus AU400e Chemistry Analyzer
Diagnostica Stago STA Compact Hemostasis Analyzer
Microscope: Olympus BX51
Orchard Harvest Laboratory Information System (LIS)
Microsoft Office Excel Software 2007 and 2010
Philips Allura Xper FD 20 C-arm System – Release 7.0.2
Siemens Biograph mCT
Siemens Magnetom Verio MRI
Medrad Stellant CT Injector
Medrad Spectris Solaris EP MR Injector
Medrad Mark V Provis Power Injector

CVP Equipment and Computerized Systems

Microscope: Olympus BX41
Spot 2 Mega Sample Digital Microscope Camera
Balance: TP-12, 12000G/1G
Balance: TP-1502, 1500G/0.01G

Super Cool Scan 9000 (LS-9000) Film Scanner
Eva-Dry EDV-2200 Electric Mid0Size Dehumidifier
Microscope Camera: Nikon Digital Sight DS-Ri1
Microscope Camera: Nikon Digital Sight Viewing Monitor
Microscope: Olympus BX46F
Apple Mac Pro #A1186
Microsoft Office 2011 Mac – Microsoft Word and Microsoft Excel software version 12.2.5
Mac Pro #A1186
Adobe Photoshop CS4 software version 11.0.2
Nikon Scan 4 version 4.0.0.3020
Microsoft Office 2011 Mac – Microsoft Word and Microsoft Excel Software version 12.2.6
Dell Computer OXPCG3
Microsoft Office 2010 – Microsoft Word and Microsoft Excel Software version 14.0.6029.1000
Dell OptiPlex 990 Small Form Computer
Microsoft Office 2010 – Microsoft Word and Microsoft Excel software version 14.0.6029.1000
Digital Camera Firmware DS-L2

Note: Texas Heart Institute is responsible for maintaining an equipment inventory list.

9. EQUIPMENT AND DEVICES

A. QUANTITY – DEVICES

Table 39. Test and Control Article Quantities

Quantity	Item
28	Test Devices – Shape Memory Polymer devices (one per aneurysm)
112	Control devices – Gugliemi Detachable Coils (GDC) (many per aneurysm)

B. TEST ARTICLE

Shape Memory Polymer (SMP) Foam is a unique catheter delivered device for management of vascular abnormalities. If the delivery method has not been developed, then the SMP may be directly placed into the aneurysm prior to the aneurysms' domes being closed.

C. TEST ARTICLE LABELING

The sterilization date will be labeled on each container/package of all devices that are to be implanted.

D. CONTROL ARTICLE AND ANCILLARY EQUIPMENT LABELING

The model number, serial number, expiration date, and storage requirements will be labeled on each container/package of all devices that are to be implanted or used to assist with the implantation procedure (e.g. introducers, guide catheters, guide wires).

E. EQUIPMENT AND DEVICE SHIPPING/RECEIVING/DISPOSITION

i) Equipment and devices will be shipped or delivered to the testing facility by commercial carrier or hand carried. If shipped the Sponsor will notify TIPS of the shipment and expected arrival date. A TIPS Chain of Custody form will accompany each shipment.

ii) Upon receipt all contents will be inspected and the Chain of Custody form will be completed, retained in the study records, and a copy will be submitted to the Sponsor.

iii) In the event that any equipment or device containers are damaged the Sponsor will be notified and the damaged articles will be retained pending instructions from the Sponsor.

iv) An inventory will be maintained of equipment and device receipt, administration, and disposition.

v) TIPS will return equipment and unused devices to the Sponsor at the end of the study and will reconcile the inventory list.

F. EQUIPMENT AND DEVICE STORAGE CONDITIONS

The Sponsor will provide the equipment and devices as listed in Table 1. The devices to be implanted will be in sterile form ready for implantation in sufficient number including backup for all proposed experimentation. All accessories and supplies intended to come in contact with the sterile field will be sterile. The items will be stored in accordance with Sponsor specifications.

