
ERSIAS

BACKGROUND

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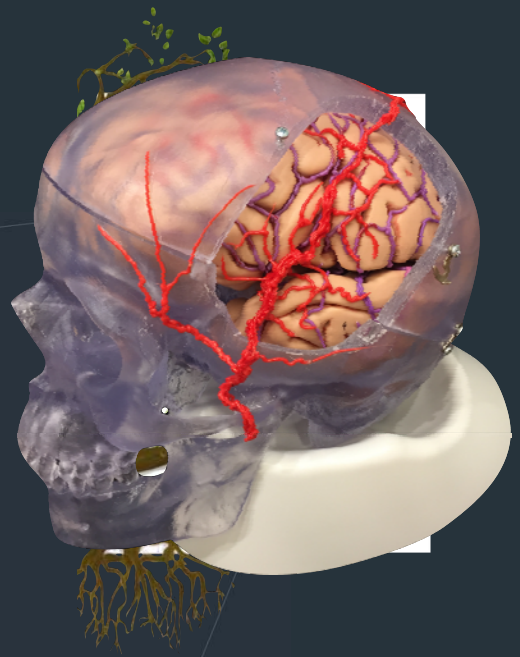
EDAS Revascularization for Symptomatic Intracranial Atherosclerosis



EDAS SURGERY

EDAS is a form of indirect revascularization in which the superficial temporal artery (STA) is re-routed under the scalp to be placed in close contact with the middle cerebral artery cortical branches. Over time, neovascularization from the STA occurs providing blood flow to the intracranial circulation.

SIGNIFICANCE

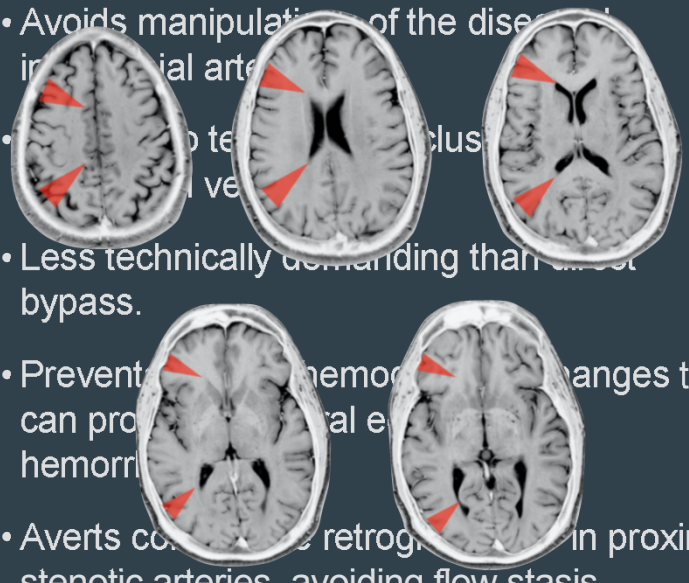
- Intracranial atherosclerotic disease (ICAD)
  - One of the most common causes of stroke and death worldwide.
  - Highest rates of recurrent stroke despite intensive medical therapy:
    - **37% for those with borderzone stroke - Hemodynamic failure.**
- Current medical management for ICAD
  - Reduces progression of endothelial damage, plaque growth, in-situ thrombosis, and artery to artery embolisms.
- Current therapy **does not correct hemodynamic aspects due to hypoperfusion** and poor collaterals.

CHALLENGE

A NEW OPTION

EDAS

- Development of gradual revascularization in hypoperfused areas.
- Avoids manipulation of the diseased intracranial artery.
- Does not require temporary occlusion of vessels.
- Less technically demanding than direct bypass.
- Prevents hemodynamic changes that can provoke cortical ischemia or hemorrhage.
- Averts competitive retrograde flow in proximal stenotic arteries, avoiding flow stasis.



