# A randomized, concurrent controlled trial to assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of large vessel occlusion in acute ischemic stroke

**Protocol**
CLP 4853.D

**Date of Protocol**
June 27, 2012

**Device Name**
Penumbra System®

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# Investigator Agreement and Certification

**A randomized, concurrent controlled trial to assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of large vessel occlusion in acute ischemic stroke**

I hereby agree to participate in the clinical investigation of the use of the Penumbra System sponsored by Penumbra, Inc. ("Study Sponsor"). I agree to conduct this investigation according to the requirements of the investigational plan provided by the Study Sponsor and in accordance with applicable regulations and conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC). I agree to supervise all use of the investigational devices at my institution and to ensure appropriate informed consent is obtained from all patients prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor or its designee. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor.

My current *curriculum vitae* is attached, along with the *curriculum vitae* of those physicians at this institution who will be using this investigational device or participating in this study as co-investigators under my supervision. These include the extent and type of our relevant experience with pertinent dates and locations.

**Accepted by:**

| **Principal Investigator Signature** | **Date** | **Printed Name** |
|---|---|---|

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| **Study Title:** | A randomized, concurrent controlled trial to assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of large vessel occlusion in acute ischemic stroke |
| **Study Objective:** | To assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of patients presenting with acute ischemic stroke secondary to intracranial large vessel occlusion. |
| **Study Design:** | Prospective, randomized, single blind, concurrent controlled, multi-center study. Patients presenting with symptoms of acute ischemic stroke who have evidence of a large vessel (≥2.5mm in diameter) occlusion in the cerebral circulation will be assigned to either the Penumbra System with the Separator 3D or the Penumbra System without the Separator 3D. Each treated patient will be followed and assessed for 3 months after randomization. |
| **Patient Population:** | Up to 230 evaluable patients at up to 50 centers presenting with acute ischemic stroke in vessels accessible to the Penumbra Separator 3D System for revascularization within 8 hours of symptom onset. They must be either refractory to or not eligible for thrombolytic therapy. Each center will have two roll-in patients before actual enrollment. These patients will not be part of the trial but will be followed for 90 days post-procedure for safety. |
| **Hypothesis Testing and Sample Size Justification:** | The sample size calculations assume that 80% of the standard Penumbra System patients experience success (TICI of 2 to 3) and 80% of the Penumbra System with Separator 3D patients experience success. Based on a binomial non-inferiority analysis with a non-inferiority margin of 15%, a study of 103 patients per group will have 85% power with a one-sided alpha of 0.05. The sample size was adjusted to 115 patients per group to account for up to10% attrition rate. |
| **Inclusion Criteria:** | • From 18 to 85 years of age<br>• Present with symptoms consistent with an acute ischemic stroke for revascularization within 8 hours from symptom onset<br>• Refractory to or not eligible for IV rtPA therapy, e.g., presenting between 0 and 3 hours from symptom onset AND contraindicated for IV rtPA, or presenting between 3 and 8 hours of symptom onset, or evidence of persistent occlusion from vascular imaging after IV rtPA<br>• Evidence of a large vessel (≥2.5mm in diameter) occlusion in the cerebral circulation<br>• NIH Stroke Scale (NIHSS) score ≥8<br>• Signed informed consent |
| **Exclusion Criteria:** | • History of stroke in the past 3 months.<br>• Females who are pregnant<br>• Pre-existing neurological or psychiatric disease that could confound the study results such as a pre-stroke mRS score ≥1<br>• Known severe allergy to contrast media<br>• Uncontrolled hypertension (defined as systolic blood pressure >185 mmHg |

| CLP 4853 Protocol Synopsis | |
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| **Study Title:** | A randomized, concurrent controlled trial to assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of large vessel occlusion in acute ischemic stroke |
| | or diastolic blood pressure >110 mmHg)<br>• CT evidence of the following conditions at randomization:<br>– Significant mass effect with midline shift<br>– Large infarct region >1/3 of the middle cerebral artery territory<br>– Evidence of intracranial hemorrhage<br>• Angiographic evidence of an arterial stenosis proximal to the occlusion that could prevent thrombus removal<br>• Angiographic evidence of preexisting arterial injury<br>• Rapidly improving neurological status prior to enrollment<br>• Bilateral stroke<br>• Intracranial tumors<br>• Known history of cerebral aneurysm or arteriovenous malformation<br>• Known hemorrhagic diathesis, coagulation deficiency, or on anticoagulant therapy with an International Normalized Ratio (INR) of >1.7<br>• Baseline platelets <50,000<br>• Use of IV heparin in the past 48 hours with PTT >1.5 times the normalized ratio<br>• Baseline glucose <50mg/dL or >300mg/dL<br>• Life expectancy less than 90 days prior to stroke onset<br>• Participation in another clinical investigation that could confound the evaluation of the study device |
| **Primary Endpoint:** | • Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by a TICI score of 2 or 3<br>• Incidence of device-related and procedure-related serious adverse event within 24 hours post-procedure |
| **Secondary Endpoints:** | • Good clinical outcome at 30 days post-procedure as defined by a 10 points or more improvement in the NIHSS at Discharge, a NIHSS score of 0-1at Discharge; or a 30-day mRS score of 0-2<br>• The proportion of patients with a modified Rankin Scale (mRS) score of ≤ 2 at 90days post procedure<br>• Good neurological outcome at 90 days post-procedure as defined by an mRS score of ≤ 2, or equal to the pre-stroke mRS score if the pre-stroke mRS score was higher than 2, or an 10 or more points improvement on the NIHSS score<br>• All cause mortality<br>• Incidence of symptomatic intracranial hemorrhage |
| **Core Laboratory and Clinical Event** | An independent Core Lab blinded to treatment allocation will review and score all imaging scans for TIMI/TICI scores and intracranial hemorrhage (ICH). A Clinical Event Committee/Data Safety Monitoring Board will adjudicate |

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| **Committee/Data Safety Monitoring Board** | serious adverse events for causality and attribution as well as monitoring safety during the trial. |
| **Study Rationale:** | Use of the Penumbra Separator 3D System offers several potential benefits, which may include a higher rate of revascularizaton with an acceptable device-related serious adverse event rate. |
| **Duration of the Trial** | It is anticipated that the trial will last 2-3 years and each patient will be in the trial for 3 months. |

# 1. Introduction

In the United States approximately 800,000 patients experience a new or recurrent stroke each year. Of these, approximately 87% are diagnosed as ischemic, while the remaining 13% are attributable to hemorrhagic events, occurring either in the subarachnoid (3%) or intraparenchymal (10%) spaces in the brain.[1] Stroke accounted for 1 in every 18 deaths in the United States, resulting in an annual mortality of 133,990 deaths/year.[1] The literature suggests a majority of these deaths are caused by intracranial large vessel occlusions. Mortality rates associated with occlusions of the basilar artery, internal carotid artery terminus, and the M1 segment of the middle cerebral artery (MCA) are particularly high despite the best available medical therapy.[2-4]

Substantial evidence in the published literature suggests that early and safe recanalization of the primary occlusion correlates with improved clinical outcome.[5] The likely basis for this correlation is that although some brain tissue experiences near immediate and non-reversible infarction during acute stroke, there remains a region of ischemic penumbra surrounding this area where at-risk tissues can be salvaged.[6] Therefore, if timely recanalization can be effected and reperfusion established, then damage to the penumbral region might be reversed, resulting in diminished neurological deficit, reduced stroke-related mortality and morbidity and improved clinical outcome.[7]

Current therapies for acute stroke are limited to the intravenous administration of a intravenous (IV) recombinant human tissue plasminogin activator (rtPA) for thrombolysis of the affected cerebral arteries within 3-4.5 hours from symptom onset, and the use of intra-arterial (IA) endovascular mechanical clot retrieval devices within 8 hours from ictus, all of which have limitations as mono therapies. For example, IV lytics have a propensity to cause intracranial hemorrhage (ICH) and they are thought to be less efficacious for large vessel occlusions. On the other hand, data is lacking on the long term effectiveness of the IA mechanical thrombectomy devices in improving patient functional outcome.[8-15] For these reasons, less than 5% of all ischemic stroke patients are treated with IV rtPA or IA treatments.[16]

In a recent study, Bhatia et al. reported that in patients with large vessel occlusion, IV rtPA therapy is indeed associated with a low rate of recanalization (~21%).[17] For those patients who were successfully recanalized, close to 80% had good outcome as vs. only 24% for those whose vessel remained closed. They concluded that while recanalization is a strong predictor of patient functional independence, IV rtPA is not particularly efficacious in patients with large vessel occlusions.

Riedel et al. suggested this lack of efficacy may in part be related to the extent of the clot burden, in particular, the actual clot length of the target vessel.[18] In their study, they measured actual clot lengths before IV rtPA therapy in patients with large vessel occlusion in the MCA using nonenhanced CT images reconstructed with 2.5-mm slice width. Transcranial Doppler, MRA or CTA were used to determine blood flow in the target vessel as an indication of recanalization. The results showed there was a significant inverse relationship between clot lengths before treatment and recanalization after IV rtPA therapy, i.e., the longer the clot length, the less likely the vessel would be

recanalized by the lytic. Based on this analysis, they concluded that IV rtPA has no potential to recanalize an occluded target vessel if the clot length exceeded 8mm.

The Penumbra System® is a new generation of neuro-embolectomy devices specifically designed to remove thrombus through aspiration.[14-15] The System has received 510(k) clearance from the US FDA for an acute ischemic stroke recanalization indication. The pivotal trial for this clearance was a prospective, single arm, 125 patient study designed to assess the safety and effectiveness of the System to reduce clot burden in acute ischemic stroke, using the Concentric clot retriever (Mountain View, CA) as the predicate device (historical control).[14] The results indicated that the Penumbra System was able to recanalize the site of primary occlusion in over 80% of the patients, which was higher than those reported for the Concentric clot retriever (43% to 54%), or the spontaneous reperfusion rate reported in the untreated control group in the PROACT-II study (18%).[12,13,19] The high recanalization rate was independent of target vessel locations. Recanalization was successful in 82.6% of patients presenting with occluded target vessels in the ICA, and in 83% of patients presenting with occluded target vessels in the MCA. Among the patients recanalized with the device, 12.8% had procedural complications of which 3.2% were considered serious. None was associated with malfunction or breakage of the device. This procedural event rate is quite favorable when compared to the published rates for other intra-arterial interventions for acute stroke.[12,13,19,20] These observations are indicative of the ability of the Penumbra System to access the cerebral arteries to safely recanalize the site of primary occlusions in most locations of the brain, and often, in patients with significant tortuosity that would normally hamper intracranial vascular access.