10. METHODS FOR CONTROL OF BIAS

Blinding of study personnel or the pathologist is not required.

11. CLINICAL PATHOLOGY

A. An appropriate sized needle and syringe will be used to enter the left or right jugular or pre-caval vein for blood collection. Approximately 1-12 cc of blood will be withdrawn for complete blood count (CBC), coagulation analysis, and chemistry analysis (basic health screen) during the quarantine period, at time of implant, and prior to euthanasia. The assays to be performed are listed in Appendix A.

B. Additional blood samples may be collected and submitted for analysis if deemed necessary for clinical evaluation of study animals at the discretion of the Study Director or TIPS Veterinarian or their designee.

12. PROCEDURES

A. FASTING

Aspirin (3-5 mg/kg PO) and Clopidogrel (Plavix) (5-10 mg/kg PO) will be given once daily beginning two days prior to surgery. Animals will be weighed within seventy-two (72) hours prior to anesthesia induction. Animals will be fasted from food and treats twelve (12) hours prior to anesthetic and sedation procedures. Water will be provided ad lib.

B. ANESTHESIA INDUCTION/MAINTENANCE

Pigs will be pre-medicated with Telazol at 5 mg/kg and Buprenorphine at 0.01-0.05 mg/kg intramuscularly (IM) prior to induction. Anesthesia will be induced with Isoflurane (~3-4%) in Oxygen.

The swine's heart rate and pulse quality, respiratory rate and character, and temperature will be evaluated and recorded at induction. In the event that abnormalities are noted the Study Director will be contacted before proceeding.

Using aseptic technique, an appropriately-sized (~18-20g) catheter will be placed, a T-port attached, and catheter secured in the auricular vein of either ear for venous access. An appropriately-sized endotracheal tube will be placed, secured in place, and the cuff inflated. The capnograph will be connected between the endotracheal tube and the breathing circuit. A pulse oximetry probe will be attached to the tongue or other appropriate location for monitoring.

Anesthesia will be maintained with Isoflurane (0.5-4%) in 100% Oxygen. The animal will be connected to the ventilator and mechanical respiration will be provided at a rate of 6-12 BPM and a tidal volume of 10-20 mL/kg.

Lactated Ringers solution will be given IV at a rate of 10-20 mL/kg/hr. Draxxin (2.5 mg/kg IM) will be given.
Areas for electrocardiogram (ECG) lead placement and for electrocautery ground plate will be shaved (if needed). The area over both of the jugular veins and femoral veins will be shaved and cleaned.

C. SURGICAL PREPARATION

The animal will be transported to the surgical suite, transferred to the operating table, and placed/secured in dorsal recumbency. ECG electrodes will be placed and ECG cables connected, and a rectal or oral temperature probe will be placed. The Bair Hugger blanket will be placed and connected to the Bair Hugger unit to provide thermal support if needed.
The surgical sites over the neck and groin will be prepared using aseptic techniques with Chlorhexidine/Alcohol solution, and draped for the surgical procedure.

D. PROCEDURE

An incision made on and/or immediately adjacent the midline of the neck. After reflecting the cervical musculature, an approximately 4 cm long segment of the external jugular vein will be isolated and excised after a 2-0 silk ligature is placed at each end of the segment. This segment of the vein will then be divided transversely, yielding two open ended pouches. The carotid arteries will then be sequentially exposed and cleaned of adventitia. Systemic anticoagulation (Heparin 200-300 IU/kg IV) will be administered to maintain activated clotting times of 1.5-3 times baseline in order to prevent thromboembolic complications related to the procedure itself. Vascular clamps will be placed at each end of the area of interest on the artery to provide temporary vessel occlusion. Nitroglycerin will be directly applied to the exposed artery as needed to dilate and/or counteract constriction of the vessel. An approximately 7mm arteriotomy will then be made, and end-to-side anastomosis of the venous pouch to the carotid artery will be performed using an appropriate sized suture. In this fashion, an aneurysm measuring 5-15 mm in diameter will be created on each carotid artery.