PRELIMINARY DATA

PREVIOUS EVIDENCE SUPPORTING EDAS

ERSIAS Phase IIa

n = 52

Endpoints	N	%
Stroke or death of any cause within 30 days of surgery, or any stroke in the territory of the qualifying artery at one year after surgery	5	**9.6**
Stroke	4	7.7
Stroke related death	0	0

* Two patients (3.8%) had surgical wound dehiscence that required an additional surgical intervention for debridement and closure

ERSIAS Phase II a	Objective performance target from SAMMPRIS
9.6%	20.1%

10.5% absolute risk reduction

Results meet the p <0.10 criterion for non-futility and advancement to phase 3 RCT

Sensitivity Analysis versus Propensity Score Matched Controls from SAMMPRIS and COSS

	n = 52		**n = 52**	
	ERSIAS		**CONTROLS**	
Primary Endpoint	N	%	N	%
Stroke or death of any cause within 30 days of surgery, or any stroke in the territory of the qualifying artery at one year after surgery	5	**9.6**	11	**21.2**

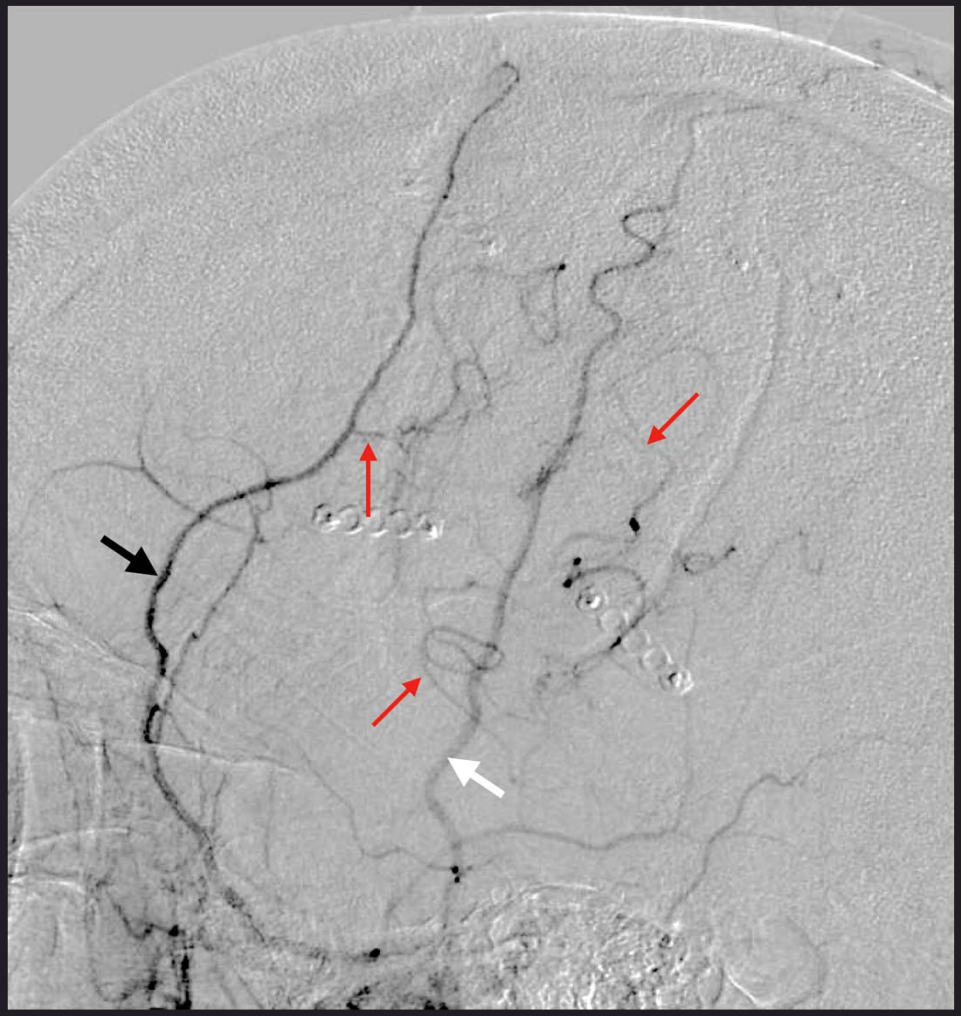
11.6% absolute risk reduction.