This favorable safety profile of the Penumbra System extends to the overall rate of 24-hour ICH of 28%, which is in the low range of the historical rates in this stroke cohort with similar demographics and time of presentation from symptom onset, such as the PROACT-II (35.9%)[19], IMS (48.8%)[20], MERCI Phase II (35.5%)[12] and Multi-MERCI (38.7%)[13]. However, the symptomatic ICH rate of 11.2% was in the higher range of those reported in these studies (ranging from 4.8% to 14%)[12,20] but comparable to those reported in the PROACT-II (10.9%)[19] and Multi-MERCI (9.0%)[13] trials. Regardless, both rates are within the 95% confidence intervals of these prior studies. These observations were later confirmed in a multicenter post-market trial in Europe and the US.[15]

The Penumbra System is intended for use to restore blood flow in the neurovasculature to remove thrombus by aspiration. This system is comprised of several devices:

- Penumbra Reperfusion Catheter
- Penumbra Separator
- Penumbra Aspiration Pump
- Penumbra Pump/Canister Tubing
- Penumbra Aspiration Tubing

The treatment paradigm of this System involves the introduction of the Reperfusion Catheter through a guide catheter into the intracranial vasculature, and guided over an appropriate guidewire to the site of primary occlusion. The Reperfusion Catheter is used in parallel with the Separator and an aspiration source (Aspiration Pump) to separate the thrombus and aspirate it from the occluded vessel. The Separator is advanced and

retracted through the Reperfusion Catheter at the proximal margin of the primary occlusion. This facilitates aspiration and debulking of the thrombus and reduces or eliminates the endovascular clot burden.

At present, there are 4 sizes of Reperfusion Catheters and Separators: 026, 032, 041 and 054. Initial approval was obtained for the three smaller sizes (026, 032, 041) and in order to facilitate more efficient aspiration, a larger 054 Reperfusion Catheter and Separator were developed and later approved for marketing. To maximize flow during removal of the thrombus, the 054 Reperfusion Catheter has a large tapered lumen with a minimum 0.054" inner diameter at the distal end and a minimum 0.064" inner diameter at the proximal end. To allow for access to the intracranial neurovasculature the outer diameter at the distal end is ≤ 0.071" and the maximum outer diameter of the catheter is ≤ 0.083" to ensure its ability to fit through a 6F sheath.

Since the approval and launch of the Reperfusion Catheter and Separator 054, a new Penumbra system MAX has been developed to maximize aspiration efficiency for smaller Reperfusion Catheters as well. Reperfusion Catheter 4MAX and 3MAX are designed to navigate more distally and efficiently to aspirate clot. The specifications of the Reperfusion Catheter and Separator 054 remained unchanged but are now being marketed as 5MAX (Table 1). The new Reperfusion Catheter 4MAX and 3MAX are similar in design to the Reperfusion Catheter 5MAX (054). The difference is the distal section of the Reperfusion Catheter 5MAX is reinforced with stainless steel wire and the Reperfusion Catheter 4MAX and 3MAX are reinforced with nitinol wire. Shown below are the specifications of the 5MAX, 4MAX and 3MAX (**Tables 1-3**).

**Table 1 -- Specifications of 5MAX**

| | **5 MAX or 054 Reperfusion Catheter** |
|---|---|
| **Distal Inner Diameter** | 0.054" |
| **Proximal Inner Diameter** | 0.064" |
| **Distal Outer Diameter** | ≤ 0.071" |
| **Proximal Outer Diameter** | ≤ 0.083" |
| **Effective Length** | 125.0 ± 2.0 cm |

**Table 2 -- Specifications of 4MAX and 041 Reperfusion Catheters**

| | **4MAX Reperfusion Catheter** | **041 Reperfusion Catheter** |
|---|---|---|
| **Distal Inner Diameter** | 0.041" | 0.041" |
| **Proximal Inner Diameter** | 0.064" | 0.041" |
| **Distal Outer Diameter** | ≤ 0.058" | ≤ 0.056" |
| **Proximal Outer Diameter** | ≤ 0.083" | ≤ 0.056" |
| **Effective Length** | 139.0 ± 2.0 cm | 137.0 ± 2.0 cm |

**Table 3 -- Specifications of 3MAX and 032 Reperfusion Catheters**

| | 3MAX Reperfusion Catheter | 032 Reperfusion Catheter |
|---|---|---|
| **Distal Inner Diameter** | 0.035” | 0.032” |
| **Proximal Inner Diameter** | 0.043” | 0.041” |
| **Distal Outer Diameter** | ≤ 0.052” | ≤0.047” |
| **Proximal Outer Diameter** | ≤ 0.063” | ≤0.047” |
| **Effective Length** | 153.0 ± 2.0 cm | 150.0 ± 2.0 cm |

The Separator 3D is another component of the current Penumbra System with an identical indication. It is a self-expanding 3 dimensional, binary Nitinol device that exhibits uniaxial stress-strain characteristics of superelastic Nitinol (**Figure 1**). The specifications of the Separator-3D are shown in **Table 4** below.

**Figure 1 -- The Penumbra Separator 3D Device**

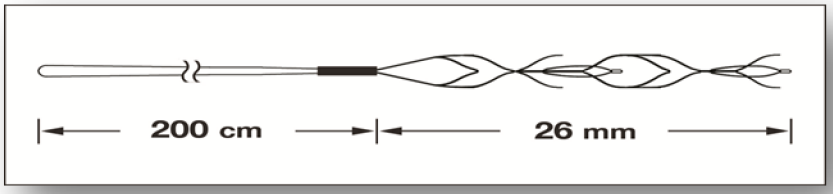



**Table 4—Separator 3D Device Specifications**

| | Wire Distal OD | Tip Diameter (Unconstrained) | Tip Length | Core Wire Flexible Length | Working Length |
|---|---|---|---|---|---|
| **Separator 3D** | 0.014” Max | 4.6-5.4 mm | 26 mm | 42 cm | 142 cm |

The Separator 3D is an additional Separator with a new tip configuration for the Penumbra System. The Penumbra System's fundamental mechanism of action is aspiration. Aspiration draws clot into the catheter to remove the clot from the body. All Separators function to break up the clot inside of the catheter to make it more amenable to removal from the body via aspiration. The current Separators function by shearing portions of the clot via a small gap between the outer diameter of the Separator cone and the inner diameter of the Reperfusion Catheter while cycling the Separator. The Separator 3D is designed to break up the clot in a 3rd radial dimension as the open body of the Separator 3D is compressed and then retrieved into the Penumbra Reperfusion Catheter. The Separator 3D is attached to the same core wire, and is delivered in the same manner as the current Separators. The tip has an open-body, three-dimensional lattice design. Like the current Separators, aspiration applied during use of the Separator 3D removes the clot from the body. The Separator 3D is compatible with Reperfusion Catheters that have a distal inner diameter of 0.041” or larger. A schematic description

of the functionality of the Separator-3D device with the Reperfusion Catheter is shown in **Figure 3** (Section 3.6.7).

The purpose of this study is to assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of large vessel occlusion (≥2.5mm in diameter) in acute ischemic stroke.

## 2. Study Overview

### 2.1 Study Design

This is a prospective, randomized, single blind, concurrent controlled, multi-center study to assess up to 230 evaluable patients at up to 50 centers presenting with acute ischemic stroke from large vessels occlusions (≥2.5mm in diameter) accessible to the Penumbra Separator 3D System for revascularization within 8 hours of symptom onset. They must be refractory to or not eligible for thrombolytic therapy and assigned to either the Penumbra System with the Separator 3D or the Penumbra System without the Separator 3D. It is anticipated that the trial will last 2-3 years and each treated patient will be followed and assessed for 3 months after the procedure. Please refer to the Schedule of Assessments (**Table 7**) in Section 3.10 below for details. Each center will have two roll-in patients before actual enrollment. These patients will not be part of the trial but will be followed for 90 days post-procedure for safety.

### 2.2 Study Objectives/Endpoints

The purpose of this study is to assess the safety and effectiveness of the Separator 3D as a component of the Penumbra System in the revascularization of patients presenting with acute ischemic stroke secondary to intracranial large vessel (≥2.5mm in diameter) occlusion.

2.2.1 The primary endpoints are:

- Angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by a TICI score of 2 or 3
- Incidence of device-related and procedure-related serious adverse event within 24 hours post-procedure

2.2.2 The secondary endpoints are:

- Good clinical outcome at 30 days post-procedure as defined by a 10 points or more improvement in the NIHSS at Discharge, a NIHSS score of 0-1at Discharge; or a 30-day mRS score of 0-2.
- The proportion of patients with a modified Rankin Scale (mRS) score of ≤ 2 at 90 days post procedure.
- Good neurological outcome at 90 days post-procedure as defined by an mRS score of ≤ 2, or equal to the pre-stroke mRS score if the pre-stroke mRS score was higher than 2, or an 10 or more points improvement on the NIHSS score.
- All cause mortality
- Incidence of symptomatic intracranial hemorrhage

## 2.3 Study Population

Patients enrolled in this clinical evaluation must meet the following criteria:

### 2.3.1 Inclusion Criteria

- From 18 to 85 years of age
- Present with symptoms consistent with an acute ischemic stroke for revascularization within 8 hours from symptom onset
- Refractory to or not eligible for IV rtPA therapy, e.g., presenting between 0 and 3 hours from symptom onset AND contraindicated for IV rtPA, or presenting between 3 and 8 hours of symptom onset, or evidence from vascular imaging of persistent occlusion after IV rtPA
- Evidence of a large vessel ($\geq$2.5mm in diameter) occlusion in the cerebral circulation
- NIH Stroke Scale (NIHSS) score $\geq$8
- Signed informed consent

### 2.3.2 Exclusion Criteria

- History of stroke in the past 3 months
- Females who are pregnant
- Pre-existing neurological or psychiatric disease that could confound the study results such as a pre-stroke mRS score $\geq$1
- Known severe allergy to contrast media
- Uncontrolled hypertension (defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg)
- CT evidence of the following conditions at randomization:
  - Significant mass effect with midline shift
  - Large infarct region >1/3 of the middle cerebral artery territory
  - Evidence of intracranial hemorrhage
- Angiographic evidence of an arterial stenosis proximal to the occlusion that could prevent thrombus removal
- Angiographic evidence of preexisting arterial injury
- Rapidly improving neurological status prior to enrollment
- Bilateral stroke
- Intracranial tumors
- Known history of cerebral aneurysm or arteriovenous malformation
- Known hemorrhagic diathesis, coagulation deficiency, or on anticoagulant therapy with an International Normalized Ratio (INR) of >1.7
- Baseline platelets <50,000
- Use of IV heparin in the past 48 hours with PTT >1.5 times the normalized ratio
- Baseline glucose <50mg/dL or >300mg/dL
- Life expectancy less than 90 days prior to stroke onset

- Participation in another clinical investigation that could confound the evaluation of the study device

## 2.4 Study Rationale

Use of the Separator 3D as a component of the Penumbra System offers several potential benefits, which may include a higher rate of recanalization with an acceptable device-related serious adverse event rate.