Treatment will be performed soon after creation of the aneurysms, as these aneurysms may spontaneously thrombose over time. Angiography will be performed after surgical preparation of the femoral areas followed by a trans-femoral access technique of accessing the artery either percutaneous or via direct

arterial cut down for placement of an introducer sheath. Following carotid angiography and assessment of patency of the aneurysm, the shape memory polymer (SMP) foam device will be implanted in one of two manners: catheter based deployment or directly placed in the aneurysm. A catheter will be advanced under continuous fluoroscopic guidance through a guiding catheter (4-8 Fr), position confirmed, and the device deployed. Direct placement of the SMP foam device will be performed by having the surgeon place the device directly into the created aneurysm just before the sac is sutured closed. Digital subtraction and 3-D Angiography will be performed post SMP foam placement to document parent vessel integrity and assess aneurysm filling. After integrity and filling have been assessed, the incision(s) will be closed. A MRA may be performed.

E. ANESTHESIA RECOVERY

The Isoflurane will be discontinued, and the subject will be weaned from oxygen. The animal will be placed on room air until the animal is showing signs of recovery (palpebral reflex, swallowing, and presence of jaw tone). At this point the animal will be extubated. Buprenorphine (0.01-0.05 mg/kg IM) may be repeated every 6-8 hours as needed for analgesia. Animals will be returned to standard animal housing only after they are fully ambulatory and have no ataxia.

F. POST SURGICAL PERIOD

The animals will be closely monitored several times during the day by technical and veterinary staff for a minimum of the first 1-3 postoperative days (24-72 hours). Once the animal is deemed healthy and hemodynamically stable by veterinary staff, daily observations will be performed at least two (2) times daily for the duration of the study by TIPS veterinary technical staff (veterinarian or trained veterinary technician). Depending upon the animal's condition, more frequent monitoring will be instituted. Aspirin (3-5 mg/kg PO) and Clopidogrel (Plavix) (5-10 mg/kg PO) will be given once daily every 24 hours until euthanasia.

13. FOLLOW-UP DATA COLLECTION PROCEDURES

At the completion of the observation period for each group, the study subjects will again be anesthetized using the previously described protocol. Angiography will be performed via the trans-femoral technique accessing the artery either percutaneously or via direct arterial cut down. Angiography will be performed to more completely characterize chronic changes in aneurysm filling, including aneurysm exclusion, intraluminal thrombus formation, or distal emboli. These study subjects may have MRA or CTA performed in addition to standard digital subtraction and 3-D

angiography to more completely characterize the SMP foam implant. After final angiographic evaluation of the aneurysms but prior to euthanizing the study subject, the animal will undergo thrombectomy device evaluation.

14. THROMBECTOMY DEVICE EVALUATION

The guiding catheter will be placed into branches of the external carotid artery, subclavian artery, and/or renal/mesenteric arteries. Baseline angiography will be performed. Vessels measuring 2-6 mm in diameter will be targeted, as this is the size of the major intracranial arteries affected clinically by thromboembolic stroke. Autologous blood clot will be prepared from blood withdrawn from the animal immediately after induction of anesthesia. This will be allowed to stand in a syringe in order to allow clot to form. Differing consistencies of clot will be created, ranging from acute thrombus with a more jelly-like consistency to denser clot created using thermocoagulation or addition of thrombin. An amount of clot will then be selected, with the size based upon the diameter of the branch vessels visualized angiographically. The clot will then be measured and photographed for comparison against the amount of retrieved clot, if any, and injected through the catheter. The animal will be heparinized to prevent *in situ* thrombus formulation during occlusion by the injected clot. Degree of arterial occlusion will be assessed angiographically using a standard grading scale, ranging from normal flow to complete occlusion. Under fluoroscopic guidance, the SMP thrombectomy devices will then be advanced through the guiding catheter, and attempts at clot extraction will be made. After these attempts, angiography will again be performed to determine degree of recanalization, if any, and to evaluate for any evidence of device-related arterial injury. Number of attempts, technical factors related to device deployment (e.g., ability to reach desired location, passage through and beyond clot, success of actuation, time to actuation, etc.), degree of recanalization, amount of clot removed, and any evidence of arterial injury will be recorded. For each animal, attempts will be made in multiple different vessels in order to maximize the number of devices that can be tested, so long as the animal remains hemodynamically stable and can continue to be maintained under anesthesia.