(p=0.09, pre-established alpha ≤ 0.1 for phase IIa)

Proportional Hazards Model p=0.02

Controls/ERSIAS HR = 2.6

(90% CI 1.1-7.2)



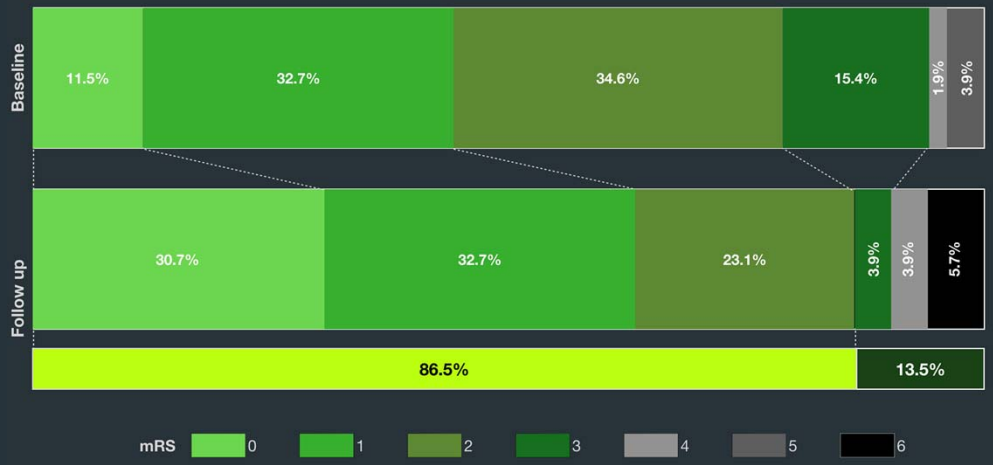
6 months post-op angiogram showing new collaterals from the STA and MMA in a 56 y/o female

PRELIMINARY DATA

ERSIAS Phase IIa

PREVIOUS EVIDENCE SUPPORTING EDAS

Functional outcomes: 86.5% functionally independent



Angiographic neovascularization

	N	%
Neovascularization (Perren Grade ≥2)	41	**97.6**
Good Collaterals (ASITN Grades 3-4)	26	**68.4**

INITIATING INVESTIGATOR

TEAM

Nestor R. Gonzalez, MD

Principal Investigator

Professor of Neurosurgery
Director Neurovascular Laboratory
Cedars-Sinai Medical Center

Jeffrey L. Saver, MD

Principal Investigator

Professor of Neurology
Senior Associate Vice Chair of Clinical Research
UCLA School of Medicine

Tanya Turan, MD

Medical Management Core Director

Professor of Neurology
Director Stroke Division
Medical University of South Carolina

Colin P. Derdeyn, MD

Imaging Core Director

Professor of Radiology
Director Iowa Institute of Biomedical Imaging
University of Iowa

Steven Piantadosi, MD, PhD.

Statistical and Study Design Support

Associate Senior Biostatistician
Division of Surgical Oncology
Brigham and Women's Hospital

PIVOTAL STUDY DESIGN

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Primary Aim

To test the hypothesis that in patients with symptomatic intracranial atherosclerotic disease, **EDAS revascularization combined with intensive medical therapy is more effective than intensive medical therapy alone for preventing stroke or death.**

PIVOTAL STUDY DESIGN

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EDAS Revascularization for Symptomatic Intracranial Atherosclerosis

Primary Outcome

A**ny stroke or death** within 40 days of enrollment or within 30 days of revascularization surgery (whichever comes later) **or recurrent ischemic stroke in the territory of the qualifying artery thereafter through two years.**

PIVOTAL STUDY DESIGN

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EDAS Revascularization for Symptomatic Intracranial Atherosclerosis

Clinical secondary endpoints:

1. Disabling ischemic stroke or death through 2 years.
2. Functional outcome at the end of follow-up measured by the mRS.
3. Cognitive decline at the end of follow-up measured by the MoCA.

Safety endpoints:

1. Any surgical complication requiring additional hospitalization, reoperation, or causing non-ischemia related patient disability.
2. Systemic hemorrhage, subdural or epidural hemorrhage.

Physiologic endpoints:

1. Degree of angiographic neovascularization evident on the multiphase CTA and CT Perfusion imaging that will be obtained at baseline and one year, using the multiphase CTA collateral score.

Screening for potential neurologic endpoint events will occur at each study visit using the Questionnaire to Verify Stroke-Free Status and by regular physical examination by site neurologists.

All potential endpoint events will be evaluated by the site study neurologist, MRI or CT will be obtained if any stroke is suspected and **confirmed by the central imaging core lab**.