## 2.5 Device Description/Principles of Operation

Detailed description of the Penumbra System is contained in the *Instructions for Use* for the device. Described herein are brief descriptions of the System and the principles of operation.

The Penumbra System is intended for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (within the internal carotid, middle cerebral – M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset.

The Penumbra System is comprised of several devices:
• Penumbra Reperfusion Catheter
• Penumbra Separator
• Penumbra Separator 3D
• Penumbra Aspiration Pump
• Penumbra Pump/Canister Tubing
• Penumbra Aspiration Tubing

The Reperfusion Catheter and Separator are available in four sizes: 026, 032, 041 and 054. The recommended selection of these devices for clot burden reduction is based on the size of the target vessel as shown in **Table 5** (Section 3.6.3).

The Reperfusion Catheter is introduced through a guide catheter or long femoral sheath into the intracranial vasculature and guided over a standard guidewire to the site of primary occlusion. The Reperfusion Catheter is used in parallel with the Penumbra Separator or Penumbra Separator 3D and an aspiration source to separate the thrombus and aspirate it from the occluded vessel. The Penumbra Separator is cycled through the Reperfusion Catheter at the proximal margin of the primary occlusion. The Penumbra Separator 3D is deployed within the thrombus and then retrieved into the Penumbra Reperfusion Catheter. This facilitates aspiration and debulking of the thrombus and reduces or eliminates the endovascular clot burden. For the aspiration source, the Penumbra Reperfusion Catheter is used in conjunction with the Aspiration Pump, which is connected using the Penumbra Aspiration Tubing and the Penumbra Pump/Canister Tubing. The Penumbra Separator or Penumbra Separator 3D is provided with an introducer. In addition, the Penumbra Separator is provided with a torque device. The Penumbra Reperfusion Catheter is provided with a steam shaping mandrel

and rotating hemostasis valve, and a peelable sheath (for Reperfusion Catheter 054 size only). The devices are visible under fluoroscopy.

## 3. Study Procedures

### 3.1 Screening

Prior to entry into the study, patients presenting with acute stroke symptoms will be screened to determine if they meet the inclusion and exclusion criteria for entry into the study. Patients who are found to be ineligible for entry into the study will be excused from further participation. Patients who are eligible for the study will review and sign (or have a legally authorized representative review and sign) the Patient Information and Consent form prior to enrollment into the study. All patients enrolled will be blinded to treatment allocation and monitored throughout the required follow-up period.

### 3.2 Pre-Procedure (Admission) Evaluations

3.2.1 Obtain patient medical and therapeutic history.

3.2.2 Females of childbearing potential must have a pregnancy test.

3.2.3 Exclude all patients who are not eligible and record the reason in the screening log.

3.2.4 Perform admission NCCT scans, physical examination, neurological and functional examinations, and serum chemistries. Physical examination will include recording of supine blood pressure and heart rate. Serum chemistry will include blood urea nitrogen (BUN), creatinine, complete blood count (CBC) plus platelets, and international normalized ratio (INR), prothrombin time (PT) / partial thromboplastin time (PTT).

### 3.3 Enrollment

Each center will have two roll-in cases prior to actual enrollment. These patients will not be part of the trial but will be followed for 90 days for safety. Prior to enrollment into the study, each patient will undergo an angiographic determination of the suspected vascular occlusion. Perform an arterial access procedure using standard percutaneous technique.

Perform a digital subtraction angiography (DSA) to define the angio-architecture of the occluded vascular segment. While a DSA to define the angio-architecture of the occluded vascular segment is preferred, CTA or MRA is an acceptable substitute. When possible, an assessment of collateral blood flow by DSA should be done per institutional standard of care, particularly in cases of terminal internal carotid artery occlusion.

If the occlusion is in a treatable vessel, position an appropriate guide catheter and advance the Penumbra Reperfusion Catheter into the occluded target vessel and the patient will be randomized to one of the following arms:

1) The Penumbra Separator 3D with the Penumbra System, or

2) The Penumbra System without the Separator 3D.

The randomization code will be obtained from a system provided by a vendor. A patient is considered enrolled once a treatment arm is assigned from the randomization system.

All patients will be assessed for a period of 90 days from randomization.

Randomized patients who were excluded for angiographic reasons will be followed for 90 days. The reasons for not including these patients will be captured in the Case Report Forms.

## 3.4 Procedure Preparation for the Penumbra System

Procedure should be consistent with those listed in the *Instructions For Use* for each device. Refer to Warnings, Precautions, and Potential Adverse Events in the *Instructions For Use* for each device prior to use. However, for the purpose of this study, the Penumbra Separator 3D System should be used first for the revascularization of the target vessel if the patient was randomized to the Penumbra Separator 3D arm, to be followed by other components of the Penumbra System if necessary at the discretion of the investigators. The exception is the use of the 054 or 041 separators in the Separator 3D arm. Use of these devices in this arm will be considered a protocol deviation. Similarly, use of the Separator 3D in the control arm will be considered a protocol deviation.

### 3.4.1 
As each device of the Penumbra System is used, remove the device from the packaging, and inspect for damage or for kinks.

### 3.4.2 
Prepare Penumbra System devices for use by flushing the packaging hoop and device with heparinized saline (includes Penumbra Reperfusion Catheter and Penumbra Separator only).

### 3.4.3 
Prepare a guide catheter or long femoral sheath according to the manufacturer's *Instructions for Use.*

### 3.4.4 
Place the guide catheter or long femoral sheath into the appropriate cerebral artery that is proximal to the thrombus occlusion site.

## 3.5 Penumbra Reperfusion Catheter Preparation and Use

3.5.1 Confirm vessel diameter, and select an appropriate size Penumbra Reperfusion Catheter per the *Instructions for Use*.

3.5.2 The Penumbra Reperfusion Catheter tip may be shaped using the steam shaping mandrel provided.

3.5.3 Attach the rotating hemostasis valve provided to the Penumbra Reperfusion Catheter.

3.5.4 Insert the Penumbra Reperfusion Catheter into a rotating hemostasis valve connected to the proximal hub of a guide catheter. If a guide catheter is not used, insert the Penumbra Reperfusion Catheter through the valve of the long femoral sheath using the peelable sheath. After inserting the Penumbra Reperfusion Catheter, remove the peelable sheath from the vascular sheath, and peel from the Penumbra Reperfusion Catheter Shaft.

3.5.5 Using conventional catheterization techniques under fluoroscope guidance advance the Penumbra Reperfusion Catheter into the target vessel over an appropriate neurovascular guidewire. Position the Penumbra Reperfusion Catheter proximal to the thrombus. Remove the guidewire from the Penumbra Reperfusion Catheter.

3.6 Penumbra Separator 3D Preparation and Use

3.6.1 For the purpose of this study, the Penumbra Separator 3D System should be used first for the revascularization of the target vessel, to be followed by other components of the Penumbra System at the discretion of the investigators.

3.6.2 Attach the Penumbra Aspiration Tubing to the Aspiration Pump and turn on the Aspiration Pump (Refer to the Aspiration Pump Operation Manual). Allow the Aspiration Pump to run for at least one minute prior to use, and confirm that the Aspiration gauge reads –20inHg. Ensure the valve on the Penumbra Aspiration Tubing is switched to the OFF position.

3.6.3 Penumbra Separator 3D is offered in one size and is designed to fit into the listed Penumbra Reperfusion Catheters (see **Table 5**).

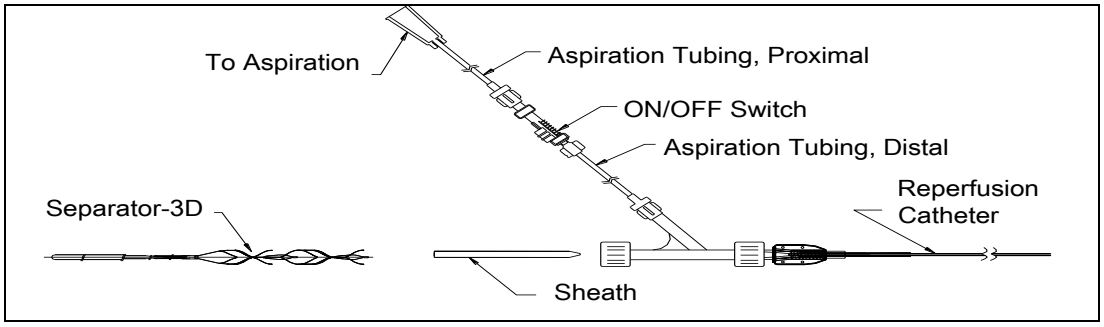
**Table 5 -- Separator-3D / Reperfusion Catheter Device Sizes**

| Vessel Size (mm) | Reperfusion Catheters for the Separator-3D |
|---|---|
| **2.5 to 3.0** | 032 / 3MAX |
| **3.0 – 4.0** | 041 / 4MAX |
| **>4.0** | 054 / 5MAX |

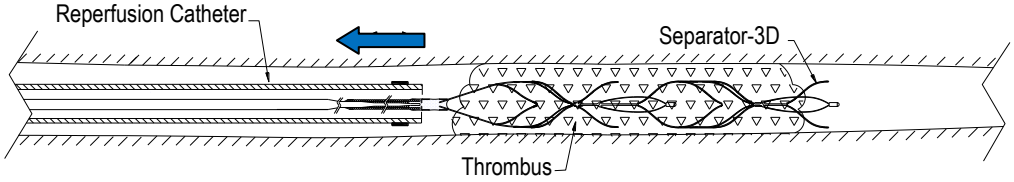
3.6.4 Advance the Penumbra Reperfusion Catheter to gently penetrate the thrombus.

**NOTE: Access to the site of occlusion may be aided by the triaxial use of a compatible inner microcatheter of 0.025" ID or greater.**

3.6.5 Using the introducer sheath provided, insert the Penumbra Separator 3D through the rotating hemostasis valve and into the proximal hub of the Penumbra Reperfusion Catheter or triaxial microcatheter.




3.6.7 Advance the 3D delivery catheter to the distal edge of the thrombus, then unsheath the Penumbra Separator 3D. To begin aspiration, open the valve on the Penumbra Aspiration Tubing to the ON position. Retract the Penumbra Separator 3D to assist with aspiration and retrieval of the thrombus as shown in **Figure 3**. If necessary, the entire thrombus can be




3.6.8 To stop aspiration, switch the valve on the Penumbra Aspiration Tubing to the OFF position, and turn off the Aspiration Pump.