15. EUTHANASIA

If the test subject becomes physically compromised as described in Section 7 E, and the condition is deleterious to the animal and/or is intractable to treatment, the animal will be euthanized.

Following the final data collection, the animals will remain anesthetized and will be given 30,000 units of Heparin IV. The Heparin will be given at least 5 minutes prior to euthanasia to allow adequate time to circulate. The animal will then be euthanized with a barbiturate derivative (80-120 mg/kg), administered intravenously.

After euthanasia the following criteria will be used to confirm that the animal is deceased: absence of all ocular reflexes, lack of audible breath and heart sounds for

longer than five minutes (via stethoscope) and lack of cardiac electrical activity (when applicable) for longer than five minutes.

16. NECROPSY

A gross necropsy with photography will be performed for all animals. The identity of the animal will be verified. The skin and body surfaces will be examined and any observations will be recorded on the necropsy form. Photographs will be taken of any abnormalities. The internal organs will be examined and any abnormalities will be noted and photographed.

The carotid arteries and other vessels of interest will be perfusion fixed per SOP CVP-07-013, Perfusion Fixation of Tissue during Necropsy, using saline and formalin. Briefly, the vasculature will be retrograde and antegrade perfused with phosphate buffered saline followed by formalin until the tissues begin to be fixed.

17. HISTOPATHOLOGY

The carotid arteries (with aneurysms) and the targeted vessels from all animals will be preserved and sent to the College of Veterinary Medicine Cardiovascular Pathology Laboratory (TAMU-CVP) for a histopathology evaluation.

The intact, perfused, formalin-fixed aneurysms will be examined and subsequently photographed. Once the quality of the gross photographs is confirmed, the aneurysms will be placed in plastic. Sections will be taken perpendicular to the long axis of the carotid vessel. The sections will be stained with Hematoxylin and Eosin (H&E) and Trichrome. Any remaining tissue will be stored as plastic blocks.

The intact, perfused, formalin-fixed vessels will be examined and subsequently photographed. Once the quality of the gross photographs is confirmed, the targeted vessels will be placed in cassettes and sent to THI. The tissue blocks will be placed in paraffin. Sections will be taken perpendicular with the long axis of the vessel. The sections will be stained with Hematoxylin and Eosin (H&E) and Trichrome. Any remaining tissue will be stored as paraffin blocks.

The histopathological results from the pathologists will consist of a descriptive narrative for the gross tissue and the microscopic results. Analysis will be performed from histological examination of the aneurysm sac, the carotid arteries adjacent to the aneurysms, and the targeted vessels. The tissue from each of the groups will be compared using the following factors: degree of inflammation, fibrosis, and tissue damage. The extent and severity of damage will be compared within the group. Microscopic images will be captured per SOP CVP-07-21 and CVP-07-043. Representative images of the stained sections will be included in the pathology report.

Organs with gross lesions will be examined microscopically and findings reported.