All potential **endpoint events will be adjudicated by a Central Clinical Event Adjudications Committee blinded to study treatment assignment**.

PIVOTAL STUDY DESIGN

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Seamless phase IIb-III design

Uncertainties remaining that justify a Phase IIb:

- EDAS surgery generalizability to more institutions.
- Phase IIa was not randomized.

Benefits of the seamless phase IIb-III design:

- If the EDAS technique is found to be futile or the surgical outcomes not generalizable, the study will be stopped with a relatively small sample size.
- If the EDAS surgery is found to be promising at the phase IIb, as the preliminary data indicates, the seamless design allows for the use of patients already randomized to contribute to the pivotal second stage (phase III).
- This design offers a significant reduction in time and costs, compared to the alternative of conducting an independent randomized phase IIb, evaluating the results of that second trial, and then moving to a third trial for confirmatory phase III.

STUDY DESIGN

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EDAS Revascularization for Symptomatic Intracranial Atherosclerosis

PROPOSED DESIGN

Seamless phase IIb - III **multicenter randomized clinical trial** enrolling **patients with TIA or non-disabling ischemic stroke attributed to ≥ 70% stenosis or occlusion of the intracranial ICA or MCA, despite optimized medical management,** randomizing participants **(1:1)** to:

- **Intensive medical management alone – IMM** (aspirin 325 mg / day for entire follow-up, clopidogrel 75mg per day for 90 days after enrollment unless cardiologist or vascular neurologist recommends continuing clopidogrel beyond 90 days, and aggressive risk factor management including targeting blood pressure < 140 / 90 mm Hg (< 130 / 80 mm Hg if diabetic) and LDL < 70 mg / dl).
- **OR**
- **EDAS revascularization plus intensive medical therapy – EDAS + IMM** (aspirin 325 mg / day for entire follow-up, ***clopidogrel 75mg per day [except during the perioperative period – 10 days before and 15 days after surgery]*** for 90 days after enrollment unless cardiologist or vascular neurologist recommends continuing clopidogrel beyond 90 days, and aggressive risk factor management including targeting blood pressure < 140 / 90 mm Hg (< 130 / 80 mm Hg if diabetic) and LDL < 70 mg / dl).

STUDY DESIGN

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EDAS Revascularization for Symptomatic Intracranial Atherosclerosis

ELIGIBILITY COMPONENTS

CLINICAL

- TIA or non-disabling ischemic stroke.*
- Within 60 days of enrollment.
- Attributed to stenosis/occlusion of the intracranial ICA or the MC), despite multimodal medical management.

IMAGING

- Confirmation by the imaging core lab of intracranial arterial stenosis/occlusion ≥70% of the corresponding artery by CTA, MRA, or catheter angiography
- Exclusion of patients with perforator infarctions*

* The inclusion characteristics of the qualifying event (TIA vs. stroke) and vascular stroke territory (borderzone vs. core territory) will be included in the stratification of the randomization process to assure balance of these features between groups