3.6.9 Remove the Penumbra Separator 3D.

3.6.10 If necessary, additional Penumbra Separators, Penumbra Separator 3Ds, and Reperfusion Catheters may be used to further remove thrombus at the discretion of the physician.

3.6.11 Using a 5cc or 10cc syringe, aspirate approximately 5cc of blood from the Penumbra Reperfusion Catheter to remove any thrombus that may remain in the catheter.

3.6.12 Obtain a post-treatment angiogram by injecting contrast media through the guide catheter.

3.7 Penumbra Separator Preparation and Use

3.7.1 Attach the Penumbra Aspiration Tubing to the Aspiration Pump and turn on the Aspiration Pump (refer to the Aspiration Pump *Operation, Service, and Maintenance Manual*). Allow the Aspiration Pump to run for at least one minute prior to use, and confirm that the Aspiration gauge reads –20inHg. Ensure the valve on the Penumbra Aspiration Tubing is switched to the OFF position.

3.7.2 Select the appropriate size Penumbra Separator corresponding to the Penumbra Reperfusion Catheter (see **Table 6** below).

**Table 6 – Separator/Reperfusion Catheter Device Size Selection**

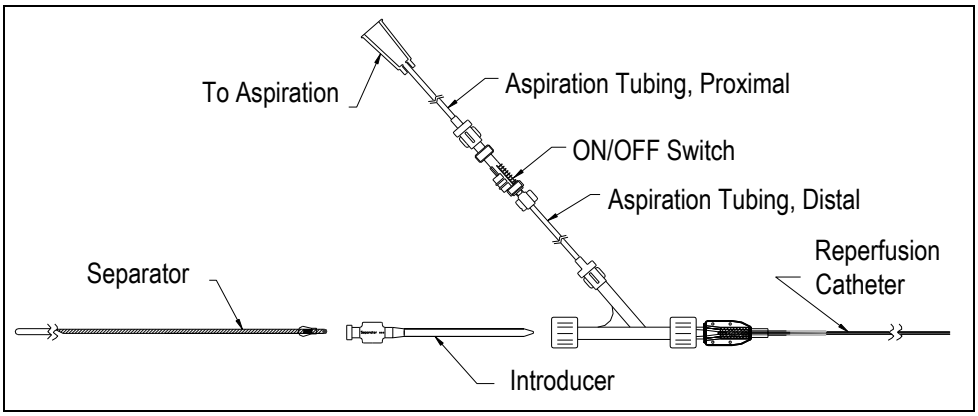
| Vessel Size (mm) | Penumbra Reperfusion Catheter | Penumbra Separator |
|---|---|---|
| **< 2.0** | 026 | 026 |
| **2.0 to 3.0** | 032/3MAX | 032/3MAX |
| **3.0 to 4.0** | 041/4MAX | 041/4MAX |
| **> 4.0** | 054/5MAX | 054/5MAX |

3.7.3 Advance the Penumbra Reperfusion Catheter to gently embed the distal tip into the thrombus. **Note: Access to the site of occlusion may be aided by the triaxial use of a compatible inner microcatheter.**

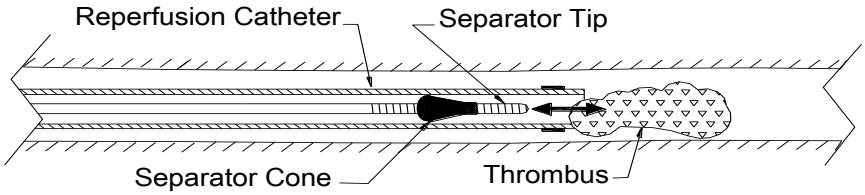
3.7.4 Using the introducer sheath provided, insert the Penumbra Separator through the rotating hemostasis valve and into the proximal hub of the Penumbra Reperfusion Catheter.

3.7.5 Connect the Penumbra Aspiration Tubing to the side port of the rotating hemostasis valve as shown in **Figure 4** below.

**Figure 4 – Assembled Aspiration System with Penumbra Separator**




3.7.6 To begin aspiration, open the valve on the Penumbra Aspiration Tubing to the ON position, and advance/retract the Penumbra Separator to assist with aspiration and removal of the thrombus as shown in **Figure 5**.




3.7.7 To stop aspiration, switch the valve on the Penumbra Aspiration Tubing to the OFF position, and turn off the Aspiration Pump.

3.7.8 Remove the Penumbra Separator.

3.7.9 If necessary, additional Penumbra Separators and Reperfusion Catheters may be used to further remove thrombus at the discretion of the investigator.

3.7.10 Using a 5cc or 10cc syringe, aspirate approximately 5cc of blood from the Penumbra Reperfusion Catheter to remove any thrombus that may remain in the catheter.

3.7.11 Obtain a post-treatment angiogram by injecting contrast media through the guide catheter.

## 3.8 Angiographic Imaging

At screening, perform a DSA to define the angio-architecture of the occluded vascular segment. While a DSA to define the angio-architecture of the occluded vascular segment is preferred, CTA or MRA is an acceptable substitute.

When possible, an assessment of collateral blood flow by DSA should be done per institutional standard of care, particularly in cases of terminal internal carotid artery occlusion.

Prior to mechanical thrombectomy by the Penumbra Device, obtain a baseline TIMI/TICI scores by DSA. CTA or MRA is not an acceptable substitute for this assessment. The investigator shall make an initial assessment of TIMI/TICI flow in the target vessel territory.

TIMI/TICI scores are to be assessed after completion of the procedure by the Separator 3D. If necessary, other components of the Penumbra System can be used at the discretion of the investigator with the TIMI/TICI scores recorded before and after each use. In the event that adjunctive treatments were used, TIMI/TICI scores should be assessed and recorded before and after each treatment. The TIMI/TICI scores after the use of the Penumbra System as well as after adjunctive treatments will be used for analysis.

Pre-procedure and post-procedure angiograms shall be sent to an unbiased Core Laboratory blinded to treatment allocation to make a final determination on TIMI/TICI flow.

## 3.9 Adjunctive Therapies and Protocol Deviation

If the Penumbra System with Separator 3D or the Penumbra System alone is unable to revascularize the target vessel to TIMI/TICI 2 or 3, use of other rescue therapies are considered a protocol deviation and must be reported in the Case Report Forms. Any use of IA tPA or other non-FDA-approved treatments for the purpose of reducing the clot burden will be considered a treatment failure. TIMI/TICI scores must be recorded before and after the use of rescue therapy.

## 3.10 Post-Procedure Evaluations

All patients will be assessed for 90 days from time of procedure.

A follow-up noncontrast CT scan will be performed at 24±12 hours after procedure, and will be reviewed to assess hemorrhagic transformation based on ECASS definitions[21,22]:

- HI 1 (small petechiae along the margins of the infarcted area without space-occupying effect),

- HI 2 (more confluent petechiae within the infarcted area but without space-occupying effect),
- PH 1 (hematoma in ≤30% of the infarcted area with some slight space-occupying effect),
- PH 2 (hematoma in >30% of infarcted area with substantial space-occupying effect).

In addition, any neurological deterioration should be evaluated by urgent CT scan and other evaluations as indicated according to investigator/hospital best practice.

A symptomatic intracranial hemorrhage will be defined as 24±12 hour CT evidence of an ECASS defined ICH and a 4-point or more worsening of the NIHSS score.

Patients will be evaluated for neurological and/or functional status immediately post- procedure, 7 days after procedure (or day of discharge from the hospital, whichever is earlier), 30 days (± 10 days), and 90 days (± 10 days) after procedure. The assessments shown in **Table 7** must be performed:

**Table 7 – Schedule of Assessments**

| Assessment | Pre-Admission Evaluation | Baseline Evaluation | Immediate Post-Procedure | 24±12 Hr Follow-Up | 7 days Follow-Up or Discharge [D] | 30 Days Follow-Up (± 10 days) | 90 Days Follow-Up (± 10 Days) |
|---|---|---|---|---|---|---|---|
| History | | √ | | | | | |
| Physical Exam [A] | | √ | | | √ | √ | √ |
| NCCT [B] | | √ | | √ | | | |
| TIMI/TICI Scores from Angiography [C] | | √ | √ | | | | |
| NIHSS | | √ | | √ | √ | √ | √ |
| mRS | √ | √ | | | | √ | √ |
| Lipids Profile | | | | | √ | | |
| Liver Enzymes | | √ | | | √ | | |
| BUN, Creatinine | | √ | | | √ | √ | |
| CBC/Platelets/ INR/PT/PTT | | √ | √ | | √ | √ | |
| Pregnancy Test | | √ | | | | | |
| Adverse Events | | | √ | √ | √ | √ | √ |

**A**: Includes recording of supine blood pressure and heart rate
**B**: In addition to the evaluation at Admission, standard CT scans must be obtained within 24±12 hours post-procedure and immediately after any neurologic decline that occurs within 90-day follow-up
**C**: From digital subtracted angiography
**D**: Assessments can be done either at 7 days from procedure or at Discharge, whichever occurs sooner.

## 4. Assessment of Safety and Effectiveness

4.1 Safety

Safety will be assessed by collecting adverse event data during the endovascular procedure, at 24 hours, 7 days or discharge (whichever occurs sooner), as well as at the 30-day and 90-day follow up.

4.2 Effectiveness

The effectiveness of the Penumbra Separator 3D will be assessed by the ability of the system to achieve TICI 2 or 3 flow in the target vessel at the site of the target occlusion. TIMI/TICI flow are classified in **Tables 8 A&B**.

**Table 8A – Thrombolysis in Myocardial Infarction (TIMI) Flow Classification***

| TIMI Score | Classification of Blood Flow |
|---|---|
| TIMI 0 | No Perfusion |
| TIMI 1 | Penetration without perfusion. Penetration past the initial occlusion, but no distal branch filling |
| TIMI 2 | Partial perfusion of the arterywith incomplete or slow distal branch filling |
| TIMI 3 | Complete perfusion of the artery |

* From *Chesebro et al. Circulation 1987;76:142-154 and Khatri et al. Stroke 2005;36:2400-2403*

**Table 8B- Modified Thrombolysis in Cerebral Infarction (TICI) Perfusion Categories****

| | |
|---|---|
| **Grade 0:** | **No Perfusion**. No antegrade flow beyond the point of occlusion. |
| **Grade 1:** | **Penetration With Minimal Perfusion**. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run. |
| **Grade 2:** | **Partial Perfusion**. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction. |
| **Grade 2a:** | **Partial filling** with <50% of the entire vascular territory is visualized. |
| **Grade 2b:** | **Partial filling** with ≥50% of the entire vascular territory is visualized. If complete filling of all of the expected vascular territory is visualized, the filling is slower than normal. |
| **Grade 3:** | **Complete Perfusion**. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery. |

** From *Higashida et al. Stroke2003;34:e109-37*and *Tomsick et al. AJNR 2008;29:582-587*

The investigator shall make an initial assessment of TIMI/TICI flow in the target

vessel. Pre-procedure and post-procedure angiograms shall be sent to an unbiased core laboratory blinded to treatment allocation to make a final determination on TIMI/TICI flow. A core laboratory with experience in performing intracranial angiographic analysis will be used.