18. DATA ANALYSIS AND REPORTING

All study data will be analyzed by the Study Director and a final report will be prepared and submitted to the Sponsor within 90 calendar days after receipt of the all of the data including the pathology report.
A Contributing Scientists' report will be included from the pathology group. The final report will describe the roles and responsibilities of each of the pathologists.
The final study report will include tables of data and analysis of the following:

- Survival and Disposition
- Clinical Findings: Total Occurrence/No. of Animals
- Animal sequence
- Sex, Body Weights, Age
- Hematology Values
- Serum Chemistry Values
- Scheduled and Unscheduled Necropsies
- Macroscopic Findings
- Microscopic Findings

19. RECORDS MANAGEMENT

All study related raw data generated by TIPS will be kept at TIPS in the archive until the signing of the final report.
Records to be maintained will include but not be limited to the following:

- Signed protocol
- Surgical reports
- Test article and ancillary equipment chain of custody
- Data sheets
- Animal health records
- USDA records (receiving records, examinations, clinical diagnostic testing, daily observations)
- Clinical pathology data
- Final report
- Amendments and Deviations
- Notes to study file
- Contributing scientists' reports (pathology)
- Necropsy photos*
- Tissue blocks*

- Tissue slides*

  * Pathology related items will be kept at CVP until the pathology report is signed. The items will then be transferred to TIPS.

Copies of all study raw data and study related records will be collected and retained in the TIPS archive for a period of five (5) year from the date the final report is signed by the study director. Original paperwork will be provided to the Sponsor. TIPS will retain an exact copy of the final report. The Sponsor will be provided with the original of the final report. At the end of five (5) years the Sponsor will be notified of the intent to dispose of the records and given the option of disposal, extended storage, or the records can be shipped to the Sponsor. Final disposition of the records will be documented in the TIPS archive with the final report.

Blood Assays

i) Hematology

Assay	Complete Blood Count (CBC)	
Components	Leukocyte count (WBC)	Automated and manual WBC differentials
	Erythrocyte count (RBC)	Hemoglobin (HGB)
	Hematocrit (HCT)	Mean corpuscular HGB (MCH)
	Mean corpuscular volume (MCV)	Mean corpuscular HGB concentration (MCHC)
	RBC distribution width (RDW)	Platelet count (PLT)
	Mean Platelet Volume (MPV)	
Specimen Type	EDTA whole blood (lavender top tube)	
Specimen Processing	None	
Specimen Storage	2-8°C if same day testing not possible	

ii) Chemistry

Assay	Chemistry Panel (Chem)	
Components	Albumin	ALT (alanine aminotransferase)
	AST (aspartate aminotransferase)	BUN (blood urea nitrogen)
	Calcium (Ca)	Creatinine
	Electrolytes (chloride, potassium, sodium)	GGT (gamma-glutamyltransferase)
	Glucose	Phosphorus
	Total bilirubin	Total Protein
Specimen Type	Serum (yellow top serum separator tube)	
Specimen Processing	Centrifuge and aliquot serum	
Specimen Storage	2-8°C if same day testing not possible	

iii) Coagulation

Assay	Coagulation Panel	
Components	PT – prothrombin time	Fibrinogen
	APTT – activated partial thromboplastin time	
Specimen Type	Sodium citrate plasma (blue top tube)	
Specimen Processing	Centrifuge and aliquot plasma	
Specimen Storage	-80°C if same day testing not possible	