STUDY DESIGN

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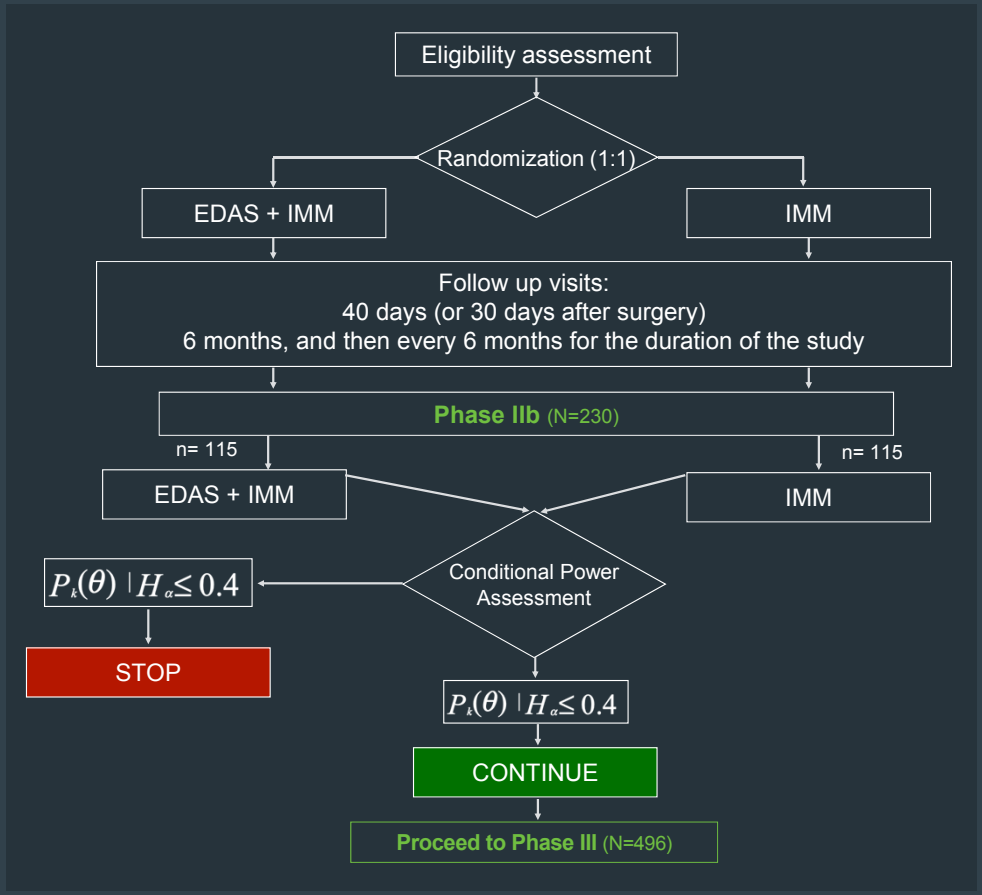
Phase II b

- Once 115 recruited subjects have completed 1-year follow up in each arm, conditional power (CP) will be calculated, without unblinding.
- CP is the probability that the final result will be significant, given the data obtained.
- If the CP falls below a prespecified boundary threshold of 0.40, the continuation of the study will be considered futile.
- This is equivalent to a futility index $1 - P\&(\theta)|H, \geq 0.6$.
- Where Pk(θ)|Ha is the conditional power assuming the distribution of the remainder of the trial data will follow the alternative hypothesis.



STUDY DESIGN

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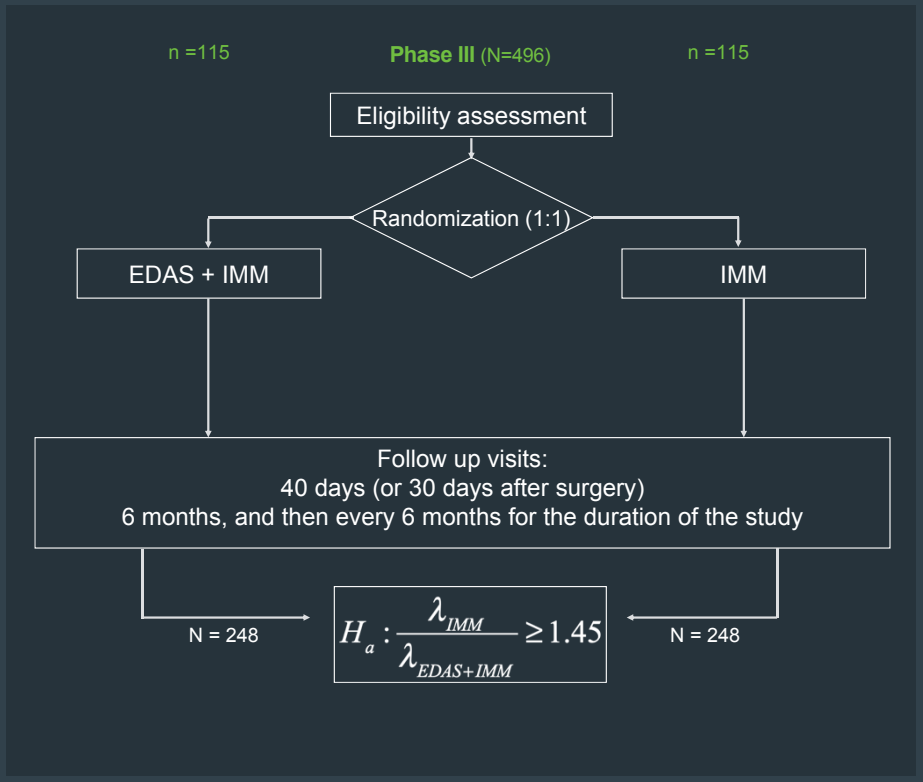
Phase III