## 4.3 Risk/Benefit Analysis

The risks associated with the Penumbra System and the Penumbra Separator 3D are similar to those associated with cerebral angiography and with other intra-arterial methods of revascularization.

### 4.3.1 Angiography

An angiographic procedure requires that a catheter be placed into the body, and in this case, threaded through the body to the neurovasculature. Once the catheter is in the proper position, contrast media is infused through the catheter to examine the vessels. Patients may encounter bleeding from vessel perforation, vessel spasm, swelling, or bruising at the access site where the catheters are placed in the body (usually the groin area). Additionally, once the catheter reaches the neurovasculature, there is a chance that the catheter could cause bleeding, hematoma, vessel thrombosis, dissection, distal embolization, psuedoaneurysm, and arteriovenous fistula formation. Patients who are allergic to contrast media are at further risk and may experience a reaction that may include hives, itching, nausea, or breathing difficulty. Contrast media may also cause kidney damage in some patients. The above risks of angiography are well known and generally unlikely to occur. However, if any of the above risks occur and are severe enough, patient death is possible.

### 4.3.2 Computed Tomography Scan (CT Scan)

The risks encountered during a CT scan are low. The risks mentioned above for contrast media allergy are possible with a CT scan. There is also a slight risk of injury from being exposed to the radiation associated with a CT scan; however, the levels of radiation, and the risks associated with radiation exposure are low.

### 4.3.3 Thrombectomy/Embolectomy

The risks of intra-arterial thrombectomy/embolectomy are similar to those associated with existing intra-arterial methods of recanalization. These risks include:

- allergic reaction and anaphylaxis from contrast media
- acute occlusion
- air embolism
- arteriovenous fistula
- death
- hematoma or hemorrhage at access site
- inability to completely remove thrombus
- infection
- intracranial hemorrhage
- ischemia
- kidney damage from contrast media

- device malfunction
- distal embolization
- emboli
- false aneurysm formation
- neurological deficits including stroke
- vessel spasm, thrombosis, dissection, or perforation

Risks directly associated with the Penumbra System and Penumbra Separator 3D are similar to the above. Considerable testing has been completed to ensure that the System does not pose a significant risk. Testing includes both *in vitro* and *in vivo* testing. In addition, the following will be performed to minimize the risks:

- Patients will be carefully evaluated before entering the study to ensure that the location of the occlusion and the time of stroke onset are appropriate for treatment with the Penumbra System.
- During the clinical study, the procedure will be performed in an Operating Room or in an angiographic suite with an Operating Room standby. Therefore, should complications arise requiring surgery or other interventions, the surgery or intervention can be initiated without delay. All sites will be carefully selected to ensure that either a stroke unit operating according to national stroke guidelines or a physician experienced in treating patients presenting with acute ischemic stroke is available.
- Patients will be carefully monitored during the study and the follow-up period. The Investigator will examine and perform various diagnostic tests before, during, and after the procedure, at 7 days or at hospital discharge, and at 30 days ($\pm$10 days) and 90 days ($\pm$10 days) after the procedure.
- In addition to monitoring data directly related to the Penumbra System, blood data will be obtained pre-operatively. This data will be used to determine the patients' coagulation status, to assess for infection as indicated by white blood cell count, and to detect significant internal bleeding with hemoglobin and hematocrit levels.
- Penumbra or its representatives will conduct site initiation visits at each investigational site before the study begins and periodically after patients have been enrolled. The first monitoring visit will be conducted at each site after inclusion of the first patients at each site in order to ensure that all aspects of the protocol are followed as well as to accurately record results, report adverse events, and keep records.

Use of the Penumbra System offers several potential benefits, which may include a higher success rate of recanalization with an acceptable device-related serious adverse rate.

Based on the above information, the benefits of the Penumbra System outweigh the potential risks associated with its clinical use.

## 5. Investigator Responsibilities

### 5.1 Institutional Review Board / Ethics Committee Approval

Prior to enrolling patients into the study, the investigator will ensure that proper Institutional Review Board (IRB)/Ethics Committee (EC) approval is obtained. The IRB/EC shall approve all study documents as appropriate, including the final protocol, amendments to the protocol, investigator brochure (where required), and the informed consent.

## 5.2 Informed Consent

The investigator is responsible for ensuring that the investigation is conducted according to this protocol and that a signed informed consent is obtained according to national and state requirements prior to inclusion of patients in the study.

## 5.3 Adverse Event Reporting

All adverse events or adverse device effects must be recorded by the investigator on the CRFs and must be carefully monitored during the entire study.

An ***Adverse Event*** is any undesirable clinical event occurring in a patient during a clinical trial, whether or not it is considered related to the investigational product. This includes a change in a patient's condition or laboratory results that has or could have a deleterious effect on the patient's health or well-being.

An ***Adverse Device Effect*** is any adverse event related to the investigational device.

A ***Serious Adverse Event***, a ***Serious Adverse Device Effect*** is an event that:

a) Led to death
b) Led to a serious deterioration in the health of the patient that:
   - Resulted in life-threatening illness or injury
   - Resulted in permanent impairment of a body structure or a body function
   - Required in-patient hospitalization or prolongation of existing hospitalization
   - Resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function
   - Led to fetal distress, fetal death or a congenital abnormality or birth defect

An ***Unanticipated Adverse Device Event*** is an event that has an ***Adverse Device Effect***, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the *Instruction for Use* or the clinical protocol.

Minimum requirements of data to be recorded are: type of event, duration of adverse event or adverse device effects (start through end), severity, seriousness, action taken, outcome and, if appropriate, causality.

The Investigator will report any serious adverse event or adverse device effect to the Sponsor or its designee as soon as possible, but no later than 24 hours after the event occurred. All serious adverse events or serious device effects must be documented on the Serious Adverse Events form along with an explanation of any medical treatment administered. The form must be completed, signed, and sent by fax or overnight courier to the Sponsor or its designee within five working days. This report must be followed by full written documentation.

An adverse event need not be reported as a serious adverse event if it represents only a relapse or an expected change or progression of the condition that was the cause of treatment without any symptoms and signs other than those present before procedure. This type of event only needs to be reported as an adverse event. The competent IRB/EC must be informed by the investigator about serious adverse events or device effects associated with the use of the product.

## 5.4 Adherence to Protocol/Amendments

The investigator shall approve and adhere to this protocol and any amendments that arise during the course of the study. Any deviations to the protocol shall be discussed with Penumbra prior to implementation, where possible, and shall be documented on the appropriate case report form. The investigator shall permit the Penumbra System to be used only under his/her supervision.

It is the investigator's responsibility to ensure that the staff assisting with the study have the appropriate qualifications, are fully instructed on the study procedures, and will respect the confidentiality statement.

The investigator will report to the Sponsor or designee immediately if, for any reason, the approval to conduct the investigation is withdrawn by the IRB/EC or Competent Authority. The report will include a complete description of the reason(s) for which approval was withdrawn

## 5.5 Case Report Form Completion

The investigator and study staff shall complete the case report forms associated with this study. Patient numbers shall be used to identify individual patients in this study. The Case Report Forms (CRFs) should be a complete and accurate record of patient data collected during the study according to ISO 14155 and Good Clinical Practices (GCP) requirements. It is the investigator's responsibility to ensure the quality of the data collected and recorded.

## 5.6 Administration of Neurological Exams and Stroke Scales

The principal investigator at each investigative site is responsible for the administration of the neurological examinations and grading of patients on the stroke scales (i.e., NIHSS, mRS). In cases where a designee is needed, the investigator must ensure that the designee is trained and has the appropriate qualifications to perform these functions.

## 5.7 Device Inventory Requirements

The investigator shall maintain records pertaining to device inventory. These records shall include:

- The disposition of each device including patient number and device lot number
- The serial numbers for investigational devices

The investigator will ensure that, for the purpose of this investigation, only trained physicians who are co-investigators in this study will use the Penumbra System.

## 5.8 Reports

The investigator shall submit all reports in a timely manner.

## 5.9 Records Retention

The investigator shall maintain the records associated with this study for a period of at least two years after either the date on which the investigation is completed or the date that the records are no longer required for supporting a premarket approval/notification submission, whichever is later. These records include the following:

- Correspondence with the Sponsor or designee, the Medical Monitor, and other investigators
- Accountability records of receipt, use, and disposition of all investigational devices and other study materials, including the following information:
  - The type and quantity of the device, the dates of receipt, and the study tracking number
  - The names of all persons who received, used, or disposed of each device
  - The number of devices that have been returned to Penumbra, discarded, or otherwise disposed of, and the reason for such action
- Patient Records, including Informed Consent Forms, copies of all completed CRFs, and supporting documents (laboratory reports and reports of diagnostic tests, medical records, etc.)
- Current study protocol with dates and details of reasons for any deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the patients
- *Instructions for Use*
- Reports of any serious adverse event or serious device effects
- A copy of all approvals related to the clinical investigation
- The approved, blank, informed consent form and blank CRFs
- Certification that the investigational plan has been approved by the IRB/EC
- Signed Investigator Agreements and current signed and dated *curriculum vitae* of the Principal Investigator and all participating co-investigators

## 6. Sponsor Responsibilities

### 6.1 Training

During study initiation, the Sponsor will train the investigator and study staff on use of the Penumbra System. Training will also be performed to ensure the study staff understands their obligations under ISO 14155.

### 6.2 Investigator List

The Sponsor shall keep a list of the names, addresses, and professional positions of the clinical investigators for the study.

### 6.3 Adverse Event Reporting

The Sponsor shall evaluate adverse event reports received from the investigational sites and found during data monitoring and shall report them to the appropriate regulatory bodies and other investigational sites as necessary.

### 6.4 Data Monitoring

Penumbra is responsible for ensuring that the study is conducted according to the appropriate regulations (US Food and Drug Administration 21 CFR §812, ISO 14155). A Penumbra employee or designate will conduct the following site visits:

- Site Qualification Visit

Conducted to ensure the investigational site has the appropriate staff, facilities, and expertise to participate in the study. This requirement is waived if the site had recently participated in a similar trial sponsored by Penumbra.