APPENDIX D

FOAM ACTIVITY DIAGRAMS

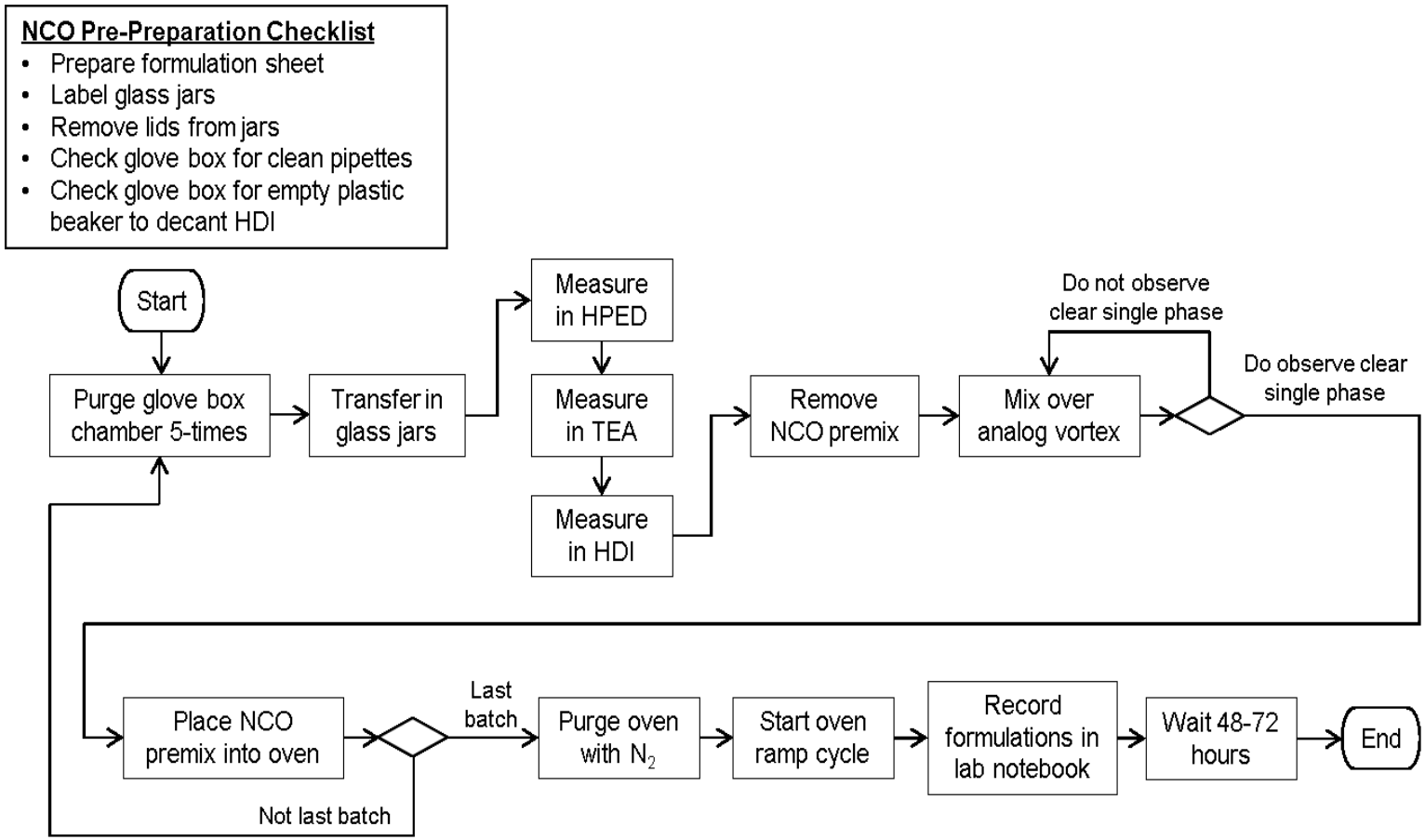

Figure 10. Activity Diagram for Preparation of NCO Premix

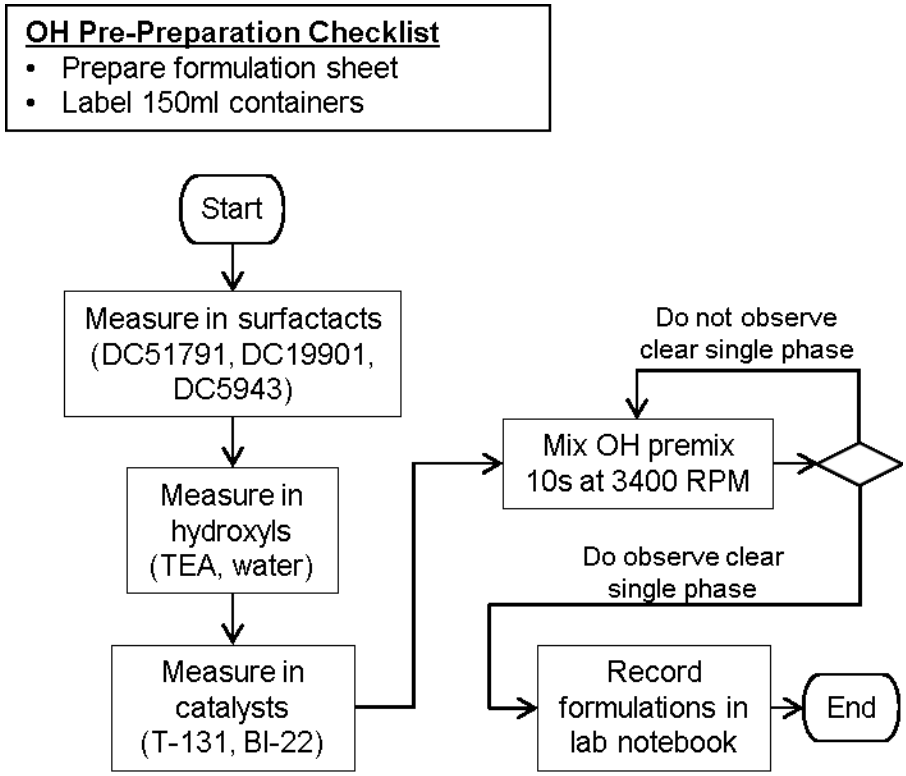