- Proportional hazards modeling will be used to test the primary hypothesis.
- The preliminary results of the phase IIa study showed a HR of 2.6 when EDAS results were compared to the PSM control group.
- We have selected a more conservative effect of 1.45, which represents a minimum clinically meaningful relative risk reduction of approximately 30%, or 5% absolute risk reduction.



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Schedule of Events

Study Visits	Screening	Enrollment and Randomization	Baseline	Treatment	Post EDAS	Visit 1 40 d	Visit 2 6 m	Visit 3 12 m	Visit 4 18 m	Visit 5 24 m	Visit 6 30 m	Visit 7 36 m	Visit 8 42 m	Visit 9 48 m
Informed Consent	X													
Medical History	X													
Medication review	X					X	X	X	X	X	X	X	X	X
Physical Exam	X				X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X													
Cardiac evaluation	X													
Enrollment and randomization		X												
NIHSSS			X		X	X	X	X	X	X	X	X	X	X
MoCA			X			X	X	X	X	X	X	X	X	X
mRS			X			X	X	X	X	X	X	X	X	X
Questionnaire for stroke			X			X	X	X	X	X	X	X	X	X
Multiphase CTA and CTP			X					X						
Blood sample			X				X	X						
Blood sample storage			X				X	X						
Sample shipment								X						
Patient travel for follow up			X			X	X	X	X	X	X	X	X	X
EDAS surgery				X										
Central IMM				X										
Anesthesia report form				X										
Adverse events assessment				X	X	X	X	X	X	X	X	X	X	X

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FEASIBILITY

- The Centers for Medicare and Medicaid Services have confirmed that if the ERSIAS Trial is funded, it will be qualified to receive Medicare coverage for the costs of surgery and clinical care.

Based on **CMS issued NCD 310.1**
Communication from Rosemary Hakim, Senior Technical Research Adviser
Coverage & Analysis Group - Center for Clinical Standards and Quality

- This coverage model was used on ERSIAS IIa.
- Recruitment data from SAMMPRIS for a similar target enrollment population

	SAMMPRIS	ERSIAS Projection
Sample size	451	496
Proposed sites	60	60
Activated sites	59	-
Sites actively recruiting	49	40
Institutional enrollment success rate	86%	66%
Mean recruitment rate per year per site	5.7 (SD 2.8)	3.3
Mean time from activation to enrollment (months)	2.5 (SD 2.03)	-
Mean enrollment period (years)	1.5 (SD 0.63)	Phase IIb:1.75. / Phase III: 2.0

- Stroke Network feasibility survey.

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Informal Feasibility Survey

- Number of contacted institutions: 21
- Interested in participating: 20
- Mean number of patients seen per year with symptomatic ICAD of ≥ 70% or occlusion = 15.3

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SAMPLE SIZE AND ENROLLMENT PLAN

- Total sample size N = 496
- Participating institutions = 40
- Duration of enrollment = 3.75 years
- Length of follow up 1.25 - 5 years

Recruitment Funnel Calculation

Funnel Parameters and Stages	
Complete enrollment period (years)	3.75
# of sites	40
Average # of potential patients at a given site per year	12
% Lost during screening	0.6
% Decline to participate	0.15
% Drop out post randomization	0.1

Total available patients	1800
Estimated number lost during screening	1080
Estimated numer declines to participate	162
Estimated drop out port randomization	16

Total estimated number enrolled	**542**

- Based on guidelines from the International Council for Harmonization (ICH) Part 4.2.1
- Carter RE, et al. Practical considerations for estimating clinical trial accrual periods: application to a multi-center effectiveness study. BMC Medical Research Methodology 2005, 5:11 doi:10.1186/1471-2288-5-11

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Nestor R. Gonzalez, MD, MSCR.

Professor of Neurosurgery
Director Neurovascular Laboratory
Program Director Neuroendovascular Surgery Fellowship
Department of Neurosurgery
Cedars-Sinai Medical Center