- Site Initiation Visit

Conducted to train the investigational staff on use of the device, study requirements, and other relevant training.

- Data Monitoring Site Visit

Conducted as needed to ensure the investigational site is operating in compliance with this protocol, continues to have the appropriate staff and facilities, and is correctly completing the Case Report Forms (CRFs) (verify against source data).

To ensure that investigators and their staff understand and accept their defined responsibilities, the Sponsor will maintain regular correspondence and perform periodic site visits during the course of the study to verify the continued acceptability of the facilities, compliance with the investigational plan, and maintenance of complete records. Clinical monitoring will include review and

resolution of missing or inconsistent data and source document checks to ensure the accuracy of the reported data. CRFs for all enrolled patients will be made available to the Sponsor for review and collection as agreed with the investigator. The Sponsor will evaluate and summarize the results of each site visit in written reports, identifying repeated data problems with any investigator and specifying recommendations for resolution of noted deficiencies.

- Study Close-Out Site Visit

Conducted at the termination of the study to resolve any outstanding data queries, and to ensure that any remaining study materials are returned to the Sponsor.

## 6.5 Data Management

All study data will be entered into an electronic data capture (EDC) system provided by a vendor. Study personnel will have individual login and password to access the clinical study information based upon each individual's roles and responsibilities. For data security, the system operates within the Secure Socket Layer (SSL) 128-bit encryption protocol. This application is designed to fully support compliance with the following regulations and guidance documents:

- Guidance for Industry 21 CFR Part 11; Electronic Records; Electronic Signatures; Scope and Application [FDA];
- 21CFR Part 820, also known as FDA Quality System Regulation (QSR);
- Guidance for Industry; E6 Good Clinical Practice: Consolidated Guidance;
- Guidance for Industry; Computerized Systems used in Clinical Investigations;
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff;
- Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Data entry will be performed at the investigational sites. Standardized electronic Case Report Forms (eCRFs) will be provided for use at all investigational sites. Investigators are responsible for completion and timely submission of the data to Penumbra, Inc. This EDC system requires no on-site software installation or specific hardware to operate. Investigators, clinical coordinators, data managers, and Penumbra clinical personnel access project information and study data centrally via a Web browser. Incoming data are to be reviewed for quality and consistency before being locked for data export. Questions or problems with submitted data will be addressed with the principal investigator via an electronic querying system, or through direct contact.

All hard copy forms and data files will be secured to ensure confidentiality. Investigators are required to maintain source documents required by the protocol, including laboratory results, patient report forms, supporting medical records, and Informed Consent Forms. The source documents will be used during the regular monitoring visits to verify information submitted on the CRFs.

## 7. Contact Information

The address of Penumbra Incorporated is:

Penumbra Incorporated
1351 Harbor Bay Parkway
Alameda, CA 94577
Tel. (510) 748-3200
Fax (510) 814-8305

Key contacts at the company include:

| | | |
|---|---|---|
| Elan Mualem | Clinical Research Associate | 510-748-3254 |
| Siu Po Sit, Ph.D. | VP, Clinical Affairs | 510-748-3221 |
| Arani Bose, M.D. | Medical Monitor | 510-748-3200 |
| Adam Elsesser | CEO | 510-748-3222 |

## 8. Ethical Requirements

### 8.1 Declaration of Helsinki

The study will be performed in accordance with ISO 14155, recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), ICH and US FDA GCP guidelines.

It is the responsibility of the investigator to obtain approval of the study protocol from the Institutional Review Board/Ethics Committee (IRB/EC) and to keep the IRB/EC informed of any serious adverse event, serious adverse device effects, and amendments to the protocol. All correspondence with the IRB/EC should be filed by the investigator and copies sent to the Sponsor or its designee.

### 8.2 Patient Information and Consent

It is the responsibility of the investigator to give each patient full and adequate verbal and written information regarding the objective and procedure of the study and the possible risks involved and to obtain signed informed consent from all patients prior to inclusion in the study unless the patient's health condition does not allow informed consent, in which case the local hospital, state, and FDA procedures will be applied. The original, signed consent is filed with the patient study records, and a copy is provided to the patient.

### 8.3 Patient Data Protection

The patients will be identified in the CRFs with patient number and initials. The patient must be informed that the data will be stored and analyzed by computer, that national regulations for handling of computerized data will be followed, and that only the investigator and the Sponsor or designee will have access to individual patient data. Furthermore, the patients should be informed about the possibility of inspection of relevant parts of the hospital records by the Sponsor or other Health Authorities including the FDA.

### 8.4 Clinical Trial Termination

A patient's participation in the clinical trial will be terminated if the investigator believes that this is in the patient's best medical interest or if the patient no longer complies with the clinical trial requirements. The patient may also decide to withdraw from the clinical trial at any time and terminate participation. Penumbra, the Competent Health Authorities, or FDA may decide to interrupt or terminate this clinical trial if they believe that this is necessary.

## 9. Statistical Procedures

### 9.1 Sample Size Justification

The sample size calculations assume that 80% of the standard Penumbra System patients experience success (TICI of 2 to 3) and 80% of the Penumbra System with Separator 3D patients experience success. Based on a binomial non-inferiority analysis with a non-inferiority margin of 15%, a study of 103 patients per group will have 85% power with a one-sided alpha of 0.05. The sample size was adjusted to 115 patients per group to account for up to10% attrition rate. Assuming that both the 3D arm and the control arm observe a rate of 80% (82/103), the 95% confidence interval for the difference between groups is (-11.0%, 11.0%).

### 9.2 Statistical Analysis

The objective of the statistical analyses is to support the demonstration of the safety and effectiveness of the Penumbra System with Separator 3D. The efficacy analysis will be conducted in the intent-to-treat (ITT) and per protocol (PP) populations and the safety analysis will be conducted in the safety population. The specific details of the statistical analyses will be described completely in the statistical analysis plan. The statistical analysis plan will be finalized prior to database lock.

Descriptive statistics will be provided. This includes the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables and counts and percents for discrete variables. Analyses will be conducted using SAS (SAS Institute, Cary, NC).[24]

Results collected at multiple visits will be summarized at each visit for which they are collected as described in **Table 7**. Summaries for all measures will include all observed data for each visit.

### 9.3 Effectiveness

#### 9.3.1 Primary Endpoint

The primary effectiveness variable is the proportion of patients with a post procedure TICI score of 2 to 3. The proportion of patients in each group who are successful based on these criteria will be calculated. The Core Laboratory data supersede the investigator-reported data in all analyses of TICI scoring.

The primary effectiveness analysis will be the difference between the Penumbra System only group (control) and the Penumbra System with the Separator 3D group. A binomial comparison will be used to test the null hypothesis that the difference in proportions is less than or equal to -.15 ($H_0$: $P_{3D} - P_{Control} \leq -.15$) vs. the one-sided alternative ($H_1$: $P_{3D} - P_{Control} > -.15$). This is equivalent to evaluating that the lower bound of the 90% confidence interval for the difference is above -15%.

### 9.3.2 Secondary Effectiveness Endpoints

The secondary effectiveness variables:

- Good clinical outcome at 30 days post-procedure. Patients meeting one of the following are evaluated as having good clinical outcome: 10 points or more improvement in the NIHSS at Discharge; a NIHSS score of 0-1 at Discharge; 30-day mRS score of 0-2.
- Good neurological outcome at 90 days post-procedure. Patients meeting one of the following are evaluated as have a good neurological outcome at 90 days:
    - mRS score ≤ 2 at 90 days
    - mRs score at 90 days equal to the pre-stroke mRS score (if the pre-stroke mRS score was higher than 2)
    - 10 or more points improvement on the NIHSS score at 90 days
- The proportion of patients with a modified Rankin Scale (mRS) of ≤ 2 at 90 days post procedure.

Frequency counts and percentage of patients within each category will be provided for categorical data. Estimates of the treatment differences and their 95% confidence intervals will be calculated. Patient rates will be compared between treatment groups with Fisher's exact test.

### 9.3.3 Effectiveness Subgroup Analysis

To evaluate the impact of baseline conditions on treatment effect, subgroup analyses will be performed for the primary efficacy variable, TICI 2-3, the secondary effectiveness variables, (good clinical outcome at 30 days, good neurological outcome at 90 days and 90-day mRS 0-2). The subgroups below will be used for these analyses:

- Age (< 65, or >= 65)
- Baseline NIHSS (< 20, or >= 20)
- Site of occlusion.

## 9.4 Safety

The denominator for the safety analyses is all enrolled patients who received the assigned treatment in the target vessel.

### 9.4.1 Primary Safety Analysis

- Analysis of device or procedure related SAE within 24 hours post procedure: The proportion of patients in each group who experience a device or procedure related SAE within 24 post procedure will be calculated. The CEC/DSMB data supersede the investigator-reported data in all analyses Adverse Events. Frequency counts and percentage of patients within each category will be provided. Estimates of the treatment differences and their 95% confidence intervals will be calculated. Subject rates will be compared between treatment groups with Fisher's exact test.

### 9.4.2 Secondary Safety Analysis

- Analysis of symptomatic ICH:
  Rates of symptomatic and asymptomatic hemorrhage will additionally be provided. Frequency counts and percentage of subjects within each category will be provided for categorical data. Estimates of the treatment differences and their 95% confidence intervals will be calculated. Patient rates will be compared between treatment groups with Fisher's exact test.

- Analysis of Deaths:
  The Kaplan-Meier product-limit method will be the primary method utilized to assess the mortality rate. With the date of randomization set at Day 0, any death occurring on or before calendar day 90 will be counted as a death. If clinical assessment is missing for a patient who has not died, the patient will be censored at the last follow-up date. Patients who are alive at day 90 will be censored at day 90. The log-rank test will be used to compare the groups. This comparison weights earlier and later differences equally. Additionally, the death data will be presented as 90 Day binary deaths. The number of deaths will be presented for each group.

## 9.5 Adverse Event Analysis

All adverse events will be summarized by showing the number and percent of patients which report the event. Events will also be reported by relationship to the procedure or device. Causality of adverse events will be adjudicated by a Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB). Operations of the CEC/DSMB is governed by the CEC/DSMB Charter for this study. The CEC/DSMB data supersede the investigator-reported data in all analyses of adverse events.