Figure 11. Activity Diagram for Preparation of OH Premix

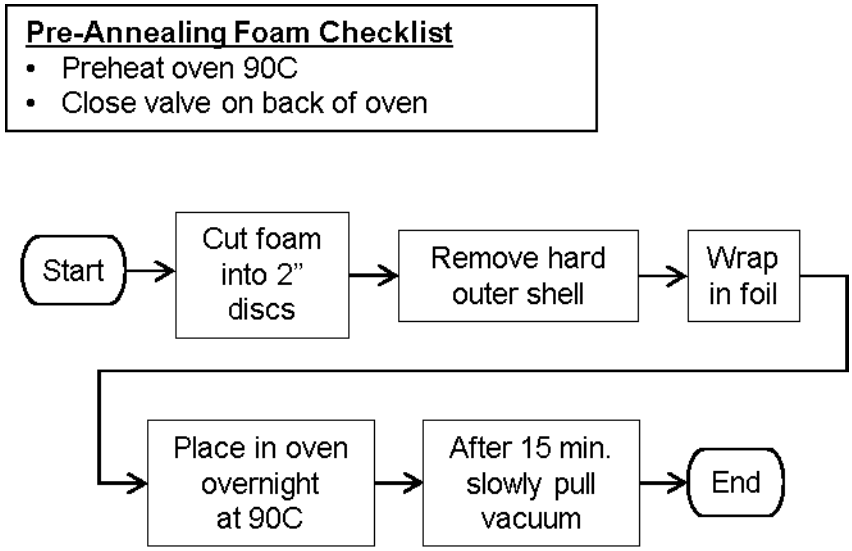

Figure 12. Activity Diagram for Annealing the SMP Foam

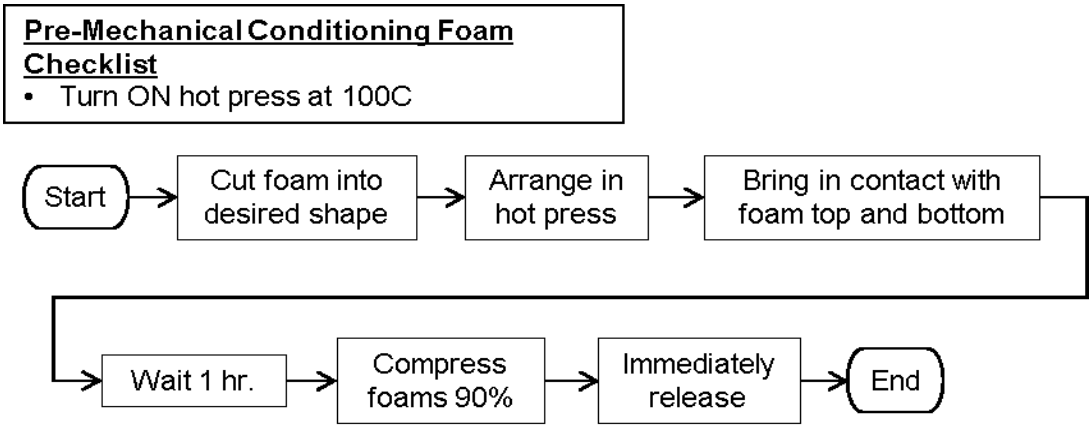

Figure 13. Activity Diagram for Mechanical Conditioning of the SMP Foam

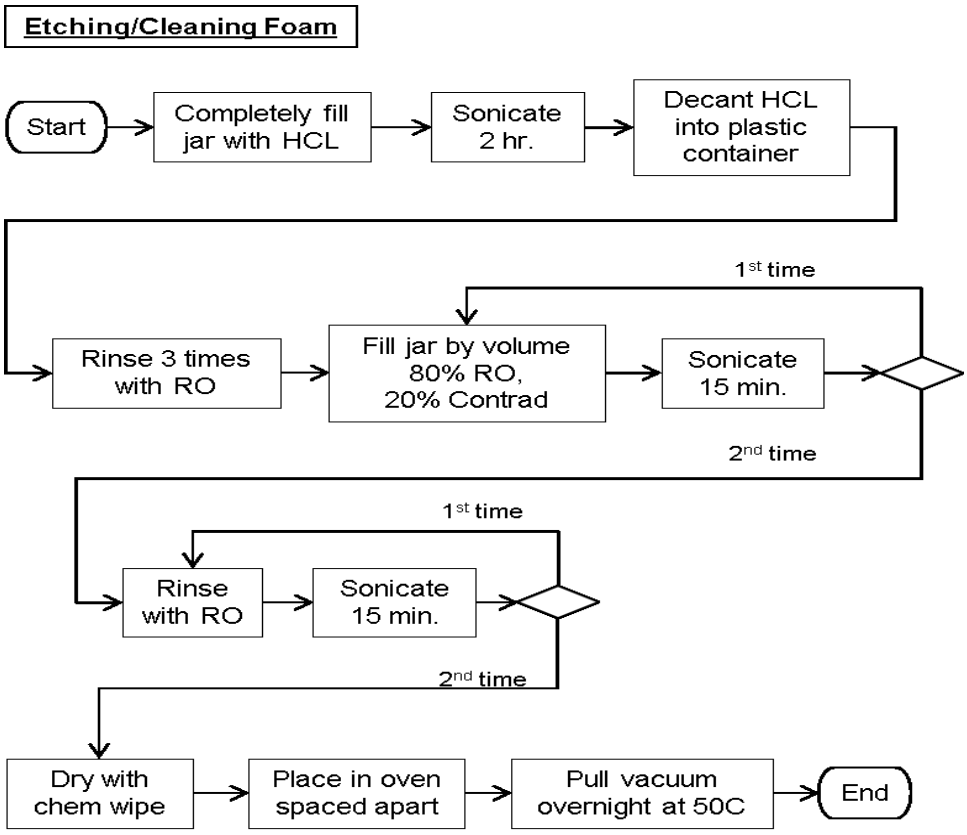

Figure 14. Activity Diagram for Etching and Cleaning the SMP Foam