## 9.6 Interim Analysis

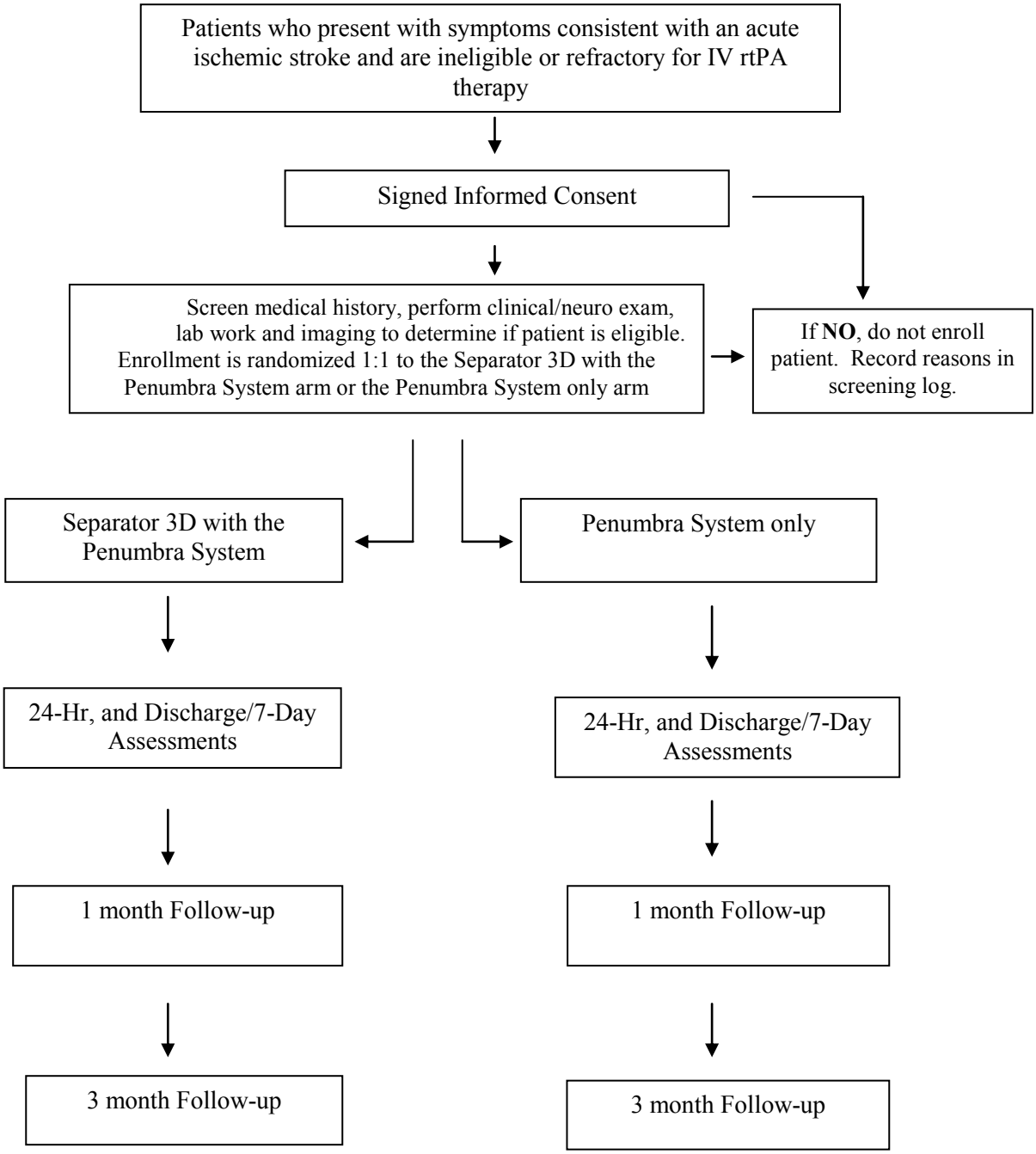
There will be no interim analysis for this study.

## 10. Publication of Information

The results of this study may be offered for publication. The investigators and the Sponsor shall collaborate in the writing of the study to ensure accuracy. All information not previously published concerning the test device and research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of Penumbra. The investigator agrees to use this information only in connection with this study and will not use it for other purposes without written permission from the Sponsor.

# 11. References

## 11.1 Schematic of Study Design



## 11.2 Acronyms

| Acronym | Definition |
|---|---|
| AHA | American Heart Association |
| ADE | adverse device effect |
| AE | adverse event |
| ASA | acetylsalicylic acid (aspirin) |
| BID | twice daily |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CEC/DSMB | Clinical Events Committee/Data Safety Monitoring Board |
| CRA | clinical research associate |
| CRF | case report form |
| CTA | computed tomography angiography |
| CVA | cerebrovascular accident |
| DSA | digital subtraction angiography |
| EC | Ethics Committee |
| EDC | electronic data capture |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practices |
| IA | Intra-arterial |
| ICH | intracranial hemorrhage |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVRS | interactive voice response system |
| MI | myocardial infarction |
| MRA | magnetic resonance angiography |
| mRS | modified Rankin Scale |
| NCCT | nonenhanced CT (without contrast) |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIHSS | National Institute of Health Stroke Scale |
| NINDS | National Institute of Neurological Disorders and Stroke |
| p.o. | *per os*; by mouth |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| QD | once daily |
| rtPA | recombinant human tissue plasminogen activator |
| SAE | serious adverse event |
| TIA | transient ischemic attack |
| TICI | thrombolysis in cerebral infarction |
| TIMI | thrombolysis in myocardial infarction |
| UADE | unanticipated adverse device effect |

11.3 Definitions

**ADVERSE EVENT**
Any undesirable clinical event occurring in a patient during a clinical trial, whether or not it is considered related to the investigational product. This includes a change in a patient's condition or laboratory results that has or could have a deleterious effect on the patient's health or well-being.

**ADVERSE DEVICE EFFECT**
Any adverse event related to the investigational device.

**CASE REPORT FORM**
A record of the data and other information on each patient in the study often abbreviated as CRF

**COMPLICATION (ANGIOGRAPHIC OR CLINICAL)**
An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to acute occlusion, air embolism, arteriovenous fistula, death, distal embolization, emboli, false aneurysm formation, hematoma or hemorrhage at access site, infection, intracranial hemorrhage, ischemia, neurological deficits including stroke, vessel spasm, thrombosis, dissection, or perforation. Complications may or may not be related to the investigational product(s).

**CEREBRAL ARTERY VASOSPASM**
Spasm of the intracranial arteries, resulting in decrease in lumen diameter. Also known as cerebral vasospasm. May occur distal to the treatment site and is generally reversed with administration of vasodilator agents or with adjunct balloon dilatation.

**DISSECTION**
Angiographic evidence of a tear in the arterial wall as defined by the occurrence of intramural hematoma

**DISTAL EMBOLIZATION**
Migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches

**EMBOLI**
Blood clots or thrombi transported by blood from a distant source

**HYPERTENSION**
Persistently high arterial blood pressure. Various criteria for its threshold have been suggested, ranging from 140 mm Hg systolic and 90 mm Hg diastolic to as high as 220 mm Hg systolic and 110 mm Hg diastolic. Hypertension may have no known cause or be associated with other primary diseases.

**HYPOTENSION**
Sustained Hypotension: Systolic blood pressure less than 80 mm Hg lasting more than 30 minutes or requiring intervention (e.g. pacing, intra aortic balloon pump (IABP), intravenous vasopressors to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self limited or readily reversible.

**INTIMAL FLAP**
An extension of the vessel wall into the arterial lumen

**INTRACRANIAL HEMORRHAGE**
Bleeding in the cranium of the brain.

**ISCHEMIA**
The deficiency, or a lack of blood flow to an organ resulting in an imbalance between the supply and demand of oxygen (or other nutrients) leading to cell damage or death

**LEUKOPENIA**
A leukocyte count of $<3.5 \times 10^9$/liter for more than 3 days

**NEOINTIMAL HYPERPLASIA**
Thickening of the neointima due to intimal cell accumulation

**NEUTROPENIA**
A decrease in the number of neutrophilic leukocytes in blood to $<1{,}000\ mm^3$

**OCCLUSION**
The cessation of blood flow in an artery due to the presence of a clot or thrombus

**OCCLUSION LOCATION**
Location according to specific cerebral artery; a standard code will be provided in the CRF to use for location descriptions

**PERFORATION**
The piercing or rupturing of a blood vessel; perforations can be detected or observed angiographically

**PROCEDURAL SERIOUS ADVERSE EVENTS**
Serious adverse events that occurred within 24 hours of the procedure

**SERIOUS ADVERSE EVENT**
Any undesirable clinical event or serious device effect that results in death, is life-threatening, causes persistent or significant disability/incapacity, requires or prolongs hospitalization, requires intervention, results in congenital abnormality, or led to a serious deterioration in the health of the patient that resulted in life-threatening illness or injury, resulted in permanent impairment of a body structure or a body function, resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function, or led to fetal distress, fetal death or a congenital abnormality or birth defect

**STROKE**
A new focal neurological deficit of presumed vascular origin persisting more than 24 hours and with a neuro-imaging study that does not indicate a different etiology. The 24-hour criterion is excluded if the patient undergoes cerebrovascular surgery or dies during the first 24 hours. It includes patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. It does not include stroke events in cases of blood disorders such as leukemia, and it excludes patients with a history of stroke secondary to trauma.

**TARGET OCCLUSION**
The occlusion treated or attempted to be treated during the index procedure

**TARGET VESSEL**
The intracranial vessel containing a target occlusion

**THROMBUS**
Discrete, mobile intraluminal filling with defined borders with or without associated contrast straining; these are classified as either absent or present.

**THROMBOCYTOPENIA**
A platelet count of <100,000 $mm^3$

**TOTAL OCCLUSIONS**
An occlusion with no flow (TIMI/TICI 0)

**TRANSIENT ISCHEMIC ATTACK (TIA)**
A focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset

**UNANTICIPATED ADVERSE DEVICE EVENT**
An event that has an ***Adverse Device Effect***, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the *Instruction for Use* or the clinical protocol.

## 11.4 Modified Rankin Scale

| | |
|---|---|
| **0** | **No Symptoms** |
| **1** | **No significant disability, despite symptoms; able to perform all usual duties and activities** |
| **2** | **Slight disability; unable to perform all previous activities but able to look after own affairs without assistance** |
| **3** | **Moderate disability; requires some help, but able to walk without assistance** |
| **4** | **Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance** |
| **5** | **Severe disability; bedridden; incontinent, and requires constant nursing care and attention** |

From Sulter, G, Steen C, De Keyser, J. "Use of the Barthel Index and Modified Rankin Scale in acute stroke trials." Stroke. 1999;30:1538-1541.

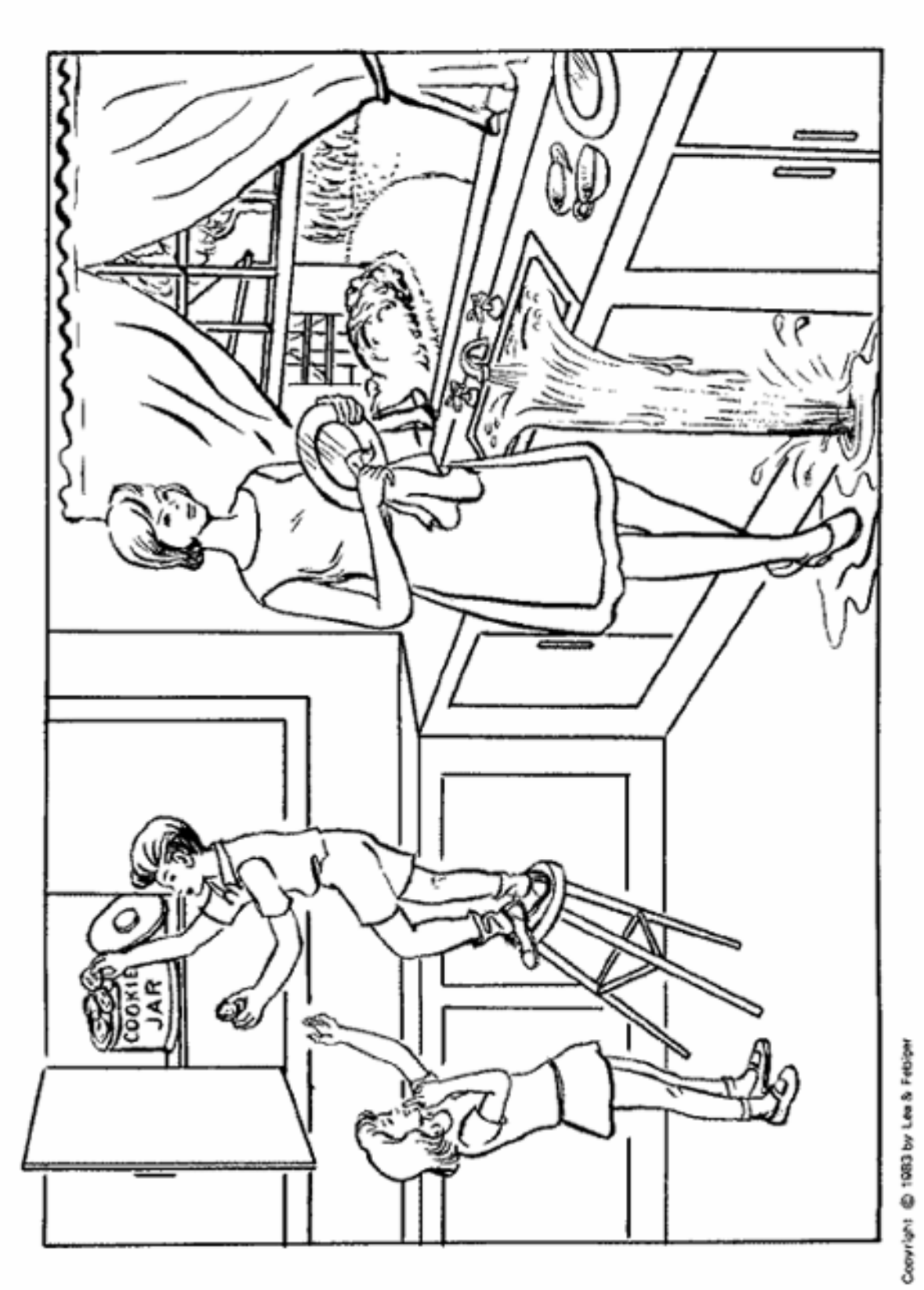
## 11.5 National Institute of Health Stroke Scale

| NIH STROKE SCALE | | |
|---|---|---|
| **Instructions** | **Scale Definition** | **Score** |
| **1a. Level of Consciousness**: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation. | 0 = Alert: keenly responsive.<br>1 = Not alert, but arousable by minor stimulation to obey, answer, or respond.<br>2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).<br>3 = Responds only with reflex motor autonomic effects or totally unresponsive, flaccid, and flexic. | ____ |
| **1b. LOC Questions**: The patient is asked the month and his/her age. The answer must be correct – there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues. | 0 = Answers both questions correctly.<br>1 = Answers one question correctly.<br>2 = Answers neither question correctly. | ____ |
| **1c. LOC Commands**: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him/her (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored. | 0 = Performs both tasks correctly.<br>1 = Performs one task correctly.<br>2 = Performs neither task correctly. | ____ |
| **2. Best Gaze**: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy. | 0 = Normal.<br>1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.<br>2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver. | ____ |
| **3. Visual**: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to answer item 11. | 0 = No visual loss.<br>1 = Partial hemianopia.<br>2 = Complete hemianopia.<br>3 = Bilateral hemianopia (blind including cortical blindness). | ____ |
| **4. Facial Palsy**: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible. | 0 = Normal symmetrical movement.<br>1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).<br>2 = Partial paralysis (total or near total paralysis of lower face).<br>3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face). | ____ |

## NIH STROKE SCALE

| Instructions | Scale Definition | Score |
|---|---|---|
| **5. Motor Arm**: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. | 0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds.<br>1 = Drift; Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds: does not hit bed or other support.<br>2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.<br>3 = No effort against gravity; limb falls.<br>4 = No movement.<br>UN = Amputation or joint fusion, explain: _____<br>**5a. Left Arm**<br>**5b. Right Arm** | ____<br>____ |
| **6. Motor Leg**: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. | 0 = No drift; leg holds 30 degrees position for full 5 seconds<br>1 = Drift; leg falls by the end of the 5 second period but does not hit bed<br>2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity<br>3 = No effort against gravity; leg falls to bed immediately<br>4 = No movement<br>UN = Amputation or joint fusion, explain: _____<br>**6a. Left Leg**<br>**6b. Right Leg** | ____<br>____ |
| **7. Limb Ataxia**: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "UN" and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position. | 0 = Absent.<br>1 = Present in one limb.<br>2 = Present in two limbs.<br>UN = Amputation or joint fusion, explain: _____ | ____ |
| **8. Sensory**: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are automatically given a 2 on this item. | 0 = Normal; no sensory loss.<br>1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched.<br>2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg. | ____ |
| **9. Best Language**: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands. | 0 = No aphasia, normal.<br>1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.<br>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.<br>3 = Mute, global aphasia; no usable speech or auditory comprehension. | ____ |

| NIH STROKE SCALE | | |
|---|---|---|
| **Instructions** | **Scale Definition** | **Score** |
| **10. Dysarthria**: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why (s)he is being tested. | 0 = Normal.<br>1 = Mild to moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.<br>2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.<br>3 = Intubated or other physical barrier,<br>explain: _____ | ____ |
| **11. Extinction and Inattention (formerly Neglect)**: Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable. | 0 = Normal abnormality.<br>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.<br>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space. | ____ |


COOKIE
JAR
Copyright © 1983 by Lee & Felcher

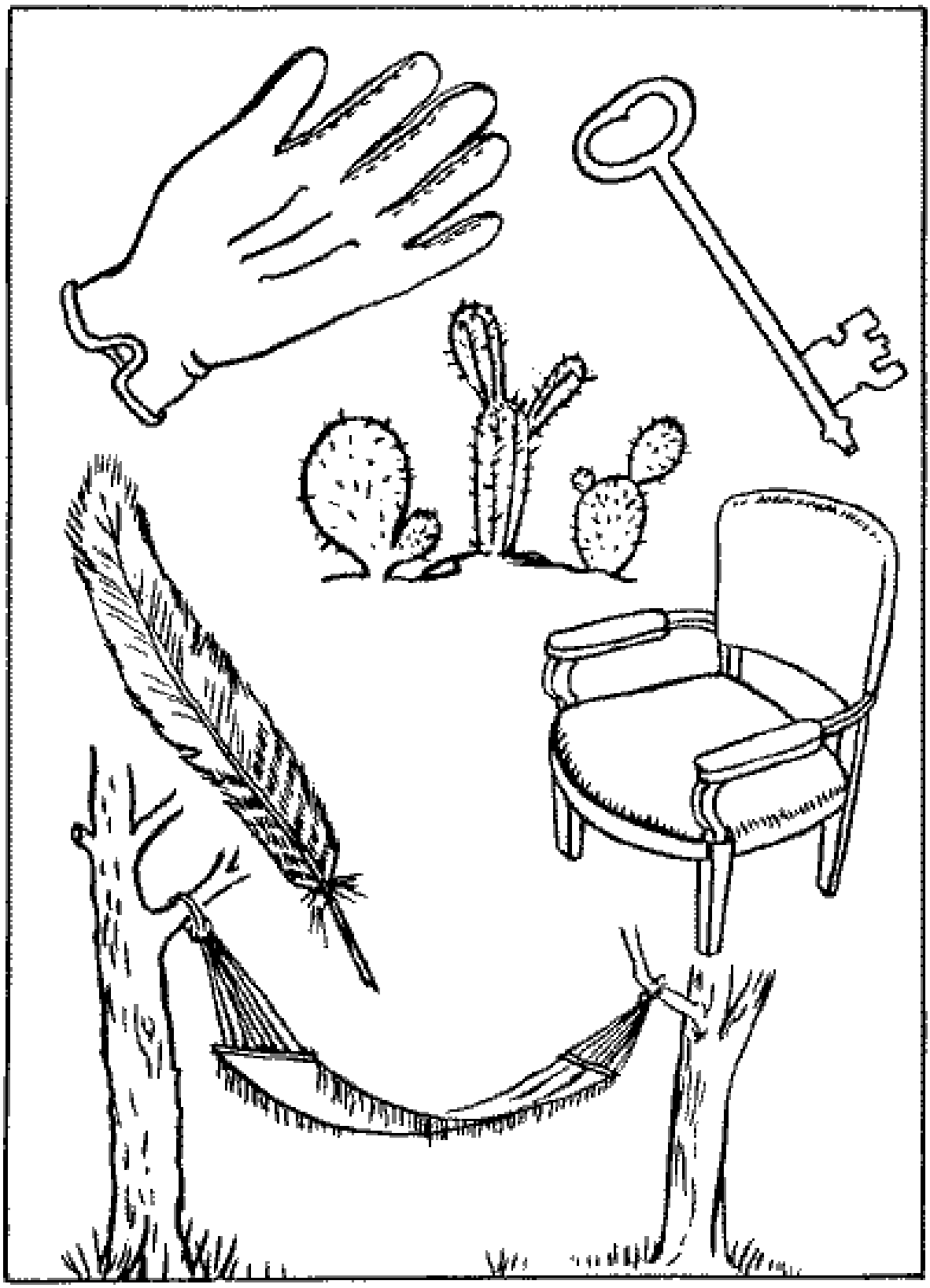
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

CATERPILLAR